Review

Fosfomycin as Partner Drug for Systemic Infection Management. A Systematic Review of Its Synergistic Properties from In Vitro and In Vivo Studies

Roberta Maria Antonello 1, Luigi Principe 2, Alberto Enrico Maraolo 3, Valentina Viaggi 4, Riccardo Pol 5, Massimiliano Fabbiani 6, Francesca Montagnani 6,7, Antonio Lovecchio 1, Roberto Luzzati 1 and Stefano Di Bella 1,*

1 Clinical Department of Medical, Surgical and Health Sciences, Trieste University, 34127 Trieste, Italy; rma.roby@gmail.com (R.M.A.); antolvc93@gmail.com (A.L.); roberto.luzzati@asugi.sanita.fvg.it (R.L.)
2 “San Giovanni di Dio” Hospital, 88900 Crotone, Italy; luigi.principe@gmail.com
3 First Division of Infectious Diseases, Cotugno Hospital, AORN dei Colli, 80131 Naples, Italy; albertomaraolo@mail.com
4 “A. Manzoni” Hospital, 23900 Lecco, Italy; v.viaggi@asst-lecco.it
5 Department of Infectious Diseases, Udine University, 33100 Udine, Italy; riccardopol91@gmail.com
6 Department of Medical Sciences, Tropical and Infectious Diseases Unit, University Hospital of Siena, 53100 Siena, Italy; massimiliano.fabbiani@gmail.com (M.F.); francesca.montagnani@unisi.it (F.M.)
7 Department of Medical Biotechnologies, University of Siena, 53100 Siena, Italy
* Correspondence: stefano932@gmail.com

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Abstract: Fosfomycin is being increasingly prescribed for multidrug-resistant bacterial infections. In patients with systemic involvement, intravenous fosfomycin is usually administered as a partner drug, as part of an antibiotic regimen. Hence, the knowledge of fosfomycin pharmacodynamic interactions (synergistic, additive, indifferent and antagonistic effect) is fundamental for a proper clinical management of severe bacterial infections. We performed a systematic review to point out fosfomycin’s synergistic properties, when administered with other antibiotics, in order to help clinicians to maximize drug efficacy optimizing its use in clinical practice. Interactions were more frequently additive or indifferent (65.4%). Synergism accounted for 33.7% of total interactions, while antagonism occurred sporadically (0.9%). Clinically significant synergistic interactions were mostly distributed in combination with penicillins (51%), carbapenems (43%), chloramphenicol (39%) and cephalosporins (33%) in Enterobacterales; with linezolid (74%), tetracyclines (72%) and daptomycin (56%) in Staphylococcus aureus; with chloramphenicol (53%), aminoglycosides (43%) and cephalosporins (36%) against Pseudomonas aeruginosa; with daptomycin (97%) in Enterococcus spp. and with sulbactam (75%) and penicillins (60%) and in Acinetobacter spp. fosfomycin-based antibiotic associations benefit from increase in the bactericidal effect and prevention of antimicrobial resistances. Taken together, the presence of synergistic interactions and the nearly total absence of antagonisms, make fosfomycin a good partner drug in clinical practice.

Keywords: fosfomycin; pharmacodynamic; synergic; synergism; synergistic; infection; multidrug resistant

1. Introduction

Antimicrobial resistance (AMR) is a health issue of global concern, burdened with elevated costs and high morbidity and mortality rates. Limited therapeutic options and the increasing occurrence of resistance to last-resort antibiotics, i.e., colistin or carbapenems, make it necessary to reassess the role of “old” drugs while waiting for new antibiotics available on the market.
Fosfomycin (FOS) is an inhibitor of the synthesis of the bacterial wall acting with a unique mechanism of action. To carry out its action, FOS enters in the bacterial cell through the L-alpha-glycerophosphate and the hexose-6-phosphate transporter systems, interfering with the formation of the peptidoglycan precursor uridine diphosphate N-acetylmuramic acid (UDP-MurNAc) [1].

FOS, after being discovered in 1969 [2], has long been prescribed orally for low urinary tract infections (UTIs) and only recently has been repurposed, also intravenously and in combination, as a meropenem- and colistin-sparing agent to treat other infections (complicated UTIs, severe soft tissue infections, osteomyelitis, prostatitis, etc.) [1,3–5]. The excellent distribution in body sites, the safety and tolerability profile, as well as its affordability, make FOS a therapeutic option worth considering to treat multidrug-resistant (MDR) bacterial infections [6,7].

FOS is generally prescribed in association with at least another active agent. The association benefits from increase in the bactericidal effect of FOS, prevention of AMR, limitation of side effects thanks to lower dosages. Examples of commonly used empirical combination regimens including FOS are: Carbapenems + FOS, colistin + FOS, ceftolozane/tazobactam + FOS and tigecycline (TIG) + FOS.

We performed a systematic literature review concerning in vitro and in vivo studies to evaluate the synergistic effect of FOS in combination with other antibiotics and offer an overall view with clinically practical tables divided by antibiotic class.

2. Materials and Methods

This systematic review was carried out following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

On 14 April 2020 we performed a MEDLINE/PubMed search using the search string “Fosfomycin”[Tw] AND (synerg*[Tw] OR association*[Tw] OR combin*[Tw] OR “together”[Tw] OR “additive”[Tw] OR “addition”[Tw] OR “checkerboard”[Tw] OR “chequerboard”[Tw] OR “time kill”[Tw] OR “time–kill”[Tw] OR “time–killing”[Tw] OR “time killing”[Tw]).

1232 papers, from inception to 14 April 2020, were identified. Of these, 870 were excluded by title screening, 84 by abstract screening, 28 after full-text reading. Fifty-eight papers were excluded because written in a language different from English. 7 papers were excluded because full text was not available either online or in paper version. 185 papers were reviewed and discussed independently by seven authors (RMA, RP, AL, SDB, VV, LP, MF).

Common criteria for the evaluation of susceptibility and synergism were adopted by all authors. Susceptibility. Susceptibility to FOS for Enterobacterales and Staphylococcus spp. was determined, according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints, when the minimum inhibitory concentration (MIC) was ≤ 32 µg/mL. Enterococcus spp. were considered susceptible when exhibiting a MIC ≤ 64 µg/mL, according to the Clinical & Laboratory Standards Institute (CLSI) breakpoints. FOS breakpoints are not defined either by EUCAST or CLSI for Pseudomonas spp., Acinetobacter spp. and Streptococcus spp. Based on literature data, susceptibility was defined as a MIC ≤ 128 µg/mL for Pseudomonas spp. (ECOFF value), MIC ≤ 32 for Acinetobacter spp. and ≤ 64 µg/mL for Streptococcus spp. [8,9].

For all the antibiotics tested in combination, EUCAST breakpoints was considered at first and CLSI breakpoints were considered when EUCAST breakpoints were not available. Breakpoints adopted are specified in each paragraph.

Synergistic effect. Checkerboard assay: fractional inhibitory concentration index (FICI) ≤ 0.5. FICI is defined as follows:

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FICI = \frac{MIC \text{ FOS in combination}}{MIC \text{ FOS alone}} + \frac{MIC \text{ other antibiotic in combination}}{MIC \text{ other antibiotic alone}}
\]

Time–kill assay: ratio of effective concentrations concordant with FICI or ≥ 2 log kill.
Additive effect. Checkerboard assay: 0.5 < FICI ≤ 1. Time–kill assay: ratio of effective concentrations concordant with FICI or 1 < log kill < 2.

Indifferent effect. Checkerboard assay: 1 < FICI < 4. Time–kill assay: ratio of effective concentrations concordant with FICI or ± 1 log kill.

Antagonistic effect. Checkerboard assay: FICI ≥ 4. Time–kill assay: ratio of effective concentrations concordant with FICI or < 1 log kill.

For in vitro studies using a method different from checkerboard or time–kill assay, or in case data on effective concentrations were not available, synergism was evaluated according to the authors’ judgment.

For studies performed in vivo, synergism was established with the same ratio of effective concentrations considered for checkerboard assays or with the same log kill considered for time–kill assays. When these data were not reported in the paper, synergism was evaluated according to the authors’ judgment.

3. Results

For a better comprehension, a table with reviewed papers and a summary of most relevant results is proposed for each antibiotic class.

3.1. Penicillins

Twenty-eight papers evaluating FOS in combination with penicillins, penicillins + β-lactamase inhibitors, penicillinase-resistant penicillins were reviewed (Table 1). Breakpoints for penicillins were inferred from EUCAST breakpoints [10]. Penicillins are β-lactam antibiotics that acts through the inhibition of enzymes needed for peptidoglycans cross linking. Effect of FOS in combination with penicillins varied greatly according with the bacterial species considered. The highest rates of synergistic effect were observed against Enterobacterales and Acinetobacter spp. Despite this, Avery et al. [11] reported high rates of indifferent effect of FOS + piperacillin/tazobactam (PIP/TAZ) against PIP/TAZ-resistant Enterobacterales. Antagonistic effect was observed against one isolate of S. aureus with the combination FOS + methicillin [12] and against 6 biofilm-producer Enterococcus faecalis isolates with the combination FOS + ampicillin [13]. Four studies [14–17] performed in vivo experiments, with no substantial differences in results when compared with results obtained in vitro.

The combination of penicillin + FOS retains additive/synergistic effects against ~50% of Enterobacterales, Acinetobacter spp., Staphylococcus spp., and Streptococcus spp. strains.

3.2. Cephalosporins

Forty-one papers evaluating FOS in combination with cephalosporins and cephalosporins + β-lactamase inhibitors were reviewed (Table 2). Breakpoints for cephalosporins were inferred from EUCAST breakpoints [10]. Cephalosporins are β-lactam antibiotics that acts disrupting the peptidoglycan synthesis like penicillins, but are less susceptible to β-lactamases. Some studies reported discordant results on the effect of FOS in combination with a cephalosporin against clinical isolates, particularly against Staphylococcus spp. [18–20] and Enterobacterales isolates [11,14,21]. Antagonistic effect was observed against 4 Pseudomonas aeruginosa isolates with the combination FOS + ceftazidime [22], 1 S. aureus and 1 Staphylococcus epidermidis isolates with the combination FOS + ceftriaxone [19]. 9 in vivo studies [17,23–30] performed with different strains (Escherichia coli, P. aeruginosa, S. aureus, Streptococcus pneumoniae, Streptococcus sanguis) confirmed results obtained in vitro or resulted in higher synergistic effect (additive effect only against 3 S. aureus isolates [25,26]).

Cephalosporins + β-lactamase inhibitors, often chosen by clinicians to treat MDR infections, resulted in moderate rates of synergistic effect in combination with FOS. Against Enterobacterales, the combination ceftolozane/tazobactam + FOS resulted synergistic in 16.3% of cases (49 isolates tested [11]), while the combination ceftazidime/avibactam + FOS was synergistic in 28.8% of cases (66 isolates tested [11,21,31]). Against P. aeruginosa, the combination ceftolozane/tazobactam + FOS resulted
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synergistic in 71.1% of cases (45 isolates tested [32–34]), while the combination ceftazidime/avibactam + FOS was synergistic in 31.6% of cases (38 isolates tested [21,29,33]).

The combination of cephalosporins or cephalosporins + β-lactamase inhibitors + FOS appears to be clinically appealing especially against infections sustained by Enterobacterales and Pseudomonas spp.

3.3. Carbapenems

Forty-four papers evaluating FOS in combination with carbapenems were reviewed (Table 3). Carbapenems are β-lactam antibiotics that inhibit bacterial cell wall synthesis by binding to penicillin-binding proteins. Carbapenems are β-lactams “last-resort” used intravenously to treat severe infections. Imipenem (IMI) breakpoints are ≤2 µg/mL for Enterobacterales, Acinetobacter spp., S. pneumoniae and ≤ 0.001 µg/mL for Pseudomonas spp. and Staphylococcus spp. Meropenem breakpoints are ≤2 µg/mL for Enterobacterales, Acinetobacter spp., Pseudomonas spp., S. pneumoniae and ≤ 4 µg/mL for Staphylococcus spp. Ertapenem (ERT) breakpoints are ≤0.5 µg/mL for Enterobacterales, S. pneumoniae and ≤4 µg/mL for Staphylococcus spp. [10].

Synergism rates were not unanimous on all studies, but antagonistic effect was observed only in 2 isolates of P. aeruginosa in the study by Pruekprasert et al. [22] and in 1 isolate of S. aureus in the study by Quentin et al. [35]. No evident differences in the synergistic effect was observed depending on the carbapenem tested. The association FOS + carbapenem often resulted, when reported, in FOS- and/or carbapenem-susceptibility restoration. Three authors performed in vivo experiments using methicillin-resistant Staphylococcus aureus (MRSA) isolates: in two studies [28,36] the results in vivo were concordant with those found in vitro, while in the third study the combination in vivo resulted less effective [37].

From the clinical point of view the combination of carbapenems + FOS against Enterobacterales, P. aeruginosa and Acinetobacter spp. appears appealing.

3.4. Monobactams

Five papers evaluating FOS in combination with aztreonam (ATM) were reviewed (Table 4). ATM is a synthetic antibiotic whose susceptibility is often preserved also in those strains which are resistant to other β-lactam antibiotics. The mechanism of action is similar to penicillins. ATM breakpoints are ≤1 µg/mL for Enterobacterales and ≤0.001 µg/mL for Pseudomonas spp. [10].

The largest study evaluating FOS in combination with ATM on Enterobacterales isolates [33] reported an indifferent effect on most (64.6%) isolates. The combination was reported to have an additive effect on most isolates of P. aeruginosa [33,38], sometimes leading to ATM susceptibility restoration [33,39]. There were no in vivo studies evaluating this combination.

3.5. Quinolones

Twenty-nine papers evaluating FOS in combination with quinolones were reviewed (Table 5). Quinolones are bactericidal antibiotics that directly inhibit bacterial DNA synthesis. Breakpoints for quinolones were inferred from EUCAST breakpoints [10]. Synergism rates were not unanimous on all studies for isolates of P. aeruginosa. In 1 in vivo study synergism rate was 100% according to Mikuniya et al. [40]. Antagonism was observed in 1 in vivo [41] and 1 in vitro studies [39]. For E. coli isolates there was a weak synergism. In a recent in vitro study there was complete FOS and ciprofloxacin susceptibility restoration [42]. The combinations showed different synergistic rates for Staphylococcus spp. isolates with 100% synergistic rate in 1 in vitro study [43] and in 1 in vivo study [44]. No antagonism was observed for E. coli and Staphylococcus spp. isolates. There were some differences in the synergistic effect depending on the quinolone tested. The most frequent effect of FOS + ciprofloxacin was indifferent even though it showed in vitro 95% synergistic effect with S. aureus [45]. The combination with levofloxacin showed mainly an additive effect in P. aeruginosa [38,39,46] and in Acinetobacter spp. [38] isolates.
In summary, good additive/synergistic effect rates are reported when quinolones + FOS are used against S. aureus and P. aeruginosa isolates.

3.6. Aminoglycosides

Aminoglycosides (AMG) act through inhibition of protein synthesis, resulting in a potent and broad-spectrum antibacterial activity but with a potential high nephro- and oto-toxicity [47]. In the attempt to overcome increasing aminoglycosides resistance, development of novel AMG (such as arbekacin and plazomicin) has occurred, but combination strategies are important opportunities to treat resistant bacteria and to reduce toxicity. Inhaled delivery of tobramycin, allowing for greater exposure within the lungs and reducing systemic toxicity, is also approved for the treatment of patients with chronic P. aeruginosa lung infection associated with cystic fibrosis (CF) in United States and Europe [47]. Overall, 41 papers evaluating FOS in combinations with AMG were reviewed (Table 6). Available EUCAST aminoglycosides breakpoints were applied in all studies except one [48]. Due to the peculiarity of possible AMG therapeutic use (e.g. inhaled formulation in cystic fibrosis), many studies investigated the AMG + FOS combination also when administered by inhaled topical use; moreover, the activity of this combination on biofilm formation and in anaerobic conditions was also evaluated. Different AMG were tested as partner of FOS towards several bacterial species in a total of 67 evaluations: mainly gentamicin (31.3%, n = 21), amikacin (23.9%, n = 16) and tobramycin (22.4%, n = 15) were used. Synergism rates were not unanimous on all studies, considering the different bacteria analyzed and the different types of aminoglycosides tested. Overall, a synergistic effect of FOS together with different AMG, even if with different percentages, was revealed in 51 evaluations (74.6%). No synergism was reported in 16 cases (23.9%), even regarding effects on P. aeruginosa and Acinetobacter spp. In one study, data on synergism were not available [49]: however, a potential beneficial effect was indeed reported, demonstrating that FOS enhanced the activity of tobramycin with a 100% additive effect during in vitro evaluation on P. aeruginosa biofilms on cystic fibrosis airway epithelial cells. An antagonistic effect, testing the combination of FOS with gentamicin, was reported in 1985 by Alvarez et al. in 2.7% of 148 MRSA isolates [12] and in 2005 by Pruekprasert et al. in 27% of 22 P. aeruginosa strains [22].

Focusing on different bacterial strains, generally a synergistic or additive effect of FOS + AMG was demonstrated on KPC-producing K. pneumoniae [50–52]; however, Souli et al. observed an indifferent effect of FOS + gentamycin combination in all of their tested KPC+ strains [53].

When tested, a generally positive effect of FOS and AMG combination on biofilm formation and an improved AMG activity in anaerobic conditions were also reported for P. aeruginosa and Acinetobacter spp., resulting moreover in lower required AMG doses.

Activity of FOS plus an AMG was also evaluated against Streptococcus spp. (streptomycin) and Neisseria gonorrhoeae (both, gentamicin) in two studies [14,54]: No synergistic effect was revealed but antagonism was not even reported. Interestingly, synergistic activity (assessed as a fourfold reduction of MIC when fosfomycin was combined with gentamicin 1 mcg/mL) and additive effect were revealed for 8 vancomycin-resistant E. faecium (VRE) isolates (63% and 13%, respectively) [55].

The combination of AMG + FOS against P. aeruginosa appears to be the most clinically appealing.

3.7. Macrolides

Six papers evaluating FOS in combination with macrolides, in particular with erythromycin (ERY), azithromycin (AZT), clarithromycin (CLT), or midecamycin (MDM), were reviewed (Table 7). Macrolides are a large class of antibiotics that act binding 50S ribosomal subunit, inhibiting bacterial proteins synthesis. They have broad-spectrum activity, mainly against many Gram-positive bacteria and some Gram-negative bacteria [56]. Only one in vitro study evaluated FOS + ERY combination against Enterobacterales (87 strains of E. cloacae, E. coli, Proteus spp. and Klebsiella pneumoniae), reporting synergistic effect against 52% of isolates and additive effect against 30% [14]; in the same study FOS + ERY combination was also tested against P. aeruginosa and S. aureus, proving in most
cases additive effect or, less frequently, synergistic effect [14]. When this combination was tested against *Streptococcus* spp. synergistic effect was observed against 15% of isolates, while additive (27%) or indifferent (58%) was seen against the remaining [14]. Some studies evaluated FOS + AZT combination, reporting indifferent effect in 100% of cases, either when tested against *N. gonorrhoeae* (2 studies) [54,57] or against *S. epidermidis* (1 study) [58]. Finally, FOS + CLT and FOS + MDM combinations were evaluated against *S. pseudointermedius* and *P. aeruginosa* respectively; in both cases additive or synergistic effect was demonstrated in vitro or in vivo experiments [59,60]. No antagonistic effect was observed for any combination against any isolate.

From the clinical point of view the combination of macrolides + FOS appears the less appealing.

### 3.8. Glycopeptides

Eighteen articles evaluating FOS in combination with glycopeptides (vancomycin and teicoplanin) have been reviewed (Table 8). Articles were from Spain (n = 5), Taiwan (n = 3), China (n = 2), France (n = 2), Germany (n = 2), Italy (n = 2), Austria (n = 1), and Brazil (n = 1).

Glycopeptides possess an antimicrobial activity selectively directed against Gram-positive bacteria, while Gram-negatives are protected by the outer membrane that is impermeable to these antibiotics. Glycopeptides inhibit the peptidoglycan synthesis by interacting with the terminal D-alanyl-D-alanine present on the pentapeptide side chains of the peptidoglycan precursors.

384 strains have been studied, belonging to several species as *S. aureus* (n = 219), *S. epidermidis* (n = 52), *E. faecalis* (n = 39), *S. pneumoniae* (n = 28), *Acinetobacter baumannii* (n = 20), *Enterococcus faecium* (n = 16) and other coagulase-negative staphylococci (CoNS) (n = 10). Synergy was detected with FOS-vancomycin (VAN) combination (40 out of 308 strains tested, 13%) in 33.3% of *E. faecalis*, 30% of *E. faecium*, 16.7% of *S. aureus*, 13.5% of *S. epidermidis*, and 3.6% of *S. pneumoniae*. Higher rates of synergistic interactions were detected with FOS-teicoplanin (TEC) combination (63 out of 130 strains tested, 48.5%) in 71.8% of *E. faecalis*, 43.7% of *E. faecium*, 60% of other CoNS, 34.3% of *S. aureus* and 33.3% *S. epidermidis*. Synergistic concentration ranges were 1-64 mg/L for FOS, 1-7.5 mg/L for VAN and only 8 mg/L for TEC. Regarding resistant isolates, FOS-VAN synergy was detected in one heterogeneous glycopeptide-intermediate *Staphylococcus aureus* (hGISA), 27 MRSA, 5 *S. aureus* strains with borderline MIC values for VAN (2 mg/L) and in 6 VRE strains, while FOS-TEC in 10 MRSA and 11 VRE strains. Antagonism FOS-VAN was detected in 5 *S. aureus* and one *S. epidermidis* strains. Only in 8 FOS-resistant *S. aureus* strains the activity of FOS was restored in combination with VAN. In vivo application of FOS-VAN combinations showed significant survival of ≥50% of treated animals or patients with infections caused by *S. aureus* or *S. epidermidis* [24,36,61–63].

In summary the combination of VAN + FOS resulted in good synergistic effect rates against *Enterococcus* spp. isolates and seems to be the most clinically relevant combination.

### 3.9. Tetracyclines

Ten papers evaluating FOS in combination with tetracyclines, mostly with minocycline (MIN) and in few cases with doxycycline (DOX) or tetracycline (TEC), were reviewed (Table 9). Tetracyclines are a large class of antibiotics that acts binding the 30S ribosomal subunits, inhibiting bacterial proteins synthesis. They have broad-spectrum activity, being active against many Gram-positive bacteria, Gram-negative, and atypical bacteria [64]. Almost all studies evaluated in vitro FOS + MIN combination against different bacterial species. When evaluated against Enterobacteriales (20 strains), FOS + MIN proved to have additive effect most of the time (65% of isolate), but only in few cases synergistic effect [38]. Similar results were observed when it was tested against multdrug-resistant *P. aeruginosa* [38] and *A. baumannii* isolates; furthermore, in the last case, complete restoration of susceptibility of MIN was reported [65]. Only one study evaluated FOS + TEC combination against Enterobacteriales (100 isolates), observing indifference in almost 100% of cases [66]. 2 studies evaluated FOS + MIN combination against vancomycin-resistant *E. faecium* or *E. faecalis* (51 strains), reporting most often indifferent effect and some sporadic case of synergism [13,67]. Otherwise, FOS + DOX combination was
tested once against 24 isolates of vancomycin-resistant *E. faecium*, demonstrating to have synergistic or additive effect in most of cases [68]. Finally, when FOS + MIN was tested against MRSA (152, strains, 3 studies) proved to have synergistic effect in numerous cases [18,69,70]. No study reported any case of antagonism.

The combination of minocycline + FOS against *A. baumannii* appears interesting.

### 3.10. Polymyxins

Thirty-two papers evaluating FOS in combination with polymyxins were reviewed (Table 10). Polymyxins are bactericidal drugs that bind to lipopolysaccharide (LPS) and phospholipids in the outer cell membrane of Gram-negative bacteria and leads to disruption of this. Twenty-eight papers evaluated colistin. Colistin breakpoints are $\leq 2 \mu g/mL$ for Enterobacterales, *Acinetobacter* spp. and *Pseudomonas* spp. according to the EUCAST [10]. Synergism rates were not unanimous on all studies but was reported in 23/29 papers. Synergism rates were 100% in 2 in vitro studies against *K. pneumoniae* [50,71] and 2 in vivo studies respectively against *A. baumannii* and *E.coli* [72,73]. The overall effect was indifferent on most isolates of *P. aeruginosa* and Enterobacterales. Antagonism was reported in vitro against *K. pneumoniae* and *A. baumannii*. In particular the combination was antagonist in 100% of all *K. pneumoniae* OXA-48 isolates according to Evren et al. [74].

Four papers evaluated polymyxin B. Polymyxin B breakpoints for Enterobacterales, *Acinetobacter* spp. and *Pseudomonas* spp. are $\leq 2 \mu g/mL$ according to CLSI. Synergism was observed in 100% of in vitro isolates of CP *K. pneumoniae* according to Bulman et al. [75]. FOS + polymyxin had a prevalent additive effect in vitro against *Pseudomonas* spp. [76] and *A. baumannii* [65]. In a study there was a complete polymyxin B susceptibility restoration [65]. No antagonistic effect was observed either in in vitro or in vivo studies.

The combination of polymyxins and FOS appears a good option against Enterobacterales and *P. aeruginosa* strains.

### 3.11. Daptomycin

Thirteen papers evaluating FOS in combination with daptomycin (DAP) were reviewed (Table 11). DAP is a cyclic lipopeptide administered intravenously for Gram-positive infections, acting through bacterial membrane depolarization [77]. Its breakpoints are $\leq 1 \mu g/mL$ for *Staphylococcus* spp. and $\leq 2 \mu g/mL$ for *Enterococcus* spp. [10,78].

When evaluated against *S. aureus* isolates, the combination FOS + DAP had a synergistic effect in vitro against 37–100% of isolates (synergistic effect of the combination against 100% of the tested isolates was reported in 4 in vitro studies [63,79–81] and 2 in vivo studies [37,79]). DAP showed excellent synergistic activity in association with FOS against *Enterococcus* spp., resulting in synergistic effect in all 34 tested isolates (4 studies). FOS + DAP also exhibited a greater efficacy against *E. faecalis* biofilm formation than FOS or DAP alone. Efficacy in vivo sometimes differed from the results obtained in vitro, resulting in greater [37] or less [82] efficacy. No antagonistic effect was observed either in in vitro or in vivo studies.

The combination of daptomycin + FOS has good synergistic effect rates against *S. aureus* and *Enterococcus* spp. and deserves clinical interest.

### 3.12. Tigecycline

Fourteen papers evaluating FOS in combination with TIG were reviewed (Table 12). TIG is the first glycyclcline antibiotic, a broad-spectrum class of bacteriostatic derivate from tetracyclines, that acts binding the 30S ribosomal subunits, inhibiting bacterial proteins synthesis. It is only available for intravenous administration and shows activity against either Gram-positive or Gram-negative or atypical bacteria [64]. Its breakpoint are $\leq 0.5 \text{mg/L}$ both for *S. aureus* and Enterobacterales and $\leq 0.25 \text{mg/L}$ for *Enterococcus* spp. [10].
When evaluated in vitro against Enterobacterales or *A. baumannii* (10 studies, 338 isolates) FOS + TIG had synergistic effect approximately in 17% of cases and additive effect in the 43%, while indifference was reported for all remaining cases [38,73,74,83–89]. Furthermore, indifferent effect against all isolates was observed in one in vivo experiment against *E. coli* [73]. Mostly indifference was observed also when it was tested against *N. gonorrhoeae* or *P. aeruginosa* [54,86]. When tested against 61 isolates of *Enterococcus* spp. (3 studies) many cases of synergistic effect was reported in vitro (about 40% of cases) [55,90,91] and in vivo against *E. faecalis* [90]. Finally, 2 studies evaluated FOS + TIG combination in vitro against MRSA, but with inconclusive results (total indifference or almost total synergism) [69,90]. In all in vitro studies only 2 cases of antagonism were reported, against *K. pneumoniae* [89].

According to the literature the combination of TIG + FOS appears to be particularly interesting (good synergistic effect rates) against Enterobacterales and *Enterococcus* spp.

### 3.13. Linezolid

Thirteen papers evaluating FOS in combination with linezolid (LZD) were reviewed (Table 13). LZD is a synthetic antibiotic which binds rRNA on both 30S and 50S ribosomal subunits, inhibiting bacterial proteins synthesis [92]. It is used for Gram-positive infections treatment, including MRSA and *E. faecium* vancomycin-resistant (VREF) infections [93]. Its breakpoint is ≤0.06 µg/mL both for *S. aureus* and *E. faecium*.

When evaluated against *S. aureus* isolates (9 studies), combination FOS + LZD had a synergistic effect in vitro approximately in 95% of cases (synergistic effect of the combination against 100% of the tested isolates was reported in 6 in vitro studies [36,43,63,94,95]) and even against staphylococcal biofilm cultures [69]; furthermore, the only 2 in vivo studies performed proved FOS + LZD combination to have higher efficacy than FOS or LZD alone [36,95]. One study evaluated the combination on 2 strains of *S. epidermidis* proving synergism on both [43]. Otherwise, in the 4 studies in which it was tested against *E. faecalis*, this combination showed in most cases additive effect and only few cases of synergism. In no case was reported synergistic effect against *E. faecalis* (2 studies). No antagonistic effect was observed either in in vitro or in vivo studies.

The good synergistic effects reported make LZD + FOS a promising combination against *staphylococci*.

### 3.14. Rifampin

Fourteen papers evaluating FOS in combinations with rifampin were reviewed (Table 14). Rifampin breakpoints are ≤0.06 µg/mL for *Staphylococcus* spp., *Streptococcus* spp. and ≤0.125 µg/mL for *S. pneumoniae*. Rifampin inhibits bacterial DNA-dependent RNA polymerase with a concentration related effect. It is used for the treatment of intracellular pathogens and it has a broad-spectrum antibacterial activity. Rifampin breakpoints are not defined either by EUCAST or by CLSI for *Acinetobacter* spp., Enterobacterales and *Enterococcus* spp. Based on literature data, susceptibility was defined as a MIC ≤ 1 µg/mL for *Enterococcus* spp. [71]. Rifampin showed synergistic activity in association with FOS against *Enterococcus* spp., resulting in synergistic effect in 20–100% of cases. High activity was reported in vitro and in vivo in a recent paper where FOS + RIFA also exhibited a greater efficacy against *E. faecalis* biofilm formation [90]. When evaluated against *S. aureus* isolates, the combination FOS + rifampin had a synergistic effect in vitro against 34–100% of isolates. Synergistic effect of the combination against 100% of the tested isolates was reported in 3 in vitro studies [43,90,96] and 2 in vivo studies [37,96]. Antagonistic effect was observed only in 33% of isolates in the study by Quentin et al. [35] where the antibiotic combination was antagonist for the isolates susceptible and intermediate to rifampin and indifferent for those resistant. No antagonistic effect was observed in other studies.

In clinics RIF + FOS should be considered (usually with a third agent) against *S. aureus* sustained infections, especially when biofilm production is likely.
3.15. Miscellanea

Two papers evaluating FOS in combination with metronidazole (MTZ) were reviewed (Table S1). MTZ is a bacteriostatic antimicrobial, active on bacteria (mainly anaerobic) and parasites. When evaluated in vitro against Helicobacter pylori, combination FOS + MTZ had a prevalent indifferent effect, an additive effect in only 21% of cases and an antagonist effect in 4% [97]. In vivo study showed a significantly decrease mortality and increase cure rates if the animal treated with MTZ + FOS [98].

One paper evaluating FOS in combination with spectinomycin (SCM) was reviewed (Table S1). SCM is an aminocyclitol aminoglycoside antibiotic with bacteriostatic activity, used to treat gonorrhea. In vitro study reported that antimicrobial combinations of SMC + FOS no synergistic effect was found [54].

One paper evaluating FOS in combination with sulfamethoxazole (SLB) was reviewed (Table S1). SLB is an irreversible β-lactamase inhibitor capable to binding to penicillin-binding proteins and with weak antimicrobial activity. When evaluated in vitro against A. baumannii OXA-23, combination FOS + SLB had a synergistic effect in 75% of case, and an indifferent effect in 25% of cases [99].

One paper evaluating FOS in combination with lincomycin (LMN) was reviewed (Table S1). LMN is a protein synthesis inhibitor with activity against gram positive and anaerobic bacteria. When evaluated in vitro against S. aureus, combination FOS + LMN had a synergistic effect in 81% of case and an additive effect in 25% of cases [14].

One paper evaluating FOS in combination with nitrofurantoin (NTX) was reviewed (Table S1). NTX is a urinary antibacterial agent active against susceptible Gram-positive and Gram-negative organisms. In vitro study, NTX was synergistic with FOS in only 12% of cases and in other cases showed an indifferent effect (88%) [66].

Two papers evaluating FOS in combination with fusidic acid (FSA) were reviewed (Table S1). FSA is a bacteriostatic antibiotic with acts as a bacterial protein synthesis inhibitor. When evaluated in vitro against MRSA, combination FOS + FSA had a various behavior, showing a synergistic effect in 88–100% of case or an indifferent effect in 25% of cases. No antagonism was found [69,101,102].

Four papers evaluating FOS in combination with chloramphenicol (CHL) were reviewed (Table S1). CHL is a synthetic broad-spectrum antimicrobial, mainly bacteriostatic, active on numerous Gram-positive and Gram-negative, aerobic and anaerobic bacteria; it acts binding 50S ribosomal subunit, inhibiting bacterial protein synthesis [103]. Its breakpoint is ≤8 mg/L both for S. aureus and Enterobacterales [10]. When evaluated in vitro against either Enterobacterales (468 isolates, 4 studies), combination FOS + CHL had synergistic effect approximately in 40% of cases, while additive effect in 35% and indifferent effect in the remaining cases [14,66,104,105]. Furthermore, one study tested this combination against S. aureus, with similar results (synergistic effect against 44% of isolates) [14]. No antagonistic effect was observed.

Three papers evaluating FOS in combination with trimethoprim-sulfamethoxazole (TMP-SMX) were reviewed (Table S1). TMP-SMX is a fixed combination of 2 antimicrobials that inhibits bacterial synthesis of tetrahydrofolate, a necessary cofactor for bacterial DNA synthesis. It is available in oral or intravenous preparation and it is mainly used for treatment of urinary and respiratory infections [106]. Its breakpoint is ≤2 µg/mL both S. aureus and Enterobacterales [10]. When evaluated in vitro against either S. aureus (148 isolates) or Enterobacterales (120 isolates), combination FOS + TMP-SMX had indifferent effect approximately against 92% of isolates [12,38,66]. Only in few cases, against Enterobacterales, was reported synergistic or additive effect (1 study) [38] and even antagonistic effect was reported in 4 cases when tested against S. aureus [12].

Two papers evaluating FOS in combination with nitrofurantoin (NTF) were reviewed (Table S1). NTF is a synthetic antibiotic administered orally mainly for treatment of lower urinary tract infections.
Its breakpoint is $\leq 64 \, \mu g/mL$ both *E. faecalis* and Enterobacterales [10]. When evaluated in vitro against either vancomycin-resistant *E. faecium* (32 isolates) or Enterobacterales (100 isolates), combination FOS + NTF had indifferent effect against 100% of isolates [66,67]. No synergistic, additive or antagonistic effect was observed.

3.16. Non-Antibiotic Molecules

One paper evaluating FOS in combination with auranofin (AF) was reviewed (Table S2). AF is an orally active gold compound for the treatment of rheumatoid arthritis. When evaluated in vitro against *Staphylococcus* spp., combination FOS + AF had showed a reduction of bacterial load for both MSSA and MRSA strains. In vivo, this combination had showed a synergistically inhibition of abscess and inflammation formation. No interactions were showed against *S. epidermidis* MS [107]. Three paper evaluating FOS in combination with dilipid ultrashort cationic lipopeptides, tobramycin-efflux pump inhibitor (TOB-EPI) conjugates or amphiphilic lysine-tobramycin conjugates (ALT) against *P. aeruginosa*, were reviewed (Table S2). For all combinations, in vitro studies had showed a synergistic effect (100%). Furthermore, in presence of TOB-EPI or ALT conjugates MICs of FOS were dramatically reduced [108–110]. One paper evaluating FOS in combination with $\beta$-chboro-L-alanine ($\beta$-CLA) was reviewed (Table S2). $\beta$-CLA is an amino acid analog of FOS. When evaluated in vitro against MRSA, combination FOS + $\beta$-CLA had showed a synergistic effect on biofilm production [111]. One paper evaluating FOS in combination with plectasini NZ2114, compound capable to inhibits a cell wall biosynthesis, was reviewed (Table S2). When plectasini NZ2114 evaluated in vitro against *E. faecalis*, in combination with FOS it no show a synergistic effect [112]. One paper evaluating FOS in combination with 2 quinolone derivatives (A and B) was reviewed (Table S2). When evaluated in vitro against *E. faecalis* VRE and MRSA, combination FOS + A had always showed a synergistic effect, while FOS + B had showed a synergistic effect in 64% of cases and in other cases shoed an additive effect (36%) [113]. One paper evaluating FOS in combination with N-acetylcysteine (NAC), a mucolytic agent, was reviewed (Table S2). The in vitro analysis against *E. coli*, had showed a capable of NAC to reduce biofilm if used in combination with FOS. The most effective combination was that obtained using FOS at 2000 mg/L and NAC at 2 mg/mL [114]. One paper evaluating FOS in combination with sophoraflavone G (SFG), a phytoalexins, was reviewed (Table S2). When evaluated in vitro against MRSA, combination FOS + SFG had showed a synergistic effect (100%) [115]. One paper evaluating FOS in combination with arenaemycin (ARM), also called pentalenolactones, was reviewed (Table S2). When evaluated in vitro against *P. vulgaris* and *S. gallinarum*, combination FOS + ARM had showed a synergistic effect (100%) [116]. One paper evaluating FOS in combination with chlorogenic acid (CHA) and caffeic acid (CFA) was reviewed (Table S2). When evaluated in vitro against Resistant *Listeria monocytogenes*, combination FOS + CHA had showed a reduction in the cell growth equal to 98% and FOS + CFA as to 85,2%. Moreover, CHA restored a FOS susceptibility in 100%, if 3 mg/L [117]. One paper evaluating FOS in combination with silver (AgNPs) and zinc oxide (ZnONPs) nanoparticles, are molecules known to affect bacterial membranes, was reviewed (Table S2). When evaluated in vitro against *S. aureus, S. enterica*, and *E. coli*, combination FOS + AgNPs or ZnONPs had showed a synergistic effect (100%) [118].

4. Discussion

FOS is an inhibitor of bacterial wall synthesis with a unique mechanism of action. Its use in clinic is increasing as is often active against MDR bacteria. Intravenous FOS is often administered in combination with other antibiotics therefore the knowledge of pharmacodynamic interactions is of fundamental importance. In this review, we have investigated the role of FOS as partner drug, by analyzing literature studies in which it has been used in vitro and in vivo in combination with other antibiotics and evaluating the antimicrobial activity of combinations against the most common bacterial pathogens. From this huge data collection, no clinically significant antagonistic effect came out between FOS and any most common used antibiotics for the treatment of nosocomial infections.
FOS has been studied in combination with the major antibiotic classes (penicillins, cephalosporins, carbapenems, monobactams, quinolones, aminoglycosides, macrolides, glycopeptides, tetracyclines, polimyxins, lipopeptides, oxazolidinones, and rifampicin) against both Gram-negative and Gram-positive bacteria. A total of 185 literature reports accounted for 9,927 study isolates. FOS-based synergistic interactions were detected in 33.7% of total isolates, although additive and indifferent interactions were more prevalent (65.4%). Antagonism occurred sporadically (0.9% of total isolates).

Clinically significant synergistic interactions were mostly distributed in combination with penicillins (51%), carbapenems (43%), chloramphenicol (39%), and cephalosporins (33%) in Enterobacterales; with linezolid (74%), tetracyclines (72%), and daptomycin (56%) in S. aureus; with chloramphenicol (53%), aminoglycosides (43%) and cephalosporins (36%) against P. aeruginosa; with daptomycin (97%) in Enterococcus spp. and with sulbactam (75%) and penicillins (60%) and in Acinetobacter spp.

Notably, 31.2% of synergistic interactions occurred in Enterobacterales (FOS in combination with 3 different antibiotics), followed by 31% occurred in S. aureus (FOS in combination with 4 different antibiotics) and 7.6% occurred Enterococcus spp. (FOS in combination with 5 different antibiotics).

From a clinical point of view, taking into account the antimicrobial stewardship principles and the priorities in terms of MDR impact, our work points out good pharmacodynamic interactions rates (additive/synergistic effects) when FOS is especially combined with:

1. Cephalosporins and cephalosporins + β-lactamase inhibitors, including ceftazidime/avitabactam and ceftolozane/tazobactam, for Enterobacterales and P. aeruginosa;
2. carbapenems for K. pneumoniae and P. aeruginosa;
3. quinolones for P. aeruginosa;
4. polimyxins for K. pneumoniae;
5. daptomycin for Staphylococcus spp (MRSA included), and Enterococcus spp.;
6. linezolid for Staphylococcus spp.; and
7. sulbactam for A. baumannii.

When FOS is combined with molecules other than antibiotics, chlorogenic acid and cafféic acid appeared to be good partner drugs against L. monocytogenes.

Our tables (including the summarizing Table 15) could act as a useful consultation tool for clinicians using FOS both as empirical or targeted antibiotic regimen.

5. Conclusions

In conclusion, taken together, these data, the pharmacological characteristics (i.e., excellent distribution in body sites, the safety and tolerability profile) and the encouraging positive clinical outcome of treated patients highlight the role of FOS as partner drug (mostly intravenously) for the treatment of infections caused by common (including MDR) pathogens. In particular, the presence of synergistic interactions and the almost total absence of antagonisms, make FOS a good partner drug in clinical practice. Moreover, improving FOS-based combinations could act as a meropenem- and colistin-sparing agent, mostly contributing to prevent AMR, especially related to last resource antibiotics.
Table 1. Studies on combination between fosfomycin and penicillins, penicillins + β-lactamase inhibitors, penicillinase-resistant penicillins. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain          | Year and Country | Author | Penicillin | Number of Isolates | Fosfomycin-Resistant (%) | Penicillin-Resistant (%) | Known Resistance Mechanisms or Determinants (%) | In Vitro Methods/ In Vivo (Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | Fosfomycin Susceptibility Restoration (%) | Penicillin Susceptibility Restoration (%) | Comments | Reference |
|-----------------|------------------|--------|------------|-------------------|------------------------|--------------------------|-----------------------------------------------|-------------------------------------------------|---------------------|-------------------|----------------------|-----------------------------|-----------------------------|----------------------------|----------|-----------|
| Enterobacteriaceae | 2019, USA     | Avery  | piperacillin/tazobactam | 49                | 8 E. coli: KPC (25%), NDM (75%), ESBL (62.5%); 35 Klebsiella spp: KPC (45.7%), NDM (40%); OXA (14.3%); VIM (8.6%); ESBL (66.6%); smooth (44%); 2 Citrobacter spp: KPC (50%), NDM (50%); ESBL (50%); 4 E. cloacae: KPC (75%), NDM (25%); ESBL (75%) | 49 (100%) | 20 (40.8%) | in vitro (ET) | 1 (2%) | 2 (4%) | 46 (94%) | 0% | - | - | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC50. |
| Enterobacteriaceae | 2019, USA     | Flam   | piperacillin/tazobactam | 20                | - | - | - | in vitro (CB, TK) | 12 (60%) | 7 (35%) | 0% | 0% | - | - | For 1 isolate the efficacy of FOS + PIP/TAZ remained indeterminate. |
| Enterobacteriaceae | 1978, Spain   | Olave  | ampicillin, carbenicillin | - | Ampicillin: 17 E. coli, 11 Klebsiella spp, 7 E. cloacae, 4 Proteus spp., 22 Salmonella spp. | - | - | - | in vitro (CB) | ampicillin: 31 (42%); carbenicillin: 24 (52%) | ampicillin: 31 (42%); carbenicillin: 31 (41%) | ampicillin: 9 (12%); carbenicillin: 19 (25%) | 0% | - | - | - | [14] |
| Enterobacteriaceae | 2020, Korea   | Seok   | piperacillin/tazobactam | 2                             | ESBL (100%) | 0% | 1 (50%) | in vitro (TK) | 0% | 0% | 2 (100%) | 0% | - | - | - | [119] |
| Enterobacteriaceae | 2018, France  | Berleur| temocillin     | 3                              | KPC (33.3%), OXA (33.3%) | 0% | Breakpoints NA | in vivo (mouse, peritonitis) | 0% | 0% | in vivo: 3 (100%); in vivo: 3 (100%) | 0% | - | - | - | [15] |
| Enterobacteriaceae | 2014, Sweden  | Hickam| mecillinam     | 2                              | ESBL, OXA (50%) | 0% | 0% | in vitro (CB, TK) | 2 (100%) | 0% | 0% | 0% | - | - | - | - | [120] |

For 'Enterobacteriaceae' and 'Streptococcus' sections, the number of isolates is provided for each strain. The resistance mechanisms and determinants are listed for each isolate. The in vitro and in vivo methods used are also indicated. Synergistic, additive, indifferent, and antagonistic effects are reported for each combination. Fosfomycin and penicillin susceptibilities are restored in some cases, with percentages indicated.
| Strain       | Year and Country | Author                  | Penicillin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | Fosfomycin-Resistant (%) | Penicillin-Resistant (%) | In Vitro (Methods/ In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | Fosfomycin Susceptibility Restoration (%) | Penicillin Susceptibility Restoration (%) | Comments                                                                 | Reference |
|-------------|------------------|-------------------------|------------|-------------------|------------------------------------------------|------------------------|-------------------------|-------------------------------------------------------------|------------------------|---------------------|----------------------|----------------------|---------------------------------------------|---------------------------------------------|--------------------------------------------------------------------------|-----------|
| K. pneumonia | 1977, Poland     | Borowski               | ampicillin | 10                | -                                               | -                      | -                      | in vitro (CB)                                               | 7 (70%)               | 1 (10%)             | 2 (20%)              | 0%                    | -                                            | -                                            | For 2 isolates: the effect of FOS + ampicillin remained indeterminate. The authors considered synergistic the effect for FICI up to 0.75. *S. typh*. The authors considered synergistic the effect for FICI up to < 1. They also evaluated different antibiotic combinations on patients with typhoid fever: FOS + AMP resulted in the highest rate of cures. | [121]    |
|             | 2014, Sweden     | Hickam                 | mecillinam | 1                 | ESBL, OXA (100%)                                 | 0%                     | 0%                     | in vitro (CB, TK)                                          | 1 (100%)              | 0%                  | 0%                    | 0%                    | -                                            | -                                            | [120]                                                                 |           |
|             | 1977, Spain      | Perea                  | ampicillin | 90                | -                                               | 17 (18.9%)             | 11 (12%)                | in vitro (CB, TK)                                          | 74 (92%)              | 7 (7%)               | 7 (7%)               | 0%                    | -                                            | -                                            | The authors considered synergistic the effect for FICI up to 0.75. | [104]    |
|             | 1977, Spain      | Figueras               | ampicillin | 16                | -                                               | -                      | -                      | in vitro (CB)                                              | 15 (93%)              | 1 (6%)               | 0%                    | 0%                    | -                                            | -                                            | [105]                                                                 |           |
| Salmonella spp. |               |                         |            |                   |                                                 |                        |                        |                                                             |                       |                     |                       |                       |                                              |                                              |                                                                         |           |
| Shigella spp. | 1977, Spain      | Perea                  | ampicillin | 50                | -                                               | 27 (54%)               | 30 (60%)                | in vitro (CB, TK)                                         | 27 (54%)              | 9 (18%)             | 14 (28%)             | 0%                    | -                                            | -                                            | The authors considered synergistic the effect for FICI up to 0.75. | [104]    |
|             | 2019, USA        | Avery                  | piperacillin/ tazobactam piperacillin/ tazobactam | 105 | - | NA (at least 71) | 103 (100%) | in vitro (ET) | 3 (2%) | 26 (25%) | 74 (71%) | 0% | - | 15 (14.8%) | [33] |
|             | 2019, USA        | Flamm                  | piperacillin/ tazobactam piperacillin/ tazobactam | 5  | - | - | - | in vitro (CB, TK) | 0% | 5 (100%) | 0% | 0% | - | - | - | - | [38] |
|             | 2013, Brazil, 2002, Japan | dos Santos, Okazaki, Takahasahi | piperacillin piperacillin piperacillin | 4  | - | 4 (100%) | 4 (100%) | in vitro (CB) | 4 (100%) | 0% | 0% | 0% | 2 (50%) | 1 (50%) | - | - | [46] |
|             | 1984, Japan      | Takahasahi             | piperacillin | 30 | - | 15 (50%) | 30 (100%) | in vitro (efficacy time index) | 3 (10%) | 6 (20%) | 21 (70%) | 0% | 0% | 15 (50%) | [39] |
|             | 1979, Spain      | Clay                   | carbenicillin | 20 | - | - | - | in vitro (CB) | 4 (20%) | 16 (80%) | 0% | 0% | - | - | - | - | [122] |
| P. aeruginosa | 1978, Spain      | Olley                  | carbenicillin | 2 | - | - | - | in vitro (7), in vivo (mouse, peritonitis) | - | - | - | - | - | - | - | - | [14] |
Table 1. Cont.

| Strain          | Year and Country | Author | Penicillin       | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | Fosfomycin-Resistant (%) | Penicillin-Resistant (%) | In Vitro (Methods)/ In Vivo (Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | Fosfomycin Susceptibility Restoration (%) | Penicillin Susceptibility Restoration (%) | Comments                                                                 |
|----------------|------------------|--------|------------------|--------------------|------------------------------------------------|--------------------------|--------------------------|-------------------------------------------------------------|----------------------|---------------------|----------------------|--------------------------|-----------------------------|-----------------------------|---------------------------------|------------------------------------------------------------------------|
| Acinetobacter spp. | 2019, USA        | Flam  | Piperacillin/ tazobactam (A. baumannii-calcoaceticus species complex) | 5 | - | - | - | in vitro (CB, TK) | (A. baumannii-calcoaceticus species complex) | 3 (60%) | 1 (20%) | 0% | 0% | - | - | For 1 isolate the efficacy of FOS + PIP/TAZ remained indeterminate.  |
| S. aureus       | 2015, Spain      | del Río | Amoxicillin + clavulanic acid | 10 | Methicillin-resistant Staphylococcus aureus (MRSA) | 1 (10%) | 10 (100%) | in vitro (TK) | in vitro: 8 (80%); in vivo: 2 (20%) | 0% | 0% | - | - | - | - | Addition or indifferent effect was observed for the remaining 6 strains (data not shown).  |
| S. aureus       | 2003, Japan      | Nakazawa | Ampicillin | 32 | MRSA (100%) | 20 (91%) | 31 (96%) | in vitro (efficacy time index) | 4 (12%) | 2 (6%) | 26 (81%) | 0% | - | - | - | Addition or indifferent effect was observed for the remaining 6 strains (data not shown).  |
| S. aureus       | 1997, Italy      | Ferrara | Oxacillin | 36 | MRSA (100%) | NA (at least 8) | 16 (100%) | in vitro (TK) | 3 (18%) | 3 (18%) | 4 (25%) | - | - | - | - | 1994, Japan  |
|               | S. epidermidis    | Komatsu | Oxyacillin | 38 | MRSA (60.5%) | 33 (66.8%) | 23 (60%) | in vitro (CR) | 20 (52%) | 17 (44%) | 1 (2%) | 0% | - | - | - | Data of the other 4 strains are not shown.  |
| S. epidermidis  | 1985, USA        | Alvarez | Methicillin | 148 | MRSA (100%) | NA (< 15) | 148 (100%) | in vitro (CR) | 69 (46%) | - | - | 1 (1%) | - | - | - | - | 1978, Spain  |
|               | S. epidermidis    | Olay | Ampicillin, Carbencillin | 27 | Ampicillin and Carbencillin | 4 (55%) | 10 (55%) | in vitro (CR) | 2 (11%) | - | - | - | - | - | - | Data of the other 4 strains are not shown.  |
| S. epidermidis  | 1977, Poland     | Bonowski | Penicillin G | 11 | - | - | - | in vitro (CR) | 5 (45%) | 2 (18%) | 4 (36%) | 0% | - | - | - | - | 1997, Italy  |
|               | S. epidermidis    | Ferrara | Oxacillin | 12 | MRSE (100%) | NA (at least 6) | 12 (100%) | in vitro (TK) | 6 (50%) | 1 (8%) | 1 (8%) | - | - | - | - |
| Year and Country | Author | Penicillin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | Fosfomycin-Resistant (%) | Penicillin-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | Fosfomycin Susceptibility Restoration (%) | Penicillin Susceptibility Restoration (%) | Comments | Reference |
|-----------------|--------|------------|-------------------|-------------------------------------------------|------------------------|------------------------|-------------------------------------------------|-----------------------|-----------------|---------------------|---------------------|----------------------------|----------------------------|----------|----------|
| 2017, Germany   | Gonzalez Moreno | benzylpenicillin | 3                  | -                                               | 1 (33.3%)              | 0%                    | in vitro (microcalorimetry for biofilms)           | 0%                    | 0%              | 3 (100%)            | 0%                  | -                          | -                          | S. agalactiae, S. pyogenes, S. oralis. High-dose FOS caused a delay of 8 h in the production of heat, compared with untreated controls, suggesting that the treatment could result in a reduction in the number of viable sessile cells, although not in complete biofilm eradication. S. sanguis. The mean log10 CFU per gram of vegetations in the FOS + penicillin group was significantly lower than that in the FOS groups but was not significantly lower than that in the penicillin group. | [9] |
| 1981, Spain     | Vicente | penicillin G | 17                 | -                                               | 9 (53%)                | 5 (29%)               | in vitro (CB, TK); in vivo (rabbit, endocarditis) | in vitro: 4 (23%) | in vitro: 12 (71%); in vivo: 100% | 0%                  | -                          | -                          | S. sanguis. The mean log10 CFU per gram of vegetations in the FOS + penicillin group was significantly lower than that in the FOS groups but was not significantly lower than that in the penicillin group. | [17] |
| 1979, Spain     | Olby   | ampicillin  | 37                 | -                                               | -                     | -                     | in vitro (CB)                                     | 12 (32%)             | 11 (29%)         | 14 (37%)            | 0%                  | -                          | -                          | S. sanguis. The mean log10 CFU per gram of vegetations in the FOS + penicillin group was significantly lower than that in the FOS groups but was not significantly lower than that in the penicillin group. | [14] |
| Strain       | Year and Country | Author      | Penicillin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | Fosfomycin-Resistant (%) | Penicillin-Resistant (%) | Unknown | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | Fosfomycin Susceptibility Restoration (%) | Penicillin Susceptibility Restoration (%) | Comments                                                                                           | Reference |
|-------------|------------------|-------------|------------|-------------------|-----------------------------------------------|--------------------------|--------------------------|---------|----------------------------------------------------------|-------------------------|---------------------|------------------------|------------------------|-------------------------------|---------------------------------------------|-----------------------------------------------------------------------------------------------|-----------|
| S. pneumonia | 2001, Spain      | Batón Arias | penicillin | 10                |                                               | 1 (10%)                  | 8 (80%)                  |         | in vitro (TK)                                           | 10 (100%)               | 0%                  | 0%                     | 0%                     | -                              | -                             | Synergistic effect difficult to determine. It is reported as synergistic against all isolates based on authors' considerations and on the comparison between cumulative efficacy of MIC + MIC and MIC/4 + MIC/4. | [125]     |
|             | 1996, France     | Chavanet    | amoxicillin| 1                 |                                               | 0%                       | 1 (100%)                 |         | in vivo (rabbit, throm clot infection)                  | 1 (100%)               | 0%                  | 0%                     | 0%                     | -                              | -                             | [23]                                                                                 |           |
|             | 1995, Japan      | Kikuchi     | benzylpenicillin | 51                |                                               | 0%                       | 51 (100%)                |         | in vitro (CB, TK)                                      | 9 (17%)                 | 42 (82%)             | 0%                     | 0%                     | -                              | -                             | The 3 isolates exhibiting synergistic effect were all *E. faecium*. The 6 isolates exhibiting antagonistic effect on biofilms formation were all *E. faecalis*. From the data reported in the paper it was not possible to establish the effect of the combination against the other isolates. *E. faecalis*, *E. faecium*, *E. casseliflavus*, *E. durans*. The authors did not distinguish between additive and indifferent effect. | [13]      |
| Enterococcus spp. | 2013, Taiwan  | Tang        | ampicillin | 10 *E. faecium*, 9  | VRE (100%)                                 | 13 (68%)                 | 9 (47%)                  |         | in vitro (TK, biofilm)                                 | TK: 3 (15%)             | -                   | -                      | biofilm: 6 (31%)          | -                              | -                             | [13]                                                                                 |           |
|             | 1995, France     | Postel      | penicillin | 10                |                                               | 10 (100%)                | 6 (60%)                  |         | in vitro (CB, TK)                                      | 6 (60%)                 | -                   | -                      | 0%                     | -                              | -                             | [127]                                                                                |           |
Table 1. Cont.

| Strain      | Year and Country | Author | Penicillin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | Fosfomycin-Resistant (%) | Penicillin-Resistant (%) | In Vitro (Methods/ Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | Fosfomycin Susceptibility Restoration (%) | Penicillin Susceptibility Restoration (%) | Comments | Reference |
|-------------|------------------|--------|------------|-------------------|-----------------------------------------------|------------------------|-------------------------|-----------------------------------------------|------------------------|----------------------|---------------------|----------------------|------------------------------------------|--------------------------|-----------|-----------|
| E. faecalis | 2011, Italy      | Farina | ampicillin | 27                | -                                              | 2 (7%)                | 0%                     | in vitro (ET)                          | 2 (7%)                       | 0%                   | 25 (92%)                          | 0%                     | -                      | -                      | -          | [128]     |
| E. faecium  | 2013, USA        | Descoutreze | amoxicillin | 4                | VRE (100%)                                      | 0%                    | 4 (100%)              | in vitro (TK)                          | 100%                           | 0%                   | 0%                   | 0%                    | -                      | -                      | -          | [67]      |

Table 2. Studies on combination between fosfomycin and cephalosporins, cephalosporins + β-lactamase inhibitors. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain          | Year and Country | Author | Cephalosporin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Cephalosporin-Resistant (%) | In Vitro (Methods/ Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Cephalosporin Susceptibility Restoration (%) | Comments | Reference |
|-----------------|------------------|--------|---------------|-------------------|-----------------------------------------------|-----------------|--------------------------|-----------------------------------------------|------------------------|----------------------|----------------------|----------------------|------------------------------------------|------------------------------------------|-----------|-----------|
| Enterobacteriaceae | 2019, USA        | Avey   | cefepime (FEP), ceftolozane/tazobactam (CT), ceftazidime (CTZ), ceftriaxone/avibactam (CZA) | 49 (26 tested for CZA) | 8 E. coli: KPC (25%), NDM (77%), ESBL (62%); 35 Klebsiella spp: KPC (45%), NDM (40%), OXA (14%), VIM (6%), ESBL (88%); 4 Acinetobacter spp: KPC (50%), NDM (50%), ESBL (50%); 4 E. cloacae: KPC (75%), NDM (25%), ESBL (75%) | 20 (40%) | 49 (100%) | in vitro (ET) | FEP: 2 (4%); CTZ: 8 (16%); CTZ: 3 (6%); CZA: 0% | -                      | -                      | -                      | -                      | -                      | -                      | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC50. | [11] |
| Enterobacteriaceae | 2019, USA        | Flamm  | cefazidime     | 20                | -                                              | -                | -                       | in vitro (CB, TK)                       | 8 (40%)                        | 10 (50%)                          | 0%                   | 0%                    | -                      | -                      | -                      | For 2 isolates the efficacy of FOS + CTZ remained indeterminate. | [36] |
| Enterobacteriaceae | 1978, Spain      | Olay   | cefalexin      | 23 E. coli: 29 Salmonella spp., 8 Klebsiella spp., 11 E. cloacae, 4 S. marcescens, 16 Proteus spp. | -                  | -                                              | -                       | in vitro (CB)                       | 42 (40%)                        | 46 (44%)                          | 15 (14%)                          | 0%                    | -                      | -                      | -                      | [14] |
| E. coli         | 2020, Korea      | Seok   | cefoxime       | 4                 | ESBL (50%)                                       | 0%               | 2 (50%)                 | in vitro (TK)                          | 4 (100%)                        | 0%                   | 0%                   | 0%                    | -                      | -                      | -                      | [110]    |
| E. coli         | 2014, France     | Lafort | cefoxitin      | 2                 | ESBL (50%)                                       | 0%               | breakpoint NA          | in vitro (mesone, urinary tract infection) | 4 (100%)                        | 0%                   | 0%                   | 0%                    | -                      | -                      | -                      | [30]      |
### Table 2. Cont.

| Strain       | Year and Country | Author     | Cephalosporin   | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Cephalosporin-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Cephalosporin Susceptibility Restoration (%) | Comments                                                                                           | Reference |
|--------------|------------------|------------|-----------------|--------------------|------------------------------------------------|-------------------|-----------------------------|-----------------------------------------------------------|------------------------|----------------------|------------------------|-------------------------------|-----------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------|-----------|
| K. pneumonia | 2019, Poland     | Ojdana     | ceftazidime-avibactam | 19                 | NDM (52%); KPC (42%); OXA (5%)                | 10 (53%)         | 10 (53%)                    | in vitro (ET)                                            | 9 (47%)                | 7 (36%)               | 3 (15%)                | 0%                           | -                           | -                             | It is reported only the reduction of CZA in combination and time–kill was performed only on 2 isolates randomly selected, therefore a reduction of at least 4 times was considered as synergistic. A 2-fold reduction was considered as additive. No reduction was considered as indifferent. In increase of MIC in combination was considered antagonistic. The authors reported only the number of isolates on which the combination had a synergistic effect. | [31]      |
| K. pneumonia | 2019, USA        | Mikhail    | ceftazidime-avibactam | 21                 | fosA/fosC-like, KPC, ESBL, OXA (18%)          | 15 (71%)         | 0%                          | in vitro (CB, TK)                                        | 10 (47%)               | 9 (42%)               | 2 (9%)                  | 0%                           | -                           | 0% (all S)                     | [21]                                                                                                                |           |
|              | 1977, Spain      | Daza       | cephalosporin     | 33                 | -                                              | 100%             | breakpoints NA in vitro (CB)                             | 1 (3%)                                   | -                      | -                      | -                            | -                           | -                             | Breakpoints NA (reduction of MIC from 16 to 4 µg/mL) had a synergistic effect. | [66]      |
### Table 2. Cont.

| Strain          | Year and Country | Author           | Cephalosporin                   | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Cephalosporin-Resistant (%) | In Vitro (Methods) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Cephalosporin Susceptibility Restoration (%) | Comments                                                                 |
|-----------------|------------------|------------------|---------------------------------|--------------------|-----------------------------------------------|-------------------|----------------------------|----------------------|------------------------|----------------------|------------------------|------------------------|--------------------------|------------------------|---------------------------------------------------------------|
| *P. aeruginosa* | 2020, Brazil     | Cuba             | ceftolozan/tazobactam          | 27                 | carbapenemase-producing (74%)                  | 26 (96%)          | 2e2 (81%)                  | in vitro (ET, TK)    | 24 (88%)               | 3 (11%)               | 0%                     | 0%                     | 24 (92%)                 | -                       | It is not possible to establish the % of strains with FOS susceptibility restoration because the MIC for all R strains was >64 μg/mL, and it is not reported the MIC in combination but the MIC fold reduction. It is however strongly reduced (range: 2–16 fold reduction). |
|                 | 2020, USA        | Mullane          | cepofim, ceftolozan/tazobactam | 28 CEF; 15 C/T     | -                                             | -                 | -                          | in vitro (CB, TK)    | CEF: 5 (18%);         | 2 (8%);               | 0%                     | -                      | 1 (4%); CEF 5 (33%)       | -                       | It is reported only the reduction of CZA in combination and time–kill was performed only on 2 isolates randomly selected, therefore a reduction of at least 4 times was considered as synergistic. A 2-fold reduction was considered as additive. No reduction was considered as indifferent. An increase of MIC in combination was considered antagonistic. |
| *P. aeruginosa* | 2019, USA        | Mikhail          | ceftazidime-avibactam         | 21                 | fosA/fosA-like, KPC, ESBL, OXA (100% at least 1 resistance gene) | 19 (90%)          | 5 (23%)                   | in vitro (CB, TK)    | 7 (33%)                | 6 (28%)               | 8 (38%)               | 0%                     | -                       | 1 (28%)                  | -                       | It is reported only the reduction of CZA in combination and time–kill was performed only on 2 isolates randomly selected, therefore a reduction of at least 4 times was considered as synergistic. A 2-fold reduction was considered as additive. No reduction was considered as indifferent. An increase of MIC in combination was considered antagonistic. |
| *P. aeruginosa* | 2019, USA        | Papp-Wallace     | ceftazidime-avibactam         | 1                  | -                                             | 0%                | 1 (100%)                  | in vitro (CB, TK)    | 0%                    | 0%                    | 0%                    | -                       | -                       | -                       | -                       | It is reported only the reduction of CZA in combination and time–kill was performed only on 2 isolates randomly selected, therefore a reduction of at least 4 times was considered as synergistic. A 2-fold reduction was considered as additive. No reduction was considered as indifferent. An increase of MIC in combination was considered antagonistic. |
| Strain | Year and Country | Author | Cephalosporin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Cephalosporin-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Cephalosporin Susceptibility Restoration (%) | Comments | Reference |
|--------|------------------|--------|---------------|-------------------|-----------------------------------------------|------------------|-----------------------------|-------------------------------------------------|-------------------|-----------------|------------------|------------------|-----------------------------|---------------------------------------------|----------|-----------|
| 2019, USA | Avery | cefepime (FEP), ceftolozane/tazobactam (CTZ), ceftazidime (CAZ), avibactam (AVB) | 92 (FEP: 44, CTZ: 32, CAZ: 16, AVB: 14) | Carbapenem-resistant (100%) | - | 100% | in vitro (ET) | FEP: 22 (23%), CTZ: 7 (50%), CAZ: 42 (51%), CAZ: 4 (25%) | | | | | | | | | |
| 2019, USA | Avery | cefepime (FEP), ceftolozane/tazobactam (CTZ), ceftazidime (CAZ), avibactam (AVB) | 5 | - | - | - | in vitro (CB, TK) | 2 (40%) | 3 (60%) | 0% | 0% | - | - | - | | [33] |
| 2018, USA | Monogue | ceftazidime, ceftolozane/tazobactam (CTZ), ceftazidime (CAZ), avibactam (AVB) | 4 | - | 3 (75%) | 2 (50%) | in vitro (TK) | 1 (25%) | 2 (50%) | 1 (25%) | 0% | - | - | - | | [34] |
| 2018, USA | Monogue | ceftazidime, ceftolozane/tazobactam (CTZ), ceftazidime (CAZ), avibactam (AVB) | 3 | - | 3 (100%) | 3 (100%) | in vitro (CB) | 3 (100%) | 0% | 0% | 0% | 1 (33%) | 2 (66%) | - | | [40] |
| 2017, Japan | Okazaki | ceftazidime, cefepime, ceftobiprole | 30 | - | 15 (50%) | CAZ: 2 (40%), CEPF: 25 (83.3%) | in vitro (efficacy time index) | FEP: 2 (2%), CEPF: 7 (50%), CAZ: 20 (50%) | 1 (33%) | 5 (16%) | 0% | | | | | | [122] |
| 1999, Japan | Hayami | ceftazidime | 26 | - | NA (at least 13) | NA (at least 5) | in vitro (CB, TK) | 7 (26%) | 14 (53%) | 0% | | - | - | - | | | [130] |
| 1997, France | Tessier | ceftazidime | 40 | - | 21 (52%) | 14 (35%) | in vitro (CB) | 0% | 8 (20%) | 32 (80%) | 0% | 20 (95%) | 8 (57%) | - | | [131] |
| 1984, Japan | Takahashi | cefoperazone, cefadroxil | 20 (cefoperazone), 23 (cefadroxil) | - | - | - | in vitro (CB) | cefoper: 17 (85%), cefad: 19 (82%) | cefoper: 3 (15%), cefad: 4 (17%) | 0% | 0% | - | - | - | - | [122] |
| A. baumannii | 2019, USA | Flamm | ceftazidime, ceftolozane/tazobactam (CTZ), ceftazidime (CAZ), avibactam (AVB) | 5 (A. baumannii-calcoaceticus species complex) | - | - | - | in vitro (CB, TK) | 2 (40%) | 1 (20%) | 1 (20%) | 0% | - | - | - | For 1 isolate the efficacy of FOS + CTZ remained indeterminate. Only synergistic and antagonistic effect reported. | [38] |
| 1996, Spain | Martinez-Martinez | cefazidime | 34 | - | 34 (100%) | 32 (94%) | in vitro (CB) | 1 (3%) | NA | NA | 0% | - | - | - | | [132] |
| Staphylococci spp. | 1995, Italy | Marchese | ceftazidime, ceftazolin | 6 S. aureus, 8 S. epidermidis, 2 S. hominis, 2 S. xylosus, 5 S. saprophyticus, 2 S. haemolyticus | Penicillin-resistant (100%) | - | - | in vitro (CB, TK) | 4 (14%) | - | - | 0% | - | - | | The authors considered 0.5 < FICI ≤ 4 as indifferent, therefore it is not possible to establish if the effect was additive or indifferent for most strains. | [114] |
### Table 2. Cont.

| Strain          | Year and Country  | Author          | Cephalosporin                                                                 | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Cephalosporin-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Cephalosporin Susceptibility Restoration (%) | Comments                                                                 | Reference |
|-----------------|-------------------|-----------------|-------------------------------------------------------------------------------|--------------------|-----------------------------------------------|-------------------|--------------------------|----------------------------------------------------------|------------------------|-------------------|------------------------|------------------------|-------------------------------|-----------------------------------------------|---------------------------------------------------------------------------|-----------|
| S. aureus       | 2003, Japan       | Nakazawa        | flomoxef sodium (FS), cefmetazole (CEM), cefotaxime (CET), cefoperazone/ sulbactam (CS) | 32                 | MRSA (100%)                                   | 29 (91%)          | FS: 29 (91%); CEM: 16 (50%); CET: 30 (94%); CS: 27 (84%) | in vitro (efficacy time index)                          | FS: 7 (22%); CEM: 26 (81%); CET: 7 (22%); CS: 19 (59%) | 17 (70.8%) | 7 (29.2%) | 0% | 0% | - | - | [18] |
|                 | 1978, Spain       | Olay            | cepheaxin                                                                  | 24                 | -                                             | -                 | -                         | in vitro (CB)                                          | FS: 7 (22%); CEM: 26 (81%); CET: 7 (22%); CS: 19 (59%) | 17 (70.8%) | 7 (29.2%) | 0% | 0% | - | - | - | [14] |
|                 | 2015, Spain       | del Rio         | ceftriaxone                                                                 | in vitro 10; in vivo 2 | MRSA (100%)                             | 1 (10%)           | 10 (100%)                  | in vitro (TK); in vivo (rabbit, endocarditis)         | cefotaxime, cephalotin, cefoperazone, cefotamide: 10 (100%) | 1 (100%) | 0% | 0% | 0% | - | - | [28] |
|                 | 1985, Germany     | Portier         | cefotaxime, cephalotin, cefoperazone, cefotamide                           | 10                 | MRSA (100%)                                   | 0%                | 10 (100%)                  | in vitro (CB)                                          | cefotaxime, cephalotin, cefoperazone, cefotamide: 10 (100%) | 1 (100%) | 0% | 0% | 0% | - | - | [28] |
| S. aneurus      | 1990, France      | Chanvat         | cefotaxime                                                                 | 1                  | MGRSA (100%)                                 | 0%                | 1 (100%)                  | in vivo (rabbit, subcutaneous fibron clot)             | 1 (100%)                                          | 0% | 0% | 0% | 0% | - | - | - | [27] |
|                 | 1985, France      | Kazmiereczak    | cefotaxime                                                                 | 1                  | -                                             | 0%                | 1 (100%)                  | in vivo (rabbit, meningitis)                           | 0% | 1 (100%) | 0% | 0% | - | - | - | [28] |
| Strain Year and Country | Author | Cephalosporin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Cephalosporin-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Cephalosporin Susceptibility Restoration (%) | Comments | Reference |
|-------------------------|--------|---------------|-------------------|-------------------------------------------------|-----------------|-----------------------------|--------------------------------------------------------|------------------------|----------------------|------------------------|-----------------------------|-----------------------------|-----------------------------|----------|-----------|
| 1991, Japan Matsuda     | cefmetazole | 25            | MRSA (100%)       | 25 (100%)                                       | 25 (100%)       | in vitro (CB, TK)            | 11 (44%) in vitro: 10 (71%); in vivo: 5 (71%)          | 11 (44%)              | 3 (12%)              | 0%                     | -                           | -                           | -                           |          | [130]     |
| 1986, Japan Utsui       | cefmetazole | 14 in vitro, 7 in vivo | MRSA (100%)       | -                                               | 14 (100%)       | in vitro (CB, TK); in vivo (mouse) | 0% in vitro: 4 (28%); in vivo: 2 (26%)          | 0%                     | 0%                  | -                      | -                           | -                           | -                           |          | [25]      |
| 1987, France Courcol    | ceftriaxone | 6             | -                 | 1 (16%)                                         | 6 (100%)        | in vitro (CB, TK)            | CB: 1 (16%); TK: 1 (16%)                           | CB: 0%; TK: -         | -                    | -                      | -                           | -                           | -                           | Different activity of the drug combination with checkerboard assay or time–kill assay. The effect of FOS + ceftriaxone on 2 isolates remained indeterminate. The authors considered the combination antagonistic when the FICI was > 2. For the 78 remaining isolates it was not specified if the combination FOS + ceftriaxone acted with an additive or indifferent effect. | [19]     |
| 1985, USA Alvarez       | cefamandole | 148           | MRSA (100%)       | NA (<15)                                        | -               | in vitro (CB)                | 97 (66%)                                               | -                      | -                    | 0%                     | -                           | -                           | -                           | For the 78 remaining isolates it was not specified if the combination FOS + cefamandole acted with an additive or indifferent effect. | [12]     |
| 2001, Austria Grif       | cefazolin | 5             | MRSA (20%), GISA (20%) | -                                               | -               | in vitro (CB, TK)            | 5 (100%)                                               | 0%                     | 0%                  | 0%                     | -                           | -                           | -                           | [43]     |
| Strain                      | Year and Country | Author | Cephalosporin | Number of Isolates | Cephalosporin-Resistant (%) | FOS-Resistant (%) | Known Resistance Mechanisms or Determinants (%) | In Vitro (Method(s)/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Cephalosporin Susceptibility Restoration (%) | Comments                                                                 | Reference |
|----------------------------|------------------|--------|---------------|-------------------|---------------------------|-------------------|-------------------------------------------------|------------------------------------------------------------|------------------------|---------------------|------------------------|-----------------------------|-----------------------------|--------------------------------------------|------------------------------------------------|-----------|
| S. epidermidis              | 2001, Austria    | Grif et al. | Cefazolin     | 2                 | -                        | -                 | -                                               | In vitro (CB, TK)                                         | 0%                     | 0%                  | 2 (100%)               | -                          | -                          | -                          | Different activity of the drug combination with checkerboard assay or time–kill assay. | [43]       |
|                            | 1987, France     | Courcol et al. | Ceftriaxone   | 6                 | -                        | 2 (33.3%)          | 6 (100%)                                         | In vitro (CB, TK)                                         | CB: 1 (16%); TK: 5 (63.3%) | CB: 0% TK: - | CB: 5 (83%); TK: - | CB: 1 (16%); TK: - | -                          | -                          | The effect of FOS + ceftriaxone on 1 isolate remained indeterminate. The authors considered the combination antagonistic when the FICI was > 2. | [19]       |
|                            | 2006, Spain      | Ribes et al. | Ceftriaxone   | 2                 | -                        | 0%                | 2 (100%)                                         | In vitro (TK); in vivo (rabbit, meningitis)               | 0%                     | -                   | -                      | -                          | -                          | -                          | Synergistic effect difficult to determine. It is reported as synergistic against all isolates based on authors’ considerations and on the comparison between cumulative efficacy of MIC + MIC and MIC/4 + MIC/4. | [24]       |
|                            | 2001, Spain      | Bañón Arias et al. | Ceftriaxone   | 10                | -                        | 1 (10%)            | 7 (70%)                                         | In vitro (TK)                                             | 10 (100%) | 0%                  | 0%                     | 0%                          | -                          | -                          | -                                                                         | [23]       |
| S. pneumonia               | 1994, France     | Doit et al. | Ceftriaxone   | 26                | -                        | 0%                | 20 (76%)                                        | In vitro (TK)                                             | 0%                     | -                   | -                      | -                          | -                          | -                          | -                                                                         | [134]      |
|                            | 1993, France     | Barakett et al. | Cefotaxime    | 7                 | -                        | 0%                | 2 (28%)                                        | In vitro (TK)                                             | 3 (42%) | 1 (14%)             | 3 (42%)                | 0%                          | -                          | -                          | -                                                                         | [135]      |
|                            | 1995, France     | Charvet et al. | Cefotaxime, ceftriaxone | 1 | -                        | 0%                | 1 (100%)                                        | In vitro (TK); in vivo (rabbit, fibrin clot infection) | 0%         | -                   | -                      | -                          | -                          | -                          | -                                                                         | [23]       |
| Strain     | Year and Country | Author   | Cephalosporin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Cephalosporin-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Cephalosporin Susceptibility Restoration (%) | Comments | Reference |
|------------|------------------|----------|---------------|-------------------|------------------------------------------------|------------------|-----------------------------|--------------------------------------------------------|----------------------|---------------------|------------------------|--------------------------|-------------------------------|------------------------------------------|----------|-----------|
| S. sanguis | 1981, Spain      | Vicente  | Cefoxitin     | 17                | -                  | 3 (16%) | 9 (53%) | in vitro (CB, TK); in vivo (rabbit, endocarditis) | 8 (47%); in vivo: 100% | 8 (42%) | 1 (6%) | 0% | - | - | The mean log_{10} CFU per gram of vegetations in the FOS + cefoxitin groups was significantly lower than that in the FOS groups and in the cefoxitin groups. [17] |
| Enterococcus spp. | 1995, France | Pestel | Cefotaxime | 50                | -                  | 50 (100%) | 48 (96%) | in vitro (CB, TK) | 45 (90%) | - | 5 (10%) | 0% | - | - | E. faecalis, E. casseliflavus, E. durans. The authors did not distinguish between additive and indifferent effect. [127] |
| E. faecalis | 2011, Italy      | Farina   | Ceftriaxone   | 27                | -                  | 2 (7%) | 27 (100%) | in vitro (ET) | 15 (55%) | 0% | 12 (44%) | 0% | - | - | The authors did not distinguish between additive and indifferent effect, considering $0.5 < FICI \leq 4$ as indifferent. [128] |
| N. gonorrhoeae  | 2015, Switzerland | Hauser | Ceftriaxone   | 8                  | -                  | 0% | 1 (12.5%) | in vitro (CB) | 0% | 0% | - | - | - | - | - | The authors did not distinguish between additive and indifferent effect, considering $0.5 < FICI \leq 4$ as indifferent. [157] |
| N. gonorrhoeae  | 2015, The Netherlands | Wind | Ceftriaxone, Cefotaxime | 4 | - | - | - | in vitro (ET) | 0% | 0% | - | - | - | - | - | - | The authors did not distinguish between additive and indifferent effect, considering $0.5 < FICI \leq 4$ as indifferent. [156] |
| N. gonorrhoeae  | 2014, USA        | Barber   | Ceftriaxone, Cefotaxime | 32               | -                  | 0% | 32 (100%) | in vitro (ET) | 0% | 0% | 32 (100%) | 0% | - | - | - | The authors did not distinguish between additive and indifferent effect, considering $0.5 < FICI \leq 4$ as indifferent. [136] |
Table 3. Studies on combination between fosfomycin and carbapenems. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strains          | Year and Country | Author | Carbapenem | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Carbapenem-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Carbapenem Susceptibility Restoration (%) | Comments                              | Reference |
|------------------|-----------------|--------|------------|-------------------|-------------------------------------------------|------------------|--------------------------|-----------------------------------------------------|------------------------|------------------|----------------------|-----------------------------|------------------|------------------------|---------------------------|-----------|
| Entrobacterales  | 2019, USA       | Avery  | meropenem  | 49                | 8 E. coli: KPC (25%), NDM (75%), ESBL (62%); 3S E. coli spp: KPC (45%), NDM (40%); ORA (16%); VIM (8%); ESBL (9%); fosA (44%); 2 C. bovis spp: KPC (50%), NDM (50%); ESBL (50%); 4 E. faecalis: KPC (7%), NDM (25%); ESBL (7%) | 20 (40.8%)       | 49 (100%)                | in vitro (ET)                                      | 1 (2%)                  | 10 (20%)                  | 38 (77%)                   | 0%                           | -                     | -                      | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC. | [11]   |
|                  | 2020, Egypt     | El-Wafa| imipenem   | 8                 | E. coli: 3 (37.5%); 7 (87.5%)                      | 3 (37.5%)       | 7 (87.5%)                | in vitro (CB, TK)                                    | 2 (25%)                  | 5 (62%)                  | 0%                       | 0%                           | 2 (66%)                      | 6 (87%)                 | For 2 isolates the efficacy of FOS + meropenem (MDE) remained indeterminate. | [38]   |
|                  | 2019, India     | Sugathan| meropenem,  | 50                | E. coli: 0%                                        | 0%              | 8 (96%)                  | in vitro (TK)                                       | 34 (68%)                 | 14 (28%)                 | 0%                       | 0%                           | 0%                       | 0% (all 3)               | For 1 isolate the efficacy of FOS + meropenem (MDE) remained indeterminate | [42]   |
|                  | 2019, Germany   | Loose  | meropenem,  | 4                 | E. coli: 1 (25%); 3 (75%)                          | 1 (25%)         | 3 (75%)                  | in vitro (CB)                                      | 4 (100%)                 | 0%                       | 0%                       | 0%                           | -                     | -                      | The authors reported FIC1 ranging from 0.5 to 4, without distinction between additive and indifferent effect. | [137]  |
|                  | 2013, Austria   | Lingscheid| doripenem | 10                | E. coli: ESBL (80%), AmpC (20%)                      | 0%              | -                        | in vitro (CB, TK)                                    | 8 (80%)                 | -                        | 0%                       | -                            | -                     | -                      |                       | [139]   |
|                  | 2012, Greece    | Samonis| imipenem,  | 20                | E. coli: ESBL (100%)                                | 0%              | 0%                       | in vitro (ET)                                       | IML: 11 (55%); MER: 3 (25%); DOR: 6 (30%)          | -                        | -                        | 0%                       | 0%                           | -                     | -                      |                       | [86]     |
|                  | 2010, Thailand  | Netikul| imipenem,  | 8                 | E. coli: ESBL (87%)                                 | 0%              | 8 (100%)                 | in vitro (ET)                                       | ERT: 3 (62%); IML: 2 (25%); MER: 2 (25%); DOR: 1 (12%) | -                        | -                        | 0%                       | -                            | -                     | -                      |                       | [140]   |
| Strains | Year and Country | Author | Carbapenem | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Carbapenem-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOSSusceptibilityRestoration(%) | CarbapenemSusceptibilityRestoration(%) | Comments | Reference |
|---------|-----------------|--------|-------------|-------------------|-----------------------------------------------|------------------|-------------------------|---------------------------------|-------------------|----------------|---------------------|----------------------|-----------------------------|--------------------------------|---------|----------|
| K. pneumoniae |
| 2020, India | Bakthavatchalam | meropenem | 50 | OXA (78%), NDM (32%), KPC (24%) | 50 (100%) | - | in vitro (TK) | 10 (20%) | 0% | 40 (80%) | 0% | - | - | - | [141] |
| 2020, Turkey | Erturk Sengel | meropenem | 17 | OXA (70%), NDM (32%), KPC (21%) | 17 (100%) | 7 (41%) | in vitro (CB, TK) | 15 (88%) | 2 (11%) | 0% | 0% | 4 (23%) | - | - | [142] |
| 2019, Germany | Loose | meropenem, ertapenem | 3 | - | 5 (100%) | 2 (66%) | in vitro (CB) | 2 (66%) | 1 (33%) | 0% | 0% | - | - | - | [130] |
| 2019, Brazil | Perdigão Neto | meropenem | 9 | ESBL, KPC (100%); OXA (4%), fosA (100%) | 9 (100%) | 9 (100%) | in vitro (CB, TK) | 8 (88%) | 0% | 1 (11%) | 0% | 2 (22%) | 0% | - | [143] |
| 2017, Taiwan | Tseng | meropenem | 25 | see comments | 12 (48%) | 24 (96%) | in vitro (CB) | 25 (100%) | 0% | 0% | 0% | - | - | - | [144] |
| 2017, China | Yu | imipenem, ertapenem | 136 | KPC (100%) | 78 (52%) | 136 (100%) | in vitro (CB, TK) | IMI: 21 (15%); ERT: 30 (22%) | IMI: 114 (85%); ERT: 104 (78%) | IMI: 1 (1%); ERT: 2 (1%) | 0% | - | - | - | [89] |
| 2016, Brazil | Albinho | meropenem | 18 | KPC (100%) | 13 (72%) | 16 (89%) | in vitro (CB) | 12 (66%) | 3 (18%) | 3 (16%) | 0% | 12 (92.3%) | 4 (25%) | - | [145] |
| 2014, Sweden | Tingdén | meropenem | 4 | NDM (50%), VIM (20%), ESBL (100%) | 4 (100%) | 3 (75%) | in vitro (TK) | 0% | 0% | 4 (100%) | 0% | - | - | - | [146] |
| 2013, Turkey | Evren | meropenem, ertapenem | 12 | OXA-48 (100%) | 12 (100%) | 12 (100%) | in vitro (CB) | IMI: 5 (41%); MER: 4 (33%) | IMI: 6 (50%); MER: 6 (50%) | IMI: 1 (8%); MER: 2 (16%) | 0% | - | - | - | [74] |
| 2013, Austria | Längscheid | doripenem | 5 | ESBL (60%), AmpC (100%) | 0% | - | in vitro (CB, TK) | 5 (100%) | 0% | 0% | 0% | 0% | - | - | - | [130] |
| 2012, Greece | Samonis | imipenem, doripenem | 64 | KPC (78%); ESBL (21%) | 1 (1%) | 51 (78%) | in vitro (ET) | KPC: IMI: 37 (74%); MER: 35 (70%); DOR: 37 (74%); ESBL: IMI: 11 (79%); MER: 6 (42%); DOR: 7 (42%) | KPC: IMI: 13 (26%); MER: 15 (30%); DOR: 13 (26%); ESBL: IMI: 3 (25%); MER: 8 (57%); DOR: 8 (57%) | 0% | - | - | - | [86] |
| 2011, Greece | Souli | meropenem | 17 | KPC (100%) | 4 (23%) | 17 (100%) | in vitro (TK) | 11 (64%) | 0% | 6 (35%) | 0% | - | - | - | [53] |

The 25 isolates were randomly selected among 642 isolates with the following resistance determinants: fosA3 (5.5%), foskpg2 (4.2%), KPC (10.1%), IMP (1.8%), VIM (0.2%). It is not reported which carbapenemases and fosfomycinases were present in the 25 isolates tested for synergism.
Table 3. Cont.

| Strains | Year and Country | Author | Carbapenem | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Carbapenem-Resistant (%) | In Vitro (Methods)/In Vivo (Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Carbapenem Susceptibility Restoration (%) | Comments | Reference |
|---------|-----------------|--------|------------|-------------------|-----------------------------------------------|------------------|-------------------------|------------------------------------------------|-----------------------|-----------------|---------------------|------------------------|-----------------------------|----------------------------------------|----------|-----------|
| 2010, Thailand | Netikul | ertapenem, imipenem, meropenem, doripenem | 8 | ESBL (87%) | 4 (50%) | 8 (100%) | in vitro (ET) | 0% | ERT: 5 (62%); IMI: 2 (25%); MER: 1 (12%); DOR: 2 (25%) | ERT: 3 (37%); IMI: 6 (75%); MER: 7 (87%); DOR: 6 (75%) | 0% | - | - | - | [140] |
| 2019, Germany | Loose | meropenem, ertapenem | 2 | - | 2 (100%) | 1 (50%) | in vitro (CB) | 0% | 2 (100%) | 0% | 0% | - | - | - | - | [133] |
| E. cloacae | Lingscheid | doripenem | 3 | 1 (33%) | 0% | - | in vitro (CB, TK) | 1 (33%) | - | - | 0% | - | - | - | [130] |
| 2018, USA | Mullane | meropenem | 30 | - | 14 (47%) | NA (at least 71) | in vitro (CB, TK) | 8 (17%) | 9 (30%) | 16 (53%) | 0% | 0% | 0% | - | - | [129] |
| 2019, USA | Avery | meropenem | 153 | - | - | 153 (100%) | in vitro (ET) | 29 (19%) | 55 (35%) | 69 (44%) | 0% | - | 21 (13%) | - | - | [129] |
| 2019, Brazil | Albaso | meropenem | 19 | MBL (52%) | 17 (89%) | 16 (84%) | in vitro (CB) | 15 (88%) | 3 (15%) | 1 (5%) | 0% | 15 (88%) | 7 (43%) | - | - | [147] |
| 2019, USA | Flamm | meropenem | 5 | - | - | - | in vitro (CB, TK) | 1 (100%) | 0% | 0% | 0% | 1 (100%) | 1 (100%) | - | - | [147] |
| 2018, Brazil | Perdigão | meropenem | 1 | OXA, fosA (100%) | 1 (100%) | 1 (100%) | in vitro (CB, TK) | 1 (100%) | 0% | 0% | 0% | 1 (100%) | 1 (100%) | - | - | [143] |
| 2010, USA | Drusano | meropenem | 1 | - | - | - | in vitro (hollow-fiber infection model) | 1 (100%) | 0% | 0% | 0% | - | - | - | - | [140] |
| P. aeruginosa | 2017, Spain | Hamou-Segarra | imipenem, meropenem, doripenem | 4 | - | 1 (25%) | - | in vitro (TK) | 4 (100%) | 0% | 0% | 0% | - | - | - | - | [140] |
| 2015, Thailand | Kunakovcik | imipenem, meropenem, doripenem | 70 | - | - | 70 (100%) | in vitro (CB, TK) | IMI: 36%; MER: 48%; DOR: 45% | - | - | - | - | - | - | - | [150] |
| 2013, Brazil | dos Santos | imipenem | 4 | - | 4 (100%) | 2 (50%) | in vitro (CB) | 4 (100%) | 0% | 0% | 0% | 3 (75%) | 1 (50%) | - | - | [40] |

The authors reported FICI ranging from 0.5 to 4, without distinction between additive and indifferent effect.

Combination therapy was able to counterselect resistance emergence. FOS and imipenem (IMI) alone lead to bacterial regrowth, while no regrowth was observed with the combination FOS + IMI. FOS in association with a carbapenem was observed to reduce also biofilm formation.
Table 3. Cont.

| Strains       | Year and Country | Author | Carbapenem | Number of Isolates | FOS-Resistant (%) | Carbapenem-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Carbapenem Susceptibility Restoration (%) | Comments | Reference |
|---------------|------------------|--------|------------|-------------------|-----------------|--------------------------|--------------------------------------------------------|-----------------------|---------------------|-----------------------|-------------------------|----------------------------------------|------------------------------------------|----------|-----------|
| A. baumannii  | 2019, USA        | Flamm  | meropenem  | 25 (A. baumannii-calcoaceticus species complex) | -                | -                        | in vitro (CB, TK)                                      | 1 (20%)               | 3 (60%)             | 0%                    | 0%                      | -                                      | -                                        | For 1 isolate the efficacy of FOS + MER remained indeterminate | [39]    |
| A. baumannii  | 2018, China      | Zhu    | imipenem   | 21                | -                | 20 (95%)             | 21 (100%) in vitro (CB)                                   | 12 (57%)             | 3 (13.3%)          | 6 (28%)               | 0%                      | -                                      | -                                        | -                                   | [151]   |
| A. baumannii  | 2016, Thailand   | Singkham-In | imipenem, meropenem | 23                  | OXA (100%)   | 23 (100%)             | 23 (100%) in vitro (CB, TK)                               | IMI 65%; MER 0%      | IMI 30.4%; MER 87% | IMI 4%; MER 13% | 0%                      | -                                      | -                                        | -                                   | [83]     |
| A. baumannii  | 1999, Spain      | Martinez-Marti | imipenem  | 34                | -                | 34 (100%)             | NA (at least 7y) in vitro (CB)                             | 1 (3%)               | -                   | 0%                    | -                      | -                                      | -                                        | -                                   | [132]    |

The authors reported FIC ranging from 0.5 to 4, without distinction between additive and indifferent effect, and considered the combination 'indifferent' against all isolates. [130]

Although the combination had a synergistic effect on no tested strains, it is of clinical relevance as it restored FOS and IMI susceptibility in almost all R isolates. [131]

The Authors reported only the number of isolates on which the combination had a synergistic or an antagonistic effect. [83]
Table 3. Cont.

| Strains | Year and Country | Author | Carbapenem | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Carbapenem-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Carbapenem Susceptibility Restoration (%) | Comments | Reference |
|---------|------------------|--------|------------|-------------------|-----------------------------------------------|------------------|--------------------------|------------------------------------------------|----------------------|------------------|-------------------|---------------------|-------------------------------|---------------------------------|----------|-----------|
| S. aureus | 2019, Spain | Coronado-Álvarez | imipenem | 4 | MRSA (50%) | - | - | in vitro (TK) | 4 (100%) | 0% | 0% | 0% | - | - | [63] |
| S. aureus | 2015, Spain | del Rio | imipenem | 10 (in vitro), 2 (in vivo) | MRSA (100%) | 1 (10%) | 4 (40%) | in vitro (TB); in vivo (rabbit, endocarditis) | in vitro: 9 (90%); in vivo: 2 (100%) | in vitro: 1 (100%) | 0% | 0% | - | - | - | % of sterile vegetations: FOS alone 0%, IMI alone 7%; FOS + IMI 73%. The authors reported FICs ranging from 0.5 to 4, without distinction between additive and indifferent effect. |
| S. aureus | 2013, Austria | Lingscheid | doripenem | 39 | MRSA (100%) | 0% | - | in vitro (CB, TK) | 37 (94%) | - | - | 0% | - | - | [130] |
| S. aureus | 2012, Spain | Garrigós | imipenem | 1 | MRSA (100%) | 0% | 0% | in vitro (TK); in vivo (neck, foreign-body infection) | 0% | in vitro: 1 (100%) | in vivo: 0%; in vivo: 1 (100%) | 0% | - | - | - | [37] |
| S. aureus | 2011, Spain | Pachón-Biabiez | imipenem | 1 | GISA (100%) | 0% | 100% | in vitro (TK); in vivo (mouse, peritonitis) | in vitro: 1 (100%); in vivo: 1 (100%) | 0% | 0% | 0% | - | - | - | [36] |
| S. aureus | 2003, Japan | Nakazawa | imipenem, panipenem | 32 | MRSA (100%) | 29 (91%) | 28 (88%) | in vitro (efficacy time index) | IMI: 16 (50%); PAN: 21 (66%) | IMI: 3 (9%); PAN: 8 (25%) | IMI: 13 (41%); PAN: 3 (9%) | 0% | - | - | - | [18] |
| S. aureus | 1992, France | Quentin | imipenem | 5 | - | 1 (20%) | 1 (20%) | in vitro (TK) | 1 (20%) | 0% | 3 (60%) | 1 (20%) | - | - | - | [15] |
| S. aureus + S. epidermidis | 2001, Austria | Grif | meropenem | 5 (S. aureus + 2 S. epidermidis) | MRSA (28%), GISA (25%) | - | - | in vitro (CB, TK) | S. aureus: 5 (100%) | 0% | - | - | - | - | - | The study was conducted on catheters infected in laboratory. Bacterial regrowth was observed on catheters treated with FOS or IMI alone, but did not occur when the drugs were tested in combination. |
| S. aureus + S. epidermidis | 1992, Austria | Goggenmbichler | imipenem | 1 (S. aureus + 2 S. epidermidis) | - | - | - | in vitro (TK) | 3 (100%) | 0% | 0% | 0% | - | - | - | [150] |
Table 3. Cont.

| Strains                      | Year and Country | Author | Carbapenem | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Carbapenem-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Carbapenem Susceptibility Restoration (%) | Comments                                                                                   | Reference |
|------------------------------|------------------|--------|------------|-------------------|------------------------------------------------|-------------------|--------------------------|-----------------------------------------------------------|------------------------|-----------------------|-------------------------------|-------------------------------|----------------------------------|------------------------------------------|--------------------------------------------------------------------------------------------|-----------|
| Staphylococcus spp. + Enterococcus spp. | 1986, Italy     | Debbia | imipenem   | 76                |                                                 | -                 | -                        | in vitro (CB, TK)                                        | 54 (71%)               | 0%                    | 22 (29%)                        | 0%                                           | -                                | -                                        | % reported are those obtained with CB. Results of TK showed higher rates of synergism, but in the present Table are considered the results of CB as not all isolates were tested with TK. | [154]    |
| E. faecalis                   | 2011, Italy      | Farina | imipenem   | 27                |                                                 | -                 | 2 (7%)                   | in vitro (ET)                                            | 0%                     | 0%                    | 10 (37%)                        | 17 (62%)                       | -                                | -                                        | The Authors did not distinguish between additive and indifferent effect, and defined the effect of FOS + IMI indifferent. | [128]    |
| S. pneumoniae                | 1994, France     | Doit   | imipenem   | 26                |                                                 | -                 | 0%                      | in vitro (TK)                                            | 0%                     | 26 (100%)             | 0%                             | 0%                                           | -                                | -                                        | -                                                                                          | [134]    |
| N. gonorrhoeae               | 2015, The Netherlands | Wind | ertapenem  | 4                 |                                                 | -                 | -                       | in vitro (ET)                                            | 0%                     | 3 (75%)               | 1 (25%)                         | 0%                                           | -                                | -                                        | -                                                                                          | [54]      |
Table 4. Studies on combination between fosfomycin and aztreonam. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain          | Year and Country | Author | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Aztreonam-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Aztreonam Susceptibility Restoration (%) | Comments Reference |
|-----------------|------------------|--------|--------------------|-----------------------------------------------|-------------------|------------------------|------------------------------------------------------------|-----------------------|---------------------|---------------------|------------------------|-------------------------------|-----------------------------------------|-----------------|
| Enterobacteriales | 2019, USA        | Avery  | 48                 | E. coli: KPC (25%), NDM (75%), ESBL (62%); K. pneumoniae: KPC (45%), NDM (40%); OXA (14%); VIM (5%); ESBL (5%); K. oxytoca: KPC (50%), NDM (50%); E. cloacae: KPC (50%), NDM (50%); 4% of isolates had ESBL and OXA | 48 (40%) 48 (100%) in vitro (ET); 20 (40%) 48 (100%) in vitro (ET) | 4 (8%) 1 (2%) 4 (8%) 13 (27%) 20 (40%) 48 (100%) in vitro (ET) | 20 (40%) 13 (27%) 31 (64%) 0% 0% 0% | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC90. | [11] |
| Enterobacteriales | 2019, USA        | Flamm  | 20                 | E. coli: KPC (25%), NDM (75%), ESBL (62%); K. pneumoniae: KPC (45%), NDM (40%); OXA (14%); VIM (5%); ESBL (5%); K. oxytoca: KPC (50%), NDM (50%); E. cloacae: KPC (50%), NDM (50%); 4% of isolates had ESBL and OXA | 48 (40%) 48 (100%) in vitro (ET); 20 (40%) 48 (100%) in vitro (ET) | 4 (8%) 1 (2%) 4 (8%) 13 (27%) 20 (40%) 48 (100%) in vitro (ET) | 20 (40%) 13 (27%) 31 (64%) 0% 0% 0% | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC90. | [38] |
| Enterobacteriales | 2019, Sweden     | Hickam | 2                  | E. coli: KPC (25%), NDM (75%), ESBL (62%); K. pneumoniae: KPC (45%), NDM (40%); OXA (14%); VIM (5%); ESBL (5%); K. oxytoca: KPC (50%), NDM (50%); E. cloacae: KPC (50%), NDM (50%); 4% of isolates had ESBL and OXA | 48 (40%) 48 (100%) in vitro (ET); 20 (40%) 48 (100%) in vitro (ET) | 4 (8%) 1 (2%) 4 (8%) 13 (27%) 20 (40%) 48 (100%) in vitro (ET) | 20 (40%) 13 (27%) 31 (64%) 0% 0% 0% | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC90. | [120] |
| Enterobacteriales | 2014, Sweden     | Hickam | 1                  | E. coli: KPC (25%), NDM (75%), ESBL (62%); K. pneumoniae: KPC (45%), NDM (40%); OXA (14%); VIM (5%); ESBL (5%); K. oxytoca: KPC (50%), NDM (50%); E. cloacae: KPC (50%), NDM (50%); 4% of isolates had ESBL and OXA | 48 (40%) 48 (100%) in vitro (ET); 20 (40%) 48 (100%) in vitro (ET) | 4 (8%) 1 (2%) 4 (8%) 13 (27%) 20 (40%) 48 (100%) in vitro (ET) | 20 (40%) 13 (27%) 31 (64%) 0% 0% 0% | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC90. | [120] |
| Enterobacteriales | 2014, Sweden     | Hickam | 1                  | E. coli: KPC (25%), NDM (75%), ESBL (62%); K. pneumoniae: KPC (45%), NDM (40%); OXA (14%); VIM (5%); ESBL (5%); K. oxytoca: KPC (50%), NDM (50%); E. cloacae: KPC (50%), NDM (50%); 4% of isolates had ESBL and OXA | 48 (40%) 48 (100%) in vitro (ET); 20 (40%) 48 (100%) in vitro (ET) | 4 (8%) 1 (2%) 4 (8%) 13 (27%) 20 (40%) 48 (100%) in vitro (ET) | 20 (40%) 13 (27%) 31 (64%) 0% 0% 0% | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC90. | [120] |
| P. aeruginosa    | 2019, USA        | Avery  | 103                | E. coli: KPC (25%), NDM (75%), ESBL (62%); K. pneumoniae: KPC (45%), NDM (40%); OXA (14%); VIM (5%); ESBL (5%); K. oxytoca: KPC (50%), NDM (50%); E. cloacae: KPC (50%), NDM (50%); 4% of isolates had ESBL and OXA | 48 (40%) 48 (100%) in vitro (ET); 20 (40%) 48 (100%) in vitro (ET) | 4 (8%) 1 (2%) 4 (8%) 13 (27%) 20 (40%) 48 (100%) in vitro (ET) | 20 (40%) 13 (27%) 31 (64%) 0% 0% 0% | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC90. | [38] |
| P. aeruginosa    | 2019, USA        | Flamm  | 5                  | E. coli: KPC (25%), NDM (75%), ESBL (62%); K. pneumoniae: KPC (45%), NDM (40%); OXA (14%); VIM (5%); ESBL (5%); K. oxytoca: KPC (50%), NDM (50%); E. cloacae: KPC (50%), NDM (50%); 4% of isolates had ESBL and OXA | 48 (40%) 48 (100%) in vitro (ET); 20 (40%) 48 (100%) in vitro (ET) | 4 (8%) 1 (2%) 4 (8%) 13 (27%) 20 (40%) 48 (100%) in vitro (ET) | 20 (40%) 13 (27%) 31 (64%) 0% 0% 0% | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC90. | [38] |
| P. aeruginosa    | 2002, Japan      | Okazaki| 30                 | E. coli: KPC (25%), NDM (75%), ESBL (62%); K. pneumoniae: KPC (45%), NDM (40%); OXA (14%); VIM (5%); ESBL (5%); K. oxytoca: KPC (50%), NDM (50%); E. cloacae: KPC (50%), NDM (50%); 4% of isolates had ESBL and OXA | 48 (40%) 48 (100%) in vitro (ET); 20 (40%) 48 (100%) in vitro (ET) | 4 (8%) 1 (2%) 4 (8%) 13 (27%) 20 (40%) 48 (100%) in vitro (ET) | 20 (40%) 13 (27%) 31 (64%) 0% 0% 0% | Data on synergism reported without distinction for bacterial strains. % of FOS-R isolates estimated on the basis of the reported MIC90. | [38] |
**Table 5.** Studies on combination between fosfomycin and quinolones. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain               | Year and Country | Author | Quinolone | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Quinolone Susceptibility Restoration (%) | Comments                                                                                               | Reference |
|----------------------|------------------|--------|-----------|-------------------|-----------------------------------------------|--------------------------------------------------------|------------------------|---------------------|----------------------|------------------------|-------------------------------------|-------------------------------------|--------------------------------------------------------------------------------|-----------|
| Enterobacteriales    | 2019, USA        | Flamm  | Levofloxacin 20 | 5 MDR (of which 29% ESBL and 29% KPC-producer) | -                                             | in vitro (CB)                                         | 30% 60% 10% 0%        | -                   | -                    | -                      | -                                                  | -                                                  | Triple combination (FOS+IMP+CIP or FOS+CIP/TOB) increased synergism against all isolates. | [38]      |
| E. coli              | 2020, Egypt      | El-Wafa| Ciprofloxacin 8 | -                                             | 100%                                           | in vitro (CB, TK)                                     | 3 (37%) - - - 3 (100%) | 3 (100%) | -                    | -                      | -                                                  | -                                                  | The optimal combination of fosfomycin with N-acetylcysteine produces the reduction of E. coli sessile cell viability and biofilm formation up to 60–73%. | [42]      |
| E. coli              | 2019, USA        | Wang   | Ciprofloxacin 8 | -                                             | 0% 98%                                         | in vitro (CB, TK)                                     | 3 (6%) 20 (40%) 27 (54%) | 0%       | -                    | 0%                     | -                                                  | -                                                  | -                                                                 | [155]     |
| E. coli              | 2019, India      | Sugathan| Ciprofloxacin 50 | biofilm producers (100%) | -                                             | in vitro (CB, TK)                                     | 31 (38%) 0% 49 (61%) 0% 65 (81%) 3 (4%) | -       | -                    | -                      | -                                                  | -                                                  | -                                                                 | [137]     |
| S. flexneri          | 2019, China      | Liu    | Ciprofloxacin 80 | -                                             | 43 (54%) 100%                                    | in vitro (CB, TK) in vivo (Galleria mellonella)       | 31 (38%) 0% 49 (61%) 0% 65 (81%) 3 (4%) | -       | -                    | -                      | -                                                  | -                                                  | -                                                                 | [156]     |
| P. aeruginosa        | 2019, USA        | Wang   | Ciprofloxacin 7 | -                                             | 0% 14%                                         | in vitro (ET, biofilm)                                | 4 (57%) - 3 (42%) - - - | -       | -                    | -                      | -                                                  | -                                                  | -                                                                 | [155]     |
| P. aeruginosa        | 2019, USA        | Flamm  | Levofloxacin 5 | 7 MDR (of which 29% ESBL and 29% KPC-producer) | -                                             | in vitro (CB)                                         | 1 (20%) 4 (80%) 0%    | -       | -                    | -                      | -                                                  | -                                                  | The total number of experiments was 108 (9 combinations of FOS+CIP at different concentrations, in 3 different times). | [38]      |
| P. aeruginosa        | 2016, Australia  | Walsh  | Ciprofloxacin 4 | -                                             | 75% 50%                                         | in vitro (TK)                                         | 21% (21/108) 15% (16/108) 38% (41/108) | -       | -                    | -                      | -                                                  | -                                                  | -                                                                 | [76]      |
| P. aeruginosa        | 2013, Brazil     | Dos Santos | Ciprofloxacin 2 | MDR (50%)                                        | 100% 50%                                         | in vitro (CB, TK)                                     | 2 (100%) - - - 2 (100%) 0% | -       | -                    | -                      | -                                                  | -                                                  | *After 3 consecutive days' co-administration. | [48]      |
| P. aeruginosa        | 2007, Japan      | Mikuniya| Prulifloxacin, ciprofloxacin, levofloxacin 1 | biofilm forming (100%) | -                                             | in vivo (rat, UTI)                                    | 1 (100%) - - - - - -   | -       | -                    | -                      | -                                                  | -                                                  | -                                                                 | [48]      |
| P. aeruginosa        | 2007, Japan      | Yamada | Ciprofloxacin 74 | -                                             | -                                             | in vitro (CB)                                         | 20 (27%) 54 (73%) 0% 0% | -       | -                    | -                      | -                                                  | -                                                  | -                                                                 | [157]     |
Table 5. Cont.

| Strain Year and Country | Author | Quinolone | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Quinolone-Resistant (%) | In Vitro (Method)/In Vivo (Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Quinolone Susceptibility Restoration (%) | Comments | Reference |
|-------------------------|--------|-----------|--------------------|------------------------------------------------|------------------|------------------------|------------------------------------------------------|-----------------------|---------------------|---------------------|------------------|-------------------------------|-------------------------------|----------|-----------|
| 2005, Japan             | Micuniya | Ciprofloxacin, Ulofl oxacin, Levofloxacin | 1 | - | 100% | 100% | in vitro (ATP bioluminescence assay) | - | 100% | - | - | 0% | 0% | - | [46] |
| 2002, Japan             | Monden | Ofloxacin | 4 | - | 3 (75%) | 1 (25%) | in vitro (biofilm) | 3 (75%) | - | - | - | - | - | - | [158] |
| 2001, Japan             | Okazaki | Levofloxacin | 30 | MDR (50%) | 13/30 (43%) | 21/30 (70%) | in vitro (Efficacy time index) | 3/30 (1%) | 17/30 (56%) | - | - | 10/30 (33%) | - | - | [39] |
| 1999, Japan, 1997, 1997, 1999, Japan, 1997, 1997, France | Hayami | Ciprofloxacin | 26 | - | - | - | in vitro (CB, TK) | 10 (38%) | 15 (57%) | 1 (3%) | 0% | - | - | - | [130] |
| 1997, France            | Bugnon | Pefloxacin | 2 | - | - | - | in vivo (rabbit, endocarditis) | - | - | - | 100% | - | - | - | [41] |
| 1995, Japan             | Tessier | Ciprofloxacin | 40 | MDR (100%) | 23 (57%) | 19 (47%) | in vitro (CB) | 6 (15%) | 32 (80%) | 2 (5%) | - | 16 (70%) | 12 (63%) | - | [131] |
| 1994, France            | Xiong | Ciprofloxacin | 2 | MDR (50%) | 0% | 50% | in vitro (CB); in vivo (rabbit, endocarditis) | 2 (100%) | early thp; 1 (50%) Late thp | 0% early thp; 1 (50%) Late thp | - | - | - | in vivo results. | [160] |
| 1994, France            | Xiong | Pefloxacin | 2 | MDR (50%) | 0% | 50% | in vitro (CB); in vivo (rabbit, endocarditis) | 1 (50%) early thp; 1 (50%) Late thp | 1 (50%) early thp | 1 (50%) late thp | - | - | - | - | [160] |
| 1998, Germany           | Vogl | Ciprofloxacin | 25 | - | 1 (4%) | 2 (8%) | in vitro (TK) | 20% | - | - | - | - | - | - | [161] |
| 1988, USA               | Figueroa | Ciprofloxacin | - | - | - | - | in vitro (CB) | 40% (EV) | 17% (CB) | - | - | 0% | - | - | [162] |
| 1987, Germany           | Ullmann | Ciprofloxacin | 37 | - | - | - | in vitro (CB) | 29 (78%) | 8 (22%) | 0% | 0% | 100% | - | - | [45] |
| **A. baumannii**        | 1996, Spain | Martinez-Martinez | Ciprofloxacin | 34 | - | 100% | 100% | in vitro (CB) | 1 (3%) | - | - | 0% | - | - | - | [152] |
| **A. baumannii- A. calcoaceticus spp. complex** | 2019, USA | Flamm | Levofloxacin | 5 | 7 MDR (29% ESBL and 29% KPC-producer) | - | - | in vitro (CB) | 0% | 4 (80%) | 1 (20%) | 0% | - | - | - | [38] |
| **Gram negative**       | 1977, Spain | Daza | Nalidixic acid | 100 | - | 100% | - | in vitro (CB) | 0% | - | 100% | 0% | - | - | - | [66] |

Note: ETI < 0.5 antagonism; 0.5 ≤ ETI < 1 indifferent; 1 ≤ ETI < 8 additive; ETI ≥ 8 synergistic.
Table 5. Cont.

| Strain     | Year and Country | Author          | Quinolone | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Quinolone-Resistant (%) | In Vitro (Methods)/In Vivo (Animal and Site of Infection) | Syndromic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Quinolone Susceptibility Restoration (%) | Comments | Reference |
|------------|------------------|-----------------|-----------|--------------------|-------------------------------------------------|-------------------|-------------------------|---------------------------------------------------|---------------------|---------------------|------------------------|---------------------------|-----------------------------|----------------------------------------|----------|-----------|
| Staphylococcus spp: | 2003, Japan | Nakazawa | Ofloxacin | 32 | MRSA (100%) | - | - | in vitro (efficacy time index) | 3 (9%) | 2 (6%) | 27 (84%) | - | - | - | synergy = high efficacy; additive = efficacy, indifferent = invalid | [18] |
| | 2001, Austria | Grif | Moxifloxacin | 7 | MRSA (100%) | - | - | in vitro (CB) | 100% | - | - | - | - | - | - | [45] |
| | 1997, Italy | Ferrara |sparfloxacin | 16 | MRSA (100%) | >50% ~100% | - | in vitro (TK) | 0% | - | - | - | - | - | - | [123] |
| | 1988, France | Thauvin | Pefloxacin | 1 | MRSA (100%) | - | - | in vitro (rat, endocarditis) | 100% | - | - | - | - | - | - | [44] |
| | 1987, France | Weber | Ofloxacin | 8 | MRSA (97%) | - | - | in vitro (TK) | 2 (25%) | 6 (75%) | - | - | - | - | - | [160] |
| | 1987, Germany | Ullmann | Ciprofloxacin | 20 | - | - | - | in vitro (CB) | 19 (95%) | 1 (5%) | - | - | - | - | - | - | S. aureus | [46] |
| | 1987, France | Quentin | Pefloxacin | 6 | - | 16% | 0% | in vitro (TK) | 0% | 0% | 100% | 0% | - | - | - | - | S. aureus | Indifferent effect. | [18] |
| | 1997, Italy | Ferrara | Sparfloxacin | 12 | MBSE (100%) | >50% ~100% | - | in vitro (TK) | 6/12 (50%) | - | - | - | - | - | - | [123] |
| | 1997, France | Quentin | Pefloxacin | 2 | - | 50% | - | in vitro (TK) | 0% | 0% | 100% | 0% | - | - | - | - | - | Indifferent effect. | [18] |
| | 2019, USA | Avery | Tobramycin | 45 | - | - | - | in vitro (ET) | 0% | - | - | - | - | - | - | - | [54] |
| Enterobacteriaceae | 2019, USA | Flamm | Gentamicin | 20 | - | - | - | in vitro (CB, TK) | 6 (30%) | 13 (65%) | 1 (5%) | 0% | - | - | - | - | - | [10] |

Table 6. Studies on combination between fosfomycin and aminoglycosides. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain     | Year and Country | Author | Aminoglycoside | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Aminoglycoside-Resistant (%) | In Vitro (Methods)/In Vivo (animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Aminoglycoside Susceptibility Restoration (%) | Comments | Reference |
|------------|------------------|-------|----------------|--------------------|-------------------------------------------------|-------------------|-----------------------------|---------------------------------------------------|---------------------|---------------------|------------------------|---------------------------|-----------------------------|----------------------------------------|----------|-----------|
| Enterobacteriaceae | 2019, USA | Avery | Tobramycin | 45 | - | - | - | in vitro (ET) | 0% | - | - | - | - | - | - | - | [11] |
| | 2019, USA | Flamm | Gentamicin | 20 | - | - | - | in vitro (CB, TK) | 6 (30%) | 13 (65%) | 1 (5%) | 0% | - | - | - | - | - | [10] |
| Year and Country | Author | Aminoglycoside | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | In Vitro (Method) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Aminoglycoside Susceptibility Restoration (%) | Comments | Reference |
|------------------|--------|----------------|-------------------|-----------------------------------------------|------------------|------------------------|---------------------|------------------------|------------------------|--------------------------------------|----------------------------------------|----------|----------|
| 1977, Spain      | Olay   | Streptomycin, gentamicin, kanamycin | -                   | Streptomycin: 18 (E. coli), Gentamicin: 30 (E. coli), 24 K. pneumoniae, 39 S. marcescens, 33 Proteus spp., Kanamycin: 21 E. coli, 12 K. pneumoniae, 14 Proteus spp., 5 E. cloacae, 22 S. marcescens | in vitro (CB)    | streptomycin: 0% (E. coli), gentamicin: 36 (12%), kanamycin: 21 (27%) | 2 (25%) | 0% | 0% | 0% | 2 (66%) | 2 (25%) | For 6 isolates the efficacy of FOS + TOB remained indeterminate. | [14]  |
| 2020, Egypt      | El-Wafa| Tobramycin     | 8                  | -                          | in vitro (CB, TK) | 2 (25%) | 0% | 0% | 0% | 2 (66%) | 2 (25%) | - | - | - | [43] |
| 2019, USA        | Wang   | Gentamicin     | 8                  | -                          | in vitro (ET, biofilm) | 75% (6/8) | 0% | (2/8) 25% | 0% | - | 1/2 50% | - | The Authors also studied the efficacy of combination of FOS + AMK and found it reduced significantly biofilm formation. | [135] |
| 2019, India      | Sugathan| Amikacin      | 50                 | -                          | in vitro (TK) | 29 (58%) | 21 (42%) | 0% | 0% | 0% (all S) | 22 (44%) | - | - | - | [137] |
| 2013, Switzerland| Corvec | Gentamicin     | 1                  | CTX-M15, ESBL              | in vitro (TK); in vitro (foreign-body infection model) | 0% | 100% | 0% | 0% | - | - | - | - | - | [73] |
| 2011, Greece     | Simonis| Netilmicin     | 20                 | ESBL                       | in vitro (ET) | 25% (5/20) | - | - | - | - | - | - | - | - | [86] |
| 1977, Poland     | Boroszki| Streptomycin  | 10                 | -                          | in vitro (CB) | 7 (70%) | 3 (30%) | 0% | 0% | - | - | - | - | - | - | [112] |
| 2020, Turkey     | Erturk Sengel | Amikacin   | 17                | OXA-48, NDM              | in vitro (CB) | 29% | 29% | 24% | 0% | - | - | Combination of FOS plus amikacin seems not a good choice for NDM producing strains. | [142] |
| 2018, China      | Yu     | Amikacin      | 3                  | -                          | in vitro (TK) | 100% (3/3) | 0% | 0% | 0% | - | - | - | - | - | - | - | [164] |
| 2017, China      | Yu     | Amikacin      | 3                  | KPC-2                      | in vitro (TK) | 66% | 0% | 33% | 0% | - | - | - | - | - | - | - | [56] |
| 2017, China      | Yu     | Amikacin      | 136                | KPC (100%)                | in vitro (CB, TK) | 7 (5%) | 109 (80%) | 20 (14%) | 0% | - | - | - | - | - | - | - | [89] |
Table 6. Cont.

| Strain       | Year and Country | Author                | Aminoglycoside | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | Synergistic Effects (%) | Additive Effects (%) | Indifferent Effects (%) | Antagonistic Effects (%) | FOS Susceptibility Restoration (%) | Aminoglycoside Susceptibility Restoration (%) | Comments                                                                 |
|--------------|------------------|-----------------------|----------------|-------------------|-----------------------------------------------|------------------------|----------------------|-----------------------|-----------------------------------|------------------------------------------|------------------------------------------|--------------------------------------------------------------------------|
| 2015, Spain  | Rodriguez-Avila et al | Plazomicin           | 4 (CB); 2 (TK) | Carbapenemase-producing strains (KPC, VIM) | FOS-resistant (100%) in vitro (CB, TK) | 25–100%                           | 50–0%               | 25–0%                  | 0%                        | -                          | -                          | Synergy defined: reduction of FOS and AMK MIC when used in combination. |
| 2014, USA    | Montgomery        | Amikacin             | 20             | KPC-2 (20%); KPC-3 (15%) | NA in vitro (agar dilution, antibiotic potentiation study in A:F 5:2 ratio) | 100%                           | -                    | -                    | 0%                        | -                          | -                          |                                                                 | [51]                                                      |
| 2011, Greece | Samonis           | Netilmicin           | 65             | serine carbapenem-producing (50/65); ESBL (14/65); MBL (1/65) | 98% in vitro (ET)                       | 41% (27/65) overall. In ESBL 42% (6/14). In serine enzymes 42% (2/50) | -                    | -                    | -                        | 54% (25/46)                      | -                          |                                                                 | [52]                                                      |
| 2011, Greece | Souli             | Gentamicin           | 17             | KPC (100%) | 4 (22%); 7 (41%) in vitro (TK) | 0%                            | 0%                   | 15/15 (100%)          | -                        | -                          | -                          | Efficacy of FOS + GEN was not evaluated in 2 isolates.                      | [53]                                                      |
| 1977, Spain  | Daza              | Tobramycin           | 23             | - | in vitro (CB) | 2/23 (8%) | - | - | - | 54% (25/46) | - |                                                                 | [54]                                                      |
| M. morganii  | 1977, Spain       | Daza                 | Gentamicin     | 2 | - | - | in vivo (CB) | 50% (1/2) | - | - | 0% | - | - |                                                                 | [55]                                                      |
| 2019, USA    | Wang              | Gentamicin           | 7              | - | in vitro (ET, biofilm) | 0% (57%) | 0% | 3 (42%) | 0% | - | 0% | - | No difference in P. aeruginosa lung tissue concentration, bronchoalveolar lavage concentration and lung histopathology score when amikacin and FOS were administered by aerosol alone or in combination therapy. | [56]                                                      |
| 2019, USA    | Avery             | Tobramycin           | 42             | - | NA (at least 71) | 42 (27%) | 8 (19%) | 13 (33%) | 21 (50%) | 0% | - | 8 (19%) | - |                                                                 | [57]                                                      |
| P. aeruginosa| 2019, New Zealand | Li Bassi             | Amikacin       | 15 | Strains resistant to nebulized fosfomycin and amikacin (100%) | - | - | - | in vivo (pigs, pneumonia) | 0% | 0% | 100% | 0% | - | - |                                                                 | [58]                                                      |
| 2019, USA    | Flamm             | Gentamicin, amikacin | 5              | - | - | in vitro (CB, TK) | 0% | genta 4 (90%); amika 4 (80%) | - | - | - | - | - | Synergy tested in biofilm. | [59]                                                      |
| 2018, Spain  | Daza-Aguilar      | Tobramycin           | 6              | - | 100% | 67% | in vivo (CB) | 83% | 17% | 0% | 0% | - | - |                                                                 | [60]                                                      |
Table 6. Cont.

| Strain       | Year and Country | Author                  | Aminoglycoside | Number of Isolates | Known Resistance Mechanisms on Determinants (%) | FOS-Resistant (%) | Aminoglycoside-Resistant (%) | In Vitro (Method/In Vivo (animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Aminoglycoside Susceptibility Restoration (%) | Comments | Reference |
|--------------|------------------|-------------------------|----------------|-------------------|-------------------------------------------------|------------------|-----------------------------|--------------------------------------------------------|------------------------|------------------|-----------------------|--------------------------|------------------------|-----------------------------|----------|-----------|
| 2015, Australia | Walsh           | Tobramycin             | 3              |                   | 1/4 (25%) in vitro (TK) | 18% (15/81) | 25% (20/81) | - | - | - | - | - | - | - | [76] |
| 2015, Spain    | Diez-Aguilar    | Tobramycin             | 8              | mexZ mutation (25%), ANT(2')-I enzyme (27.5%), GES-1, OXA-2 plus OXA-10 plus VM-2, OXA 14, VM-4 (each, 48%), VIM-2 (15%) | 100% | 37% in vitro (TK) | 25% | 0% | 75% | 0% | - | - | - | [166] |
| 2014, USA      | Montgomery      | Amikacin               | 21             | IMP-R (100%)       | 100% in vitro (broth microdilution, CB) | 100% | 0% | 0% | 0% | 100% | 0% | - | - | [52] |
| 2013, Brazil   | Ferrari dos Santos Lima | Tobramycin          | 2              | IMP-R (100%)       | 100% in vitro (-effects on biofilms on CF airway epithelial cells) | - | 100% | 0% | 0% | - | - | - | - | [40] |
| 2013, USA      | Anderson        | Tobramycin             | 1              |                   | - | - | - | - | - | - | - | - | - | [49] |
| 2012, UK/USA   | McCaughey       | Tobramycin             | 15             |                   | in vitro (agar dilution, TK) | 100% | - | - | 0% | - | - | - | - | [167] |
| 2011, Greece   | Samonis         | Netilmicin             | 15             | MDR               | 93% | 13% in vitro (ET) | 13% (2/15) | - | - | - | - | - | - | - | [66] |

Synergy defined: reduction of FOS and AMK MIC when used in combination. Authors do NOT report FOS and AMK MIC (they referred to CLSI criteria except for FOS-Eucast S ≤ 32 µg/mL; FOS MIC restoration 32. FOS:TOBRA (4:1) formulas for inhalation treatment; results suggest that fosfomycin enhanced the activity of tobramycin (much less level of tobramycin needed). FOS alone does NOT result in biofilm inhibition; TOBRA alone require HIGHER doses for biofilm inhibition. Synergism defined as FOS:TOBRA bactericidal activity; Time kill studies in a subset of isolates; biofilm studies were also performed.
Table 6. Cont.

| Strain   | Year and Country | Author | Aminoglycoside | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Aminoglycoside-Resistant (%) | In Vitro (Methods/En Vivo (animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Aminoglycoside Susceptibility Restoration (%) | Comments | Reference |
|----------|-----------------|--------|----------------|-------------------|-----------------------------------------------|------------------|-----------------|---------------------------------|----------------------|------------------|---------------------|----------------------|-----------------------------|-----------------------------|----------|-----------|
| 2009, China | Cai | Amikacin | 20 | - | NA (MIC90 32) | in vitro (CB); in vivo (rat, biofilm-infected model) | 80% | 15% | - | 0% | - | MBC90 decrease of 64-fold | F + T (lowest FICI amikacin and sisomicina) had synergistic effect on planctonic P. aeruginosa. | [168] |
| 2009, China | Cai | Gentamicin | 20 | - | NA (MIC90 36) | in vitro (CB); in vivo (rat, biofilm-infected model) | 70% | 15% | - | 0% | - | MBC90 decrease of 8-fold | F + T (lowest FICI amikacin and sisomicina) had synergistic effect on planctonic P. aeruginosa. | [168] |
| 2009, China | Cai | Netilmicin | 20 | - | NA (MIC90 36) | in vitro (CB); in vivo (rat, biofilm-infected model) | 60% | 20% | - | 0% | - | MBC90 decrease of 8-fold | F + T (lowest FICI amikacin and sisomicina) had synergistic effect on planctonic P. aeruginosa. | [168] |
| 2009, China | Cai | Tobramycin | 20 | - | NA (MIC90 8) | in vitro (CB); in vivo (rat, biofilm-infected model) | 60% | 20% | - | 0% | - | MBC90 decrease of 2-fold | F + T (lowest FICI amikacin and sisomicina) had synergistic effect on planctonic P. aeruginosa. | [168] |
| 2005, Thailand 2002, Japan 1999, Nigeria | Prukpresert | Gentamicin | 22 | - | - | in vitro (CB) | 1 (4%) | 9 (42%) | 6 (27%) | 6 (27%) | - | - | - | - | [22] |
| | Okazaki | Gentamicin | 30 | - | 15 (50%) | 19 (63%) | in vitro (efficacy time index) | 0% | 9 (30%) | 21 (70%) | 0% | 0% | 15 (50%) | - | - | [39] |
| | Hayami | Amikacin | 25 | - | NA (at least 13) | NA (< 5) | in vitro (CB, TK) | 0% | 10 (38%) | 16 (62%) | 0% | - | - | - | - | [130] |
| | Chimuaba | Gentamicin | 8 | - | - | 0% | in vitro (CB, TK) | 0% | 0% | 100% | 0% | - | - | - | - | [169] |
| 1997, France | Tessier | Amikacin | 40 | - | 23 (57%) | 13 (32%) | in vitro (CB) | 3 (7%) | 21 (52%) | 16 (40%) | 0% | 18 (78%) | 11 (84%) | - | - | [131] |
| 1978, Spain | Olaf | Gentamicin, Kanamycin | 77 | gentamicin: 55 (71%); kanamycin: 4 (26%) | gentamicin: 17 (22%); kanamycin: 8 (103%) | gentamicin: 5 (6%); kanamycin: 3 (20%) | - | - | - | 0% | - | - | - | [14] |
Table 6. Cont.

| Strain       | Year and Country | Author            | Aminoglycoside | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Aminoglycoside-Resistant (%) | In Vitro (Method)/In Vivo (animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Aminoglycoside Susceptibility Restoration (%) | Comments | Reference |
|--------------|------------------|-------------------|----------------|-------------------|------------------------------------------------|------------------|---------------------------|--------------------------------------------------------|------------------------|-------------------|----------------------|--------------------------|-----------------------------|-----------------------------------------------|----------|-----------|
| *A. baumannii* | 2019, USA        | Flamm             | gentamicin, amikacin | 5 (*A. baumannii-cacoaceticus specios species complex*) | - | - | - | in vitro (CB, TK) | genta: 2 (40%); amika: 2 (40%) | genta: 3 (60%); amika: 3 (60%) | 0% | 0% | - | - | - | - | [38] |
|              | 2016, Brazil     | Leite             | gentamicin, amikacin | 20 OXA (100%), IMP (15%) | 20 (100%) | genta: 11 (55%); amika: 19 (95%) | in vitro (CB, TK) | 0% | genta: 2 (10%); amika: 0% | genta: 18 (90%); amika: 20 (100%) | 0% | - | - | - | - | [63] |
| *A. baumannii* | 2014, USA        | Montgomery        | Amikacyn         | 21 OXA-23 plus OXA-51 (23.8%); OXA-24 plus OXA-51 (8.5%); OXA-51, OXA-51 plus OXA-58 (each, 4.8%) | - | - | 100% | in vitro (agar dilution, antibiotic potentiation study in A:F 5:2 ratio) | 100% | - | - | 0% | - | - | - | [52] |
| *Gram-negative* | 1996, Spain    | Martinnez-Martinez | amikacin, tobramycin | 34 | - | 34 (100%) | amika: 31 (91%); tobra: 33 (97%) | in vitro (CB) | amika: 15 (44%); tobra: 11 (32%) | - | - | 0% | - | - | - | - | [132] |
| *S. aureus* | 2017, Spain      | Lopez-Diaz       | Plazomicin      | 12 (BC); 5 (TK) | MDR Strains carrying aminoglycoside-modifying enzymes (100%) | 66% | - | - | in vitro (CB, TK) | 33.3–0% | 66–100% | 0% | 0% | - | - | - | - | [46] |
|              | 2012, UK/USA     | McLaughay         | Tobramycin      | 5 | MRSA | 100% | - | - | - | in vitro (agar dilution, TK) | 60% | - | - | 0% | - | - | - | - | [167] |
Table 6. Cont.

| Strain Year and Country | Author | Aminoglycoside | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Aminoglycoside-Resistant (%) | In Vitro (Methods) | In Vivo (animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Aminoglycoside Susceptibility Restoration (%) | Comments | Reference |
|------------------------|--------|----------------|-------------------|-----------------------------------------------|------------------|-----------------------------|-------------------|----------------------------------------|----------------------|--------------------|----------------------|----------------------|-----------------|-----------------------------|-----------------------------|-----------------------------|------------------|
| 2005, Japan Morikawa | Arbekacin | 1 | MRSA | 100% | 100% | MIC 0.5 (no available breakpoint) | in vivo (rat, carboxymethyl cellulose pouch infection model) | 100% | - | - | - | - | | | | [171] |
| 1994, Japan Kono | Arbekacin | 96 | MRSA | 38% | - | in vitro | 66% (60/90) | - | - | 0% | - | - | | | | [172] |
| 1987, Spain Rodriguez | Gentamicin | 1 | MRSA | 0% | 0% | in vivo (endocarditis in 10 rabbits) | 100% (1/1) 0% n. of rabbits' death (0/10) | 0% | 0% | 0% | - | - | | | | [61] |
| 1985, USA Alvarez | Gentamicin | 148 | MRSA | - | - | in vitro (microtiter technique in a 1:1 ratio) | (10/148) 7% | 0% | 90% (134/148) | (4/148) 3% | - | - | | | | [12] |
| 1978, Spain Olay | Streptomycin, gentamicin, kanamycin | 18 | streptomycin, 29 gentamicin, 21 kanamycin | - | - | - | in vitro (CB) | streptomycin: 1 (5%); gentamicin: 0%; kanamycin: 0 (43%); streptomycin: 10 (53%); gentamicin: 3 (10%); kanamycin: 7 (33%); streptomycin: 7 (38%); gentamicin: 26 (89%); kanamycin: 5 (20%); streptomycin: 0% | - | - | - | - | | | | [14] |

NOT available arbekacin EUCAST breakpoints; Synergistic effect was evaluated by i) morphological and histological studies showing dramatic change in biofilm and inflammatory response and by ii) decrease in the number of viable bacteria in vivo. Better results of FOS-arbekacin combination in FOS susceptible strains. Synergy was indicated if the MICs of both drugs decreased by at least one-fourth. If the MIC of one drug showed a fourfold or greater increase, it was assumed to be an indication of antagonism.
Table 6. Cont.

| Strain          | Year and Country | Author | Aminoglycoside | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | In Vitro (Methods/In Vivo (animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Aminoglycoside Susceptibility Restoration (%) | Comments | Reference |
|-----------------|------------------|--------|----------------|-------------------|------------------------------------------------|--------------------------------------------------------|------------------------|----------------------|------------------------|------------------------|-------------------------------|------------------------------------------|----------|-----------|
| *Streptococcus* spp. | 1978, Spain      | Olay   | streptomycin   | 16                | -                                              | in vitro (CB)                                          | 0%                    | 9 (56%)              | 7 (43%)                | 0%                     | -                             | -                                          | -        | [14]      |
| *E. faecium*     | 2019, Thailand   | Hemapanpairoa | Gentamicin     | 8                 | VRE (100%)                                      | in vitro (ET for FOS, broth microdilution for gentamicin) | 63%                   | 13%                  | 25%                    | 0%                     | 63%                           | -                                          | -        | [55]      |
| *N. gonorrhoeae* | 2015, The Netherlands | Wind   | gentamicin     | 4                 | -                                               | in vitro (ET)                                          | 0%                    | 1 (25%)              | 3 (75%)                | 0%                     | -                             | -                                          | -        | [54]      |
| Miscellaneous    | 2009, USA        | MacLeod| Tobramycin     | 27 (4 *S. aureus*, 17 *P. aeruginosa*, 5 *E. coli*, 1 *H. influenzae*) | -                                              | in vitro (CB, TK), in vivo (rat, pneumonia)           | 7% (1 *P. aeruginosa*, 1 *E. coli*) | -                    | 93%                    | 0%                     | -                             | -                                          | -        | [173]     |
Table 7. Studies on combination between fosfomycin and macrolides. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain | Year and Country | Author | Macrolide | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Macrolide-Resistant (%) | In Vitro (Methodology)/In Vivo (animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Macrolide Susceptibility Restoration (%) | Comments | Reference |
|--------|-----------------|--------|-----------|-------------------|-----------------------------------------------|------------------|-------------------------|---------------------------------------------------|----------------------|------------------|-------------------|--------------------------|---------------------------|-----------------------------|----------|-----------|
| E. coli | 1978, Spain     | Olay   | Erythromycin | 14                | -                                             | -                | -                       | in vitro (CB)                                      | 42%                  | 29%              | 28%               | 0%                       | -                         | -                          |          | [14]      |
| Klebsiella spp. | 1978, Spain   | Olay   | Erythromycin | 44                | -                                             | -                | -                       | in vitro (CB)                                      | 50%                  | 23%              | 27%               | 0%                       | -                         | -                          |          | [14]      |
| E. cloacae | 1978, Spain    | Olay   | Erythromycin | 16                | -                                             | -                | -                       | in vitro (CB)                                      | 62%                  | 38%              | 0%                | 0%                       | -                         | -                          |          | [14]      |

Authors considered Synergistic effect when MIC of both antimicrobials was at least fourfold lower over initial MIC; partial synergy when MIC of one antimicrobial was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; Indifferent effect when MIC of both antimicrobials was 2 times lower; antagonism when MIC of both increased 4 times over initial MIC.
Table 7. Cont.

| Strain          | Year and Country | Author | Macrolide | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Macrolide-Resistant (%) | In Vito (Method/In Vivo Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Macrolide Susceptibility Restoration (%) | Comments |
|-----------------|------------------|--------|-----------|--------------------|-----------------------------------------------|-------------------|-------------------------|-------------------------------------------------|------------------------|-------------------|------------------------|------------------------|-------------------------------|------------------------------------------|----------|
| *P. aeruginosa* | 1978, Spain      | Olley  | Erythromycin | 13                | -                                             | -                 | -                       | in vitro (CB)                                  | 53%                    | 46%               | 0%                     | 0%                     | -                             | -                                         |          |
|                 |                  |        |           |                    |                                               |                   |                         |                                                 |                        |                   |                        |                        | Authors considered synergistic effect when MIC of both antimicrobials was at least fourfold lower over initial MIC, partial synergy when MIC of one antimicrobial was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; indifferent effect when MIC of both antimicrobials was 2 times lower; antagonism when MIC of both increased 4 times over initial MIC. |          |
|                 | 1982, Japan      | Kasai  | Midecamycin | 2                 | 0%                                            | 2 (100%)          | 0%                      | in vitro (TK/Animal: peritonitis or subcutaneous infection) | 0%                     | 2 (100%) | 0%                     | 0%                     | -                             | -                                         |          |
|                 |                  |        |           |                    |                                               |                   |                         |                                                 |                        |                   |                        |                        | Authors considered synergistic effect when MIC of both antimicrobials was at least fourfold lower over initial MIC, partial synergy when MIC of one antimicrobial was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; indifferent effect when MIC of both antimicrobials was 2 times lower; antagonism when MIC of both increased 4 times over initial MIC. |          |
| *P. aeruginosa* | 1978, Spain      | Olley  | Erythromycin | 29                | -                                             | -                 | -                       | in vitro (CB)                                  | 38%                    | 59%               | 3%                     | 0%                     | -                             | -                                         |          |

References:
[14]
Table 7. Cont.

| Strain       | Year and Country | Author | Macrolide | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Macrolide-Resistant (%) | In Vitro (Method/In Vivo (animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Macrolide Susceptibility Restoration (%) | Comments                                      | Reference |
|--------------|-----------------|--------|-----------|-------------------|-----------------------------------------------|------------------|-------------------------|-------------------------------------------------|-----------------------|-------------------|--------------------------|-------------------------------|---------------------------------|----------------------------------------|-----------------------------------------------|-----------|
| *S. aureus*  | 1978, Spain     | Olay   | Erythromycin | 34                | -                                             | -                | -                       | in vitro (CB)                                | 26%                   | 68%               | 6%                       | 0%                             | -                               | -                                      | Authors considered Synergistic effect when MIC of both antimicrobials was at least fourfold lower over initial MIC; partial synergy when MIC of one antimicrobial was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; Indifferent effect when MIC of both antimicrobials was 2 times lower; antagonism when MIC of both increased 4 times over initial MIC. | [14] |
| *S. epidermidis* | 2009, Austria   | Presterl | Azithromycin | 11                | -                                             | 2 (18%)          | 5 (45%)                 | in vitro (Microtitre plate assay on Biofilm culture) | -                     | -                 | -                        | -                             | -                               | -                                      | Combination of azithromycin with any of the tested antimicrobial agents did not reduce the biofilm OD compared to the ODs of biofilms treated with single agents. | [56] |
| *S. pseudintermedius* | 2014, Canada   | DiCicco | Clarithromycin | 8                | MRSP (100%)                                    | 5 (62%)          | 8 (100%)                 | in vitro (Microtitre plate assay)              | 5 (62%)               | 2 (25%) | 0%                        | 0%                            | -                               | -                                      | FICI for 1 strains was reported as “Not available”. | [60] |
| Streptococcus spp. | 1978, Spain     | Olay   | Erythromycin | 26                | -                                             | -                | -                       | in vitro (CB)                                | 15%                   | 27%               | 57%                      | 0%                             | -                               | -                                      | Authors considered Synergistic effect when MIC of both antimicrobials was at least fourfold lower over initial MIC; partial synergy when MIC of one antimicrobial was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; Indifferent effect when MIC of both antimicrobials was 2 times lower; antagonism when MIC of both increased 4 times over initial MIC. | [14] |
| *N. gonorrhoeae* | 2015, Switzerland | Hauser | Azithromycin | 8 (4 TK) | AZT-HER (32,%) | 0%             | 1 (12%)                   | in vitro (CB, TK)                            | CK 0%, TK 0%          | CK 0%, TK 0%      | CK 0%, TK 4 (100%) | CK 0%, TK 0%          | 8 (100%) | 4 (100%) | Only 4 strains were tested with TKA. Authors used Enterobacterales FOS breakpoint as presumptive breakpoint for *N. gonorrhoeae* (EUCAST: S $\leq$ 32 mg/L; CLSI: S $\leq$ 64 mg/L). | [57] |
| *N. gonorrhoeae* | 2015, Netherlands | Wind   | Azithromycin | 4                | Anthromycin and Ceftriaxone Resistant (100%) | -                | -                       | in vitro (ET)                                | 0%                    | 0%                | 4 (100%)                | -                             | -                               | -                                      |                           | [54] |
### Table 8. Studies on combination between fosfomycin and glycopeptides. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain         | Year and Country | Author               | Glycopeptide | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Glycopeptide-Resistant (%) | In Vitro Method/Animal and Site of Infection | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Glycopeptide Susceptibility Restoration (%) | Comments | Reference |
|----------------|------------------|----------------------|--------------|--------------------|-------------------------------------------------|-------------------|-----------------------------|-----------------------------------------------|------------------------|-------------------|------------------------|------------------------|-------------------------------|------------------------------------------|----------|-----------|
| A. baumannii   | 2016, Brazil     | Leite                | Vancomycin   | 20                 | OXA-23 (50%), OXA-143 (35%), IMP-type (15%), depletion of OMP 43 kDa (20%) | 19 (95%)          | Natural resistance          | in vitro (CB, TK)                          | 0%                     | 0%                | CB: 20 (100%)           | 0%                     | 0%                            | Breakpoints not available             | TK showed indifferent in all strains. | [83]       |
|                | 2018, China      | Xu                   | Vancomycin   | 3                  | -                                                              | 1 (33%)           | 0%                          | in vitro (CB)                          | 0%                     | 2 (66%) | 1 (33%)               | 0%                     | 1 (100%) | No resistant isolates|                        | In vitro concentrations - VAN (0.5, 1, 2 mg/L), FOS (0.2, 0.4 mg/L). The study also evaluated 15 patients with bacteremia caused by MRSA were treated with FOS in combination with VAN. Of these, 7 patients (46.7%) had negative blood cultures after 48 h of combination therapy. Synergistic concentrations were 64 mg/L for FOS and 2 mg/L for VAN, at 24 h. Indifference was detected with 8 mg/L for TEC at 24 h. Significant reduction of colony count in biofilm model when FOS was in combination with either VAN and TEC after 5 days. All strains had borderline MIC values for VAN (2 mg/L) and TEC (4 mg/L). | [174]     |
|                | 2017, Spain      | Coronado-Alvarez     | Vancomycin   | 4                  | Methicillin resistance (50%)                                 | -                | -                           | in vitro (TK)                          | 0%                     | 4 (100%) | 0%                     | 0%                     | -                             | -                           | The study also evaluated 15 patients with bacteremia caused by MRSA were treated with FOS in combination with VAN. Of these, 7 patients (46.7%) had negative blood cultures after 48 h of combination therapy. Synergistic concentrations were 64 mg/L for FOS and 2 mg/L for VAN, at 24 h. Indifference was detected with 8 mg/L for TEC at 24 h. Significant reduction of colony count in biofilm model when FOS was in combination with either VAN and TEC after 5 days. All strains had borderline MIC values for VAN (2 mg/L) and TEC (4 mg/L). | [63]       |
| S. aureus      |                  |                      |              |                    |                                                                |                  |                             |                                               |                        |                   |                        |                        |                               |                                           |          |           |
|                | 2012, Taiwan     | Tang                 | Vancomycin, teicoplanin | 8           | Methicillin resistance (100%)                                 | 2 (6%)           | VAN: 0%, TEC: 0%            | in vitro (TK)                          | VAN: 8 (100%)            | 0%                | TEC: 8 (100%)           | 0%                     | 0%                            | No resistant isolates                  | No resistant isolates                  | [69]       |
|                | 2011, Taiwan     | Tang                 | Vancomycin   | 5                  | Methicillin resistance (100%)                                 | 0%                | 0%                          | in vitro (TK)                          | 5 (100%)              | 0%                | 0%                     | 0%                     | No resistant isolates                  | No resistant isolates                  | In vitro synergistic concentrations were 2 mg/L for VAN and 64 mg/L for FOS. | [175]     |
### Table 8. Cont.

| Strain Year and Country | Author | Glycopeptide | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Glycopeptide-Resistant (%) | In Vitro (Methods) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Glycopeptide Susceptibility Restoration (%) | Comments | Reference |
|-------------------------|--------|--------------|--------------------|-----------------------------------------------|------------------|---------------------------|-------------------|------------------------|--------------------|------------------------|--------------------------|----------------------------------------|----------------------------------------|----------|---------|
| 2010, Spain             | Pachon-Ibanez | Vancomycin | 1 | hGISA (100%) | 0% | 0% | in vitro (TK); in vivo (mouse, peritonitis) | 1 (100%) | 0% | 0% | 0% | No resistant isolate | No resistant isolate | Resistant (4 mg/L) sub-population frequency: 3.6 × 10⁻⁶ CFU/mL; in vitro synergistic concentrations were 1–2–4 mg/L for FOS and 1–2 mg/L for VAN at 24 h. In vivo combination was significant and effective in reducing bacteremia rates in 57% (n = 8 out of 14) of mice treated. Synergistic concentrations were 8 mg/L for FOS and 1 × MIC for VAN (1, 2 or 4 mg/L, respectively) at 24 h. In vivo synergism at 24 and 48 h. Fixed concentrations of FOS at 8 mg/L and VAN at 1 mg/L. In vivo combination was successful in 10 rabbits (100%) showing sterile vegetations. 1 strain was resistant to VAN (MIC > 32 mg/L). | [36] |
| 2005, Italy             | Pistella   | Vancomycin, teicoplanin | 7 | Methicillin resistance (100%) | 5 (71%) | VAN: 3 (42%); TEC: 6 (85.7%) | in vitro (TK) | VAN: 7 (100%); TEC: 0% | VAN: 0%; TEC: 7 (100%) | 0% | 0% | 7 (100%) | 0% | Synergistic concentrations were 8 mg/L for FOS and 1 × MIC for VAN (1, 2 or 4 mg/L, respectively) at 24 h. In vivo synergism at 24 and 48 h. Fixed concentrations of FOS at 8 mg/L and VAN at 1 mg/L. | [176] |
| 1987, Spain             | Rodriguez  | Vancomycin | 1 | Methicillin resistance (100%) | 0% | 0% | in vitro (TK); in vivo (rabbit, endocarditis) | 1 (100%) | 0% | 0% | 0% | No resistant isolates | No resistant isolates | - | 176 |
| 1985, Spain             | Alvarez    | Vancomycin | 148 | Methicillin resistance (100%) | 15 (10%) | 1 (1%) | in vitro (CB) | 0% | 0% | 0% | 145 (98%) | 3 (2%) | - | - | In vitro synergistic concentrations at 1 mg/L for VAN and 64 mg/L for FOS at 6h and 24h. In vivo significative reduction of biofilm formation in rabbits' tissue (4, 100%). TK showed indifference for all strains, with fixed concentration of FOS at 40 mg/L and VAN at 10 mg/L. | [12] |
| S. aureus, S. epidermidis | 2014, China | Shi | Vancomycin | 3 | (2 S. aureus; 1 S. epidermidis) | Methicillin resistance (62%) | 3 (100%) | 0% | in vitro (TK); in vivo (biofilm in rabbit tissue) | 3 (100%) | 0% | 0% | 0% | 0% | No resistant isolates | In vitro synergistic concentrations at 1 mg/L for VAN and 64 mg/L for FOS at 6h and 24h. In vivo significative reduction of biofilm formation in rabbits' tissue (4, 100%). TK showed indifference for all strains, with fixed concentration of FOS at 40 mg/L and VAN at 10 mg/L. | [62] |
| S. aureus, S. epidermidis | 2001, Austria | Grill | Vancomycin | 7 | (5 S. aureus; 2 S. epidermidis) | S. aureus: GISA 1 (20%); MBSA 1 (20%) | - | 0% | in vitro (CB, TK) | 0% | 0% | CB: S. epidermidis 2 (100%); S. aureus 1 (5%) | CB: S. epidermidis 1 (5%); S. aureus 2 (28%) | - | - | Synergistic concentrations not specified. | [43] |
| S. aureus, S. epidermidis | 1999, Germany | Gehrman | Vancomycin | 33 | (15 S. aureus; 18 S. epidermidis) | - | - | - | - | - | S. aureus: 1 (6%); S. epidermidis: 1 (5%) | S. aureus: 8 (33%); S. epidermidis: 7 (30%); S. aureus: 4 (15%); S. epidermidis: 9 (50%); S. aureus: 0%; S. epidermidis: 1 (5%) | - | - | Synergistic concentrations not specified. | [177] |
### Table 8. Cont.

| Strain                  | Year and Country | Author | Glycopeptide | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Glycopeptide-Resistant (%) | In Vitro (Methods)/In Vivo (Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Glycopeptide Susceptibility Restoration (%) | Comments | Reference |
|-------------------------|------------------|--------|--------------|-------------------|-----------------------------------------------|-------------------|-----------------------------|-------------------------------------------------|------------------------|-----------------|------------------|--------------------------|--------------------------|--------------------------|-----------|-----------|
| E. faecalis, E. faecium, S. aureus, S. epidermidis, CONS | 1986, Italy | Debbia | Teicoplanin  | 76 strains: 30 E. faecalis, 6 E. faecium, 20 S. aureus, 10 S. epidermidis, 10 CoNS | Methicillin resistance (50% of S. aureus) | - | - | in vitro (CB, TK) | CB: 20 (67%) E. faecalis; 4 (67%) E. faecium; 6 (60%) S. aureus; 6 (60%) MRSA; 1 (10%) S. epidermidis; 6 (60%) CONS | CB: 10 (33%) E. faecalis; 2 (33%) E. faecium; 4 (40%) S. aureus; 4 (40%) MRSA; 9 (90%) S. epidermidis; 4 (40%) CONS | 0% | 0% | - | - | - | - | - | [178] |
| S. pneumoniae | 2006, Spain | Ribes | Vancomycin | 2 | Resistance to penicillin (50%) and cephalosporin (100%) | 0% | 0% | in vitro (KB); in vivo (rabbit, meningitis) | 1 (50%) | 1 (50%) | 0% | 0% | No resistant isolates | No resistant isolates | In vitro synergism at 24 h, at concentrations achievable in CSF. In vivo combination significant and effective in eradicating meningitis with sterile blood cultures (8, 100%). | [24] |
| | 1994, France | Doit | Vancomycin | 26 | Isolates not susceptible to penicillin (100%) | 0% | 0% | in vitro (TK) | 0% | 0% | 100% | 0% | No resistant isolates | No resistant isolates | - | - | - | [134] |
| S. epidermidis | 1990, France | Gailland | Vancomycin | 1 | - | 0% | 0% | in vitro (TK) | 1 (100%) | 0% | 0% | 0% | No resistant isolates | No resistant isolates | Synergism at 4 h. Fixed concentrations of FOS at 12.5 mg/L and VAN at 7.5 mg/L. Effective to reduce biofilm formation (1, 100%). | [179] |
| | 1990, Germany | Simon | Vancomycin, teicoplanin | 20 | Methicillin resistant (100%) | 10 (50%) | VAN: 0% TEC: 2 (10%) | in vitro (CB) | VAN: 4 (20%); TEC: 9 (45%) | VAN: 5 (25%); TEC: 6 (30%) | VAN: 11 (55%); TEC: 5 (25%) | VAN: 0% TEC: 0% | No resistant isolates; TEC: NS | - | VAN and VAN no resistant isolates; TEC and TEC no resistant isolates | - | - | [180] |
Table 8. Cont.

| Strain Year and Country | Author | Glycopeptide | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Glycopeptide-Resistant (%) | In Vitro (Methods)/In Vivo (Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Glycopeptide Susceptibility Restoration (%) | Comments | Reference |
|-------------------------|--------|--------------|-------------------|-----------------------------------------------|-------------------|--------------------------|-------------------------------------------------|------------------------|----------------------|-----------------------|-------------------------|-------------------------------|-----------------------------------------|----------|-----------|
| E. faecalis - E. faecium | 2013, Taiwan Tang | Vancomycin- teicoplanin | 19 strains: 9 E. faecalis; 10 E. faecium | Vancomycin resistant (100%) | 5 (55%) E. faecalis; 7 (70%) E. faecium | VAN: 19 (100%) both; TEC: 1 (11%) E. faecalis; 6 (60%) E. faecium | in vitro (TK) | VAN: 3 (33%) E. faecalis; 3 (30%) E. faecium; TEC: 8 (89%) E. faecalis; 3 (30%) E. faecium | 0% | | | | | | [13] |
| Enterobacteriales | 2019, USA Flamm | Minocycline | 7/30 MDR strains (A. baumannii, Enterobacteriales, P. aeruginosa) included 2 ESBL, 2 KPC Enterobacteriales | - | - | - | in vitro (CB) | 4 (20%) | 13 (65%) | 1 (5%) | 0% | - | - | | [38] |
| Enterobacteriales | 1977, Spain Daza | Tetracycline | 100 | 100 (100%) | - | - | in vitro (CB) | 2 (2%) | - | 98% | 0% | - | - | | [66] |
| P. aeruginosa | 2019, USA Flamm | Minocycline | 5 | 7/30 MDR strains (A. baumannii, Enterobacteriales, P. aeruginosa) | - | - | in vitro (CB) | 2 (40%) | 3 (60%) | 0% | 0% | - | - | | [38] |

Table 9. Studies on combination between fosfomycin and tetracyclines. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain Year and Country | Author | Tetracycline | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Tetracycline-Resistant (%) | In Vitro (Methods)/In Vivo (Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Tetracycline Susceptibility Restoration (%) | Comments | Reference |
|-------------------------|--------|--------------|-------------------|-----------------------------------------------|-------------------|--------------------------|-------------------------------------------------|------------------------|----------------------|-----------------------|-------------------------|-------------------------------|-----------------------------------------|----------|-----------|
| Enterobacteriales | 2019, USA Flamm | Minocycline | 20 | 7/30 MDR strains (A. baumannii, Enterobacteriales, P. aeruginosa) included 2 ESBL, 2 KPC Enterobacteriales | - | - | in vitro (CB) | 4 (20%) | 13 (65%) | 1 (5%) | 0% | - | - | | [38] |
| 1977, Spain Daza | Tetracycline | 100 | 100 (100%) | - | - | in vitro (CB) | 2 (2%) | - | 98% | 0% | - | - | | [66] |
| P. aeruginosa | 2019, USA Flamm | Minocycline | 5 | 7/30 MDR strains (A. baumannii, Enterobacteriales, P. aeruginosa) | - | - | in vitro (CB) | 2 (40%) | 3 (60%) | 0% | 0% | - | - | | [38] |
Table 9. Cont.

| Strain          | Year and Country | Author       | Tetracycline | Number of Isolates | Known Resistance Mechanisms or Determinants (% | FOS-Resistant (%) | Tetracycline-Resistant (%) | In Vitro (Methods/In Vivo (Animal and site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Tetracycline Susceptibility Restoration (%) | Comments |
|-----------------|------------------|--------------|--------------|-------------------|-----------------------------------------------|-------------------|-----------------------------|----------------------------------------------------------|------------------------|---------------------|----------------------|-------------------------|---------------------------------|-------------------------------------|----------|
| A. baumannii    | 2013, China      | Zhang        | Minocycline  | 25                | Pan-Drug-Resistant (100%)                      | 100%              | See Comments                | in vitro (CB)                                            | 12%                    | 56%                 | 32%                  | 0%                      | 0%                | 100%                                      | Mean MIC for Minocycline was 16, MIC range 4-16. Authors used CLSI breakpoint for MIN (S ≤ 4 mg/L). |
|                 | 2012, Taiwan     | Tang         | Minocycline  | 33 (8 TK)         | MRSA (100%)                                    | 6%                | 63%                         | in vitro (TK, Biofilm MTT-staining method)               | -                      | -                   | -                   | -                       | -                 | -                                           | Only 9 strains were tested with TK. Biofilm cultures were 94% MIN resistant and 54% FOS resistant. Cases of synergism were observed with FOS+MIN combination. Percentages or other data were not reported by authors. Combination of FOS + MIN determined a statistically significant reduction on ODRs in biofilm cultures compared to single drugs. Authors considered Indifferent effect for FICI between 0.5 and 4. CLSI breakpoint was used for MIN (S ≤ 4 mg/L) and *E. faecalis* FOS breakpoint as presumptive breakpoint for MRSA (S ≤ 64 mg/L). |
| S. aureus       | 2011, China      | Sun          | Minocycline  | 87                | MRSA (100%)                                    | 35 (40%)          | 13 (14%)                    | in vitro (CB)                                            | 76 (87%)               | -                   | 11 (12%)             | 0%                      | 100%              | 92%                                        | [70] |
|                 | 2003, Japan      | Nakazawa     | Minocycline  | 32                | MRSA (100%)                                    | 29 (91%)          | 26 (81%)                    | in vitro (Efficacy Time Index)                           | 10 (31%)               | 1 (3%)               | 21 (65%)             | -                       | -                 | -                                           | *E. faecalis* 2013, Taiwan 2019, USA Descourouez 2012, USA Davis 2015, Netherlands Wind |
| E. faecalis     | 2013, Taiwan     | Tang         | Minocycline  | 9                 | VRE (100%)                                      | 56%               | 89%                         | in vitro (TK, Biofilm Model)                             | TKA 2 (22%); BM 1 (51%) | -                   | -                   | -                       | -                 | -                                           | Additive, Indifferent and antagonistic effect were not evaluated. |
| E. faecium      | 2013, Taiwan     | Tang         | Minocycline  | 10                | VRE (100%)                                      | 70%               | 80%                         | in vitro (TK, Biofilm Model)                             | TKA 4 (48%); BM 1 (50%) | -                   | -                   | -                       | -                 | -                                           | Additive, Indifferent and antagonistic effect were not evaluated. |
|                 | 2012, USA        | Descourouez  | Minocycline  | 32                | VRE (100%)                                      | 9%                | See Comments                | in vitro (TK)                                            | 0%                     | 0%                  | 100%                 | 0%                      | -                 | -                                           | Most of strains were minocycline resistant (MIC range 4-32, mean MIC 16 mg/L). Authors used CLSI breakpoint for DOX (S ≤ 4 mg/L)and *E. faecalis* FOS breakpoint as presumptive breakpoint for VRE (S ≤ 64 mg/L). |
|                 | 2019, USA        | Davis        | Doxycycline  | 24                | VRE (100%)                                      | 96%               | 8%                          | in vitro (ET)                                            | CK 11 (46%); TK 10 (41%) | 0%                  | 0%                   | CK 9%, TK 10 (41%) | CK 0%, TK 0% | -                                           | *N. gonorrhoeae* 2015, Netherlands Wind 2019, USA Davis |
| N. gonorrhoeae  | 2013, Netherlands| Wind         | Minocycline  | 4                 | Anthracyclin and Ceftriaxone Resistant (100%)   | -                 | -                           | in vitro (ET)                                            | 0%                     | 0%                  | 4 (100%)            | -                       | -                 | -                                           | Anthracyclin and Ceftriaxone Resistant (100%) |
Table 10. Studies on combination between fosfomycin and polymyxins. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain | Year and Country | Author | Polymyxin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Polymyxin-Resistant (%) | Known Resistance Mechanisms or Determinants (FOS) | FOS-Resistant (Polymyxin) | Polymyxin-Resistant (FOS) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Polymyxin Susceptibility Restoration (%) | Comments | Reference |
|--------|-----------------|--------|-----------|-------------------|-----------------------------------------------|------------------|-------------------------|-----------------------------------------------|--------------------------|--------------------------|-----------------------------------------------|-----------------------|------------------|---------------------|----------------------|-------------------------|------------------------|----------|-----------|
| Enterobacterales | 2019, USA | Flamm | Colistin | 20 | carbapenem-resistant (5%), KPC (50%), ESBL (10%) | - | - | in vitro (CB, TK) | 1 (5%) | 5 (25%) | 8 (40%) | 0% | - | - | - | 38 |
| | | | | | | | | | For 6 isolates the effect of the combination was indeterminate. The combination was synergistic against FOS-S isolates. Against FOS-R isolates, an additive effect was observed after 12h, but then regrowth occurred. |
| | 2015, UK | Albur | Colistin | 6 | NDM-1 (100%) | 3 (50%) | 0% | in vitro (TK) | 3 (50%) | 0% | 3 (50%) | 0% | - | - | - | - | 35 |
| | E. coli | 2013, Switzerland | Corvec | Colistin | 1 | CTX-M15, ESBL (100%) | 0% | 0% | in vitro (TK), in vivo (dengue-body infection model) | 1 (100%) | 0% | 0% | 0% | - | - | - | - | 75 |
| | | | | | | | | | The combination was synergistic against FOS-S isolates. Against FOS-R isolates, an additive effect was observed after 12h, but then regrowth occurred. |
| | 2011, France | Berçot | Colistin | 1 | NDM-1 | 0% | 0% | in vitro (CB, TK) | 0% | 1 (100%) | 0% | 0% | - | - | - | - | 85 |
| | | | | | | | | | E. coli J53 |
| | 2011, Greece | Samonis | Colistin | 20 | ESBL (100%) | 0% | 0% | in vitro (ET) | 3 (15%) | - | - | 0% | - | - | - | - | 86 |
| | K. pneumoniae | 2020, Turkey | Buket Ertuluk Sengel | Colistin | 17 | KPC-2, KPC-3, NDM-1, OXA-48, VIM-1 (100%) | 3 (60%) | 2 (40%) | in vitro (TK) | 5 (31%) | 2 (12%) | - | - | - | - | - | 82 |
| | | | | | | | | | Synergistic rate inferred from 4 isolates monitored at different times. If evaluated only after 24 h, syn: 40%; add 20%. |
| | | | | | | | | | 3 isolates showed heteroresistance: the total number of experiments was 72 (3 different colistin concentrations tested in 6 different times). |
| | 2018, China | Yu | Colistin | 3 | KPC-2 (100%) | 1 (33%) | 3 (100%) | in vitro (TK) | 2 (66%) | 1 (33%) | 0% | 0% | - | - | - | - | - | 89 |
| | | | | | | | | | E. coli |
| | 2017, Taiwan | Ku | Colistin | 9 | KPC-2 (100%) | 1 (33%) | 3 (100%) | in vitro (TK) | 5 (55%) | 0% | 4 (40%) | 0% | - | - | - | - | - | 86 |
| | | | | | | | | | | | | | | | | | | | |
| | 2018, USA | Bulman | Polymyxin B | 2 | KPC-2 (100%) | 0% | 0% | in vitro (TB, CK), in vivo (infection model) | 2 (100%) | - | - | - | - | - | - | - | - | 75 |
### Table 10. Cont.

| Strain | Year and Country | Author | Polymyxin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Polymyxin-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Polymyxin Susceptibility Restoration (%) | Comments | Reference |
|--------|-----------------|--------|-----------|-------------------|-----------------------------------------------|------------------|-------------------------|-------------------------------------------------|----------------------|------------------|----------------------|------------------------|-------------------------------|---------------------------------|----------|-----------|
| 2014, Sweden | Tängde | Colistin | 4 | VIM (50%), NDM (50%) | 2 (50%) | 0% | in vitro (TK) | 3 (75%) | 0% | 1 (25%) | 0% | - | - | Synergism in 1 VIM- and 2 NDM-producing isolates, although NDM-producing isolates were FOS-R. [146] |
| 2013, Turkey | Evren | Colistin | 12 | OXA-48 (100%) | 11 (92%) | 2 (17%) | in vitro (CB) | 0% | 0% | 0% | 12 (100%) | - | - | - | [74] |
| 2011, France | Berçot | Colistin | 3 | NDM-1 (100%) | 0% | 0% | in vitro (CB, TK) | 0% | 1 (33%) | 2 (66%) | 0% | - | - | - | [68] |
| 2011, Greece | Samonis | Colistin | 50 | carbapenem-resistant (100%) | 3% | 25% | in vitro (ET) | 18 (36%) | - | - | 0% | - | - | - | [60] |
| 2011, Greece | Souli | Colistin | 14 | ESBL (100%) | 3% | 25% | in vitro (ET) | 1 (7%) | - | - | 0% | - | - | - | [66] |
| 2011, Greece | Souli | Colistin | 17 | KPC-2 (100%) | 4 (23%) | 7 (41%) | in vitro (TK) | 2 (12%) | 0% | 15 (88%) | 0% | - | - | - | [60] |
| K. oxytoca | 2011, France | Berçot | Colistin | 1 | NDM-1 | 0% | 0% | in vitro (CB, TK) | 0% | 100% | 0% | 0% | - | - | - | [68] |
| P. rettgeri | 2011, France | Berçot | Colistin | 1 | NDM-1 | 0% | 100% | in vitro (CB, TK) | 0% | 0% | 100% | 0% | - | - | - | [68] |
| 2019, USA | Flamm | Colistin | 5 | - | - | - | in vitro (CB, TK) | 0% | 1 (20%) | 4 (80%) | 0% | - | - | - | [68] |
| P. aeruginosa | 2016, Australia | Walsh | Polymyxin B | 4 | MDR (75%) | 50% | 50% | in vitro (TK) | 19 (18%) | 27 (25%) | - | - | - | - | FOS in combination with polymyxin B increased bacterial killing, but did not suppress emergence of FOS resistance. The total number of experiments was 108 (9 combinations of FOS + CIP at different concentrations, in 3 different times). [76] |
| 2011, Greece | Samonis | Colistin | 15 | MDR (100%) | 6% | 0% | in vitro (ET) | 2 (13%) | - | - | 0% | - | - | - | [68] |
| 2011, Greece | Da | Colistin | 87 | CRPA (100%) | 75% | 4% (587) | in vitro (CB, TK) | 19 (21%) | 29 (33%) | 39 (44%) | 0% | - | 3 (60%) | - | [68] |
Table 10. Cont.

| Strain | Year and Country | Author | Polymyxin | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Polymyxin-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Polymyxin Susceptibility Restoration (%) | Comments | Reference |
|--------|------------------|--------|-----------|-------------------|-----------------------------------------------|-------------------|------------------------|-----------------------------------------------------|-----------------------|-------------------|---------------------|------------------------|-----------------------------|---------------------------------------|----------|-----------|
| A. baumannii-A. calcoaceticus spp. Complex | 2019, USA | Flamm | Colistin | 5 | MDR (20%) | - | - | in vitro (CR, TK) | 2 (40%) | 1 (20%) | 1 (20%) | 0% | - | - | For 1 isolate the effect of the combination was indeterminate. [38] |
| 2020, South Korea | Su Ku | Colistin | 1 | OXA-23 (100%) | 100% | 0% | in vitro (TK), in vivo (mouse, nasal inoculation) | 1 (100%) | 0% | 0% | 0% | - | - | - | [72] |
| 2019, Turkey 2019, China | Sertozluk | Colistin | 23 | carbapenem-resistant (100%) | 100% | 26% | in vitro (CB) | 1 (4%) | 10 (43%) | 12 (52%) | 0% | - | - | - | [185] |
| 2019, China | Bian | Colistin | 9 | carbapenem-resistant (100%) | - | 0% | in vitro (CR, TK) | 1 (11%) | - | - | - | - | - | - | [186] |
| 2018, China | Zhu | Colistin | 21 | carbapenem-resistant (100%) | CoR-AB; carbapenemase-producing efflux-pump (100%) | 100% | 61% (13/21) | in vitro (CR, ET) | 4 (26%) | 7 (46%) | 4 (26%) | 0% | - | - | The authors reported 8 isolates to be colistin-R, but only 3 isolates had MIC > 2. [53] |
| 2018, Thailand | Leslasupari | Colistin | 15 | carbapenem-resistant (100%) | Carb-AB, carbapenemase-producing efflux-pump (100%) | 100% | 0% | in vitro (CR, ET) | - | - | 0% | - | - | - | Treatment in vivo (patients) with COL + FOS lead to death (2/2). [187] |
| 2017, Thailand | Lertstoaatit | Colistin | 17 | - | - | - | in vitro (CR, TK) | - | - | 0% | - | - | - | - | [188] |
| 2016, China 2016, Brazil | Fan | Colistin | 12 | XDR (100%) | OXA-23, OXA-143 (100%) | 100% | 0% | in vivo (mouse, thigh-infection model) | 1 (8%) | - | - | 0% | - | - | - | [189] |
| 2015, China | Leith | Colistin | 20 | XDR (100%) | OXA-23, OXA-143 (100%) | 100% | 33% (7/20) | in vitro (CR, TK, 2-well) | 0% | - | - | - | - | - | - | Synergy (FICI = < 0.5); Indifference (FICI, 0.5–4). Antagonism (FICI: >= 4). [190] |
| 2013, China 2013, Thailand | Wei | Colistin | 50 | XDR (100%) | 94% | 50% | in vitro (CB) | 25 (50%) | 0% | 22 (44%) | 3 (6%) | - | - | - | [190] |
| 2013, China 2011, Thailand | Zhang | Polymyxin B | 25 | FDR (100%) | carbapenem-resistant (100%) | 100% | 100% | in vitro (TK) | 4 (16%) | 11 (44%) | 10 (40%) | 0% | 0% | 25 (100%) | - | [192] |
| 2011, Thailand | Santithampongpraphit | Colistin | 8 | - | - | carbapenem-resistant (100%) | - | - | in vitro (CR, TK) | 13% | - | - | - | - | - | - | [192] |
| N. gonorrhoeae | 2014, Netherlands | Wind | Colistin | 4 | - | - | - | in vitro (ET) | 0% | - | - | - | - | - | - | [54] |
Table 11. Studies on combination between fosfomycin and daptomycin. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strains       | Year and Country | Author               | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Daptomycin-Resistant (%) | In Vitro (Methods/In Vivo (animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Daptomycin Susceptibility Restoration (%) | Comments Reference |
|--------------|-----------------|----------------------|--------------------|-------------------------------------------------|------------------|--------------------------|----------------------------------------------------------|-----------------------|---------------------|------------------------|------------------------|-------------------------------|-----------------------------|-----------------------|
| S. aureus    | 2019, Taiwan    | Lee                  | 100 MRSA (100%)    | 15 (15%)                                        | 0%               | in vitro (CB)             | 37 (57%) (in vitro (CB))                                | 44 (44%)             | 19 (19%)           | 0%                     | -                      | -                             | -                           | All isolates had MIC to daptomycin = 1 (previously selected among 1353 isolates). The authors also performed a retrospective review of 9 patients with diabetes and found that DAP + FOS was the most effective combination. [191] |
| S. aureus    | 2019, Spain     | Coronado-Alvarez     | 4 MRSA (50%)       | -                                               | -                | in vitro (TK)             | 4 (100%) (in vitro (TK))                                 | 0%                   | 0%                 | 0%                     | -                      | -                             | -                           | The authors also performed a retrospective review of 9 patients with diabetes and found that DAP + FOS was the most effective combination. [192] |
| S. aureus    | 2018, Spain     | García-de-la-Marta   | 5 (in vitro) + 1 (in vivo) MRSA (100%) | 0%                                             | 0%               | in vitro (TK)             | in vitro (100%), in vivo (100%) (rabbit, endocarditis) | 0%                   | 0%                 | 0%                     | -                      | -                             | -                           | |
| S. aureus    | 2017, Turkey    | Aktas                | 25 MRSA (100%)     | 11 (44%)                                        | 0%               | in vitro (CB)             | 25 (100%) (in vitro (CB), animals)                      | 0%                   | 0%                 | 0%                     | -                      | -                             | -                           | |
| S. aureus    | 2015, Austria   | Lingenscheid         | 1 MRSA (100%)      | 0%                                             | 0%               | in vitro (TK), in vivo (rabbit, endocarditis)            | 1 (100%) (in vitro (TK), in vivo (100%))               | 0%                   | 0%                 | 0%                     | -                      | -                             | -                           | The combination was bactericidal against 9 (52%) isolates. The authors also reported the case reports of 3 patients with S. aureus (1 MSSA, 2 MRSA) successfully treated with high-dose DAP (100 mg/kg/day) + FOS. FOS and FOS + DAP were significantly superior to placebo and to DAP alone. FOS + DAP was not more effective than FOS alone. [193] |
| S. aureus    | 2013, Spain     | Garrigos             | 1 MRSA (100%)      | 0%                                             | 0%               | in vitro (TK)             | in vitro: 0%, in vivo: 1 (100%) (fibrosis, body fluid) | 0%                   | 0%                 | 0%                     | -                      | -                             | -                           | |
| S. aureus    | 2012, Spain     | Miró                 | 14 MRSA (35%), GISA (14%) | 0%                                             | 1 (7%)           | in vitro (TK)             | 11 (79%) (in vitro: 100%), in vivo: 1 (100%) (rabbit, endocarditis) | 3 (21%)              | 0%                 | 0%                     | -                      | -                             | -                           | |
| S. aureus    | 2011, Austria   | Poeppl               | 1 MRSA (100%)      | 0%                                             | 0%               | in vitro (TK)             | 0% (in vitro (TK), osteomyelitis)                       | 0%                   | 1 (100%)           | 0%                     | -                      | -                             | -                           | |
| E. faecalis  | 2019, China     | Zheng                | 4 (TK) + 4 biofilm assay | -                                             | 1 (12%)          | 2 (25%)                  | TK: 4 (100%), Biofilm assay: 5 (75%)                    | 0%                   | TK: 0%              | Biofilm assay: 1 (25%) | -                      | -                             | -                           | TK performed on 4 linezolid-R isolates. Biofilm assay performed on 4 linezolid-S isolates. DAP + FOS demonstrated significantly more anti-biofilm activity than DAP or FOS alone. The isolate was highly R to gentamicin. DAP + FOS sterilized more values (99% VS 35%) than DAP alone. Despite this, the combination in vivo was considered 'additive' because it was not possible to demonstrate a statistically significant superiority in comparison with DAP alone. All isolates were highly R to gentamicin. The bactericidal effect of DAP alone was not increased by the addition of FOS. [194] |
| E. faecalis  | 1992, USA       | Rice                 | 1 -                | 0                                               | 1 (100%)         | in vitro (TK), in vivo (100%) (rat, endocarditis) | in vitro (TK), in vivo (100%) (rat, endocarditis) | 0%                   | 0%                 | 0%                     | -                      | -                             | -                           | |
| E. faecalis  | 1989, USA       | Rice                 | 21 -               | 0                                               | 0                  | in vitro (TK)             | 21 (100%) (in vitro (TK))                               | 0%                   | 0%                 | 0%                     | -                      | -                             | -                           | |
| E. faecalis  | 2013, USA       | Descourouez          | 4 VRE (100%)       | 0%                                             | 0%               | in vitro (TK)             | 4 (100%) (in vitro (TK))                                | 0%                   | 0%                 | 0%                     | -                      | -                             | -                           | The combination resulted strongly bactericidal. [195] |
| E. faecalis  | 1988, Italy     | Debbia               | 50 -               | -                                               | -                 | in vitro (CB, TK)        | CB: 80% (TK: 85%)                                       | 0%                   | CB: 20% (TK: 5%)    | 0%                     | -                      | -                             | -                           | A total of 50 strains was tested with CB, and only 20 strains were tested with TK. [196] |

Staphylococcus spp., Enterococcus spp. 1990, Italy Delbua 50 - - in vitro (CB, TK) CB: 80% (TK: 85%) 0% CB: 20% (TK: 5%) 0% - - A total of 50 strains was tested with CB, and only 20 strains were tested with TK. [197]
Table 12. Studies on combination between fosfomycin and tigecycline. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain | Year and Country | Author | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Tigecycline-Resistant (%) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Tigecycline Susceptibility Restoration (%) | Comments | Reference |
|--------|------------------|--------|--------------------|-----------------------------------------------|------------------|--------------------------|-----------------------|---------------------|---------------------|--------------------------|-------------------------------------|---------------------------------|-----------|-----------|
| Enterobacterales | 2019, USA | Flamm | 20 | 7/30 MDR strains (A. aerogenes, Enterobacteriaceae e P. aeruginosa) included 2 ESBL e 2 KPC | - | - | in vitro (CB) | 5 (25%) | 10 (50%) | 5 (25%) | 0% | - | - | Authors considered Partial Synergy when FICI was between 0.5–1 and Additive effect for FICI = 1. [38] |
| | 2017, Taiwan | Ku | 9 | ESBL KP producing | 4 (44.4%) | 4 (44%) | in vitro (TK) | 6 (66%) | 0% | 3 (33%) | 0% | - | - | - | [84] |
| | 2011, France | Bericot | 9 | NDM-1 KPC (100%) | 2 (22%) | 3 (33%) | in vitro (CB) | 0% | - | 9 (100%) | 0% | - | - | - | [65] |
| | 2013, Switzerland | Corvec | 1 | % HSE-1 (100%) | ESBL and Ciprofloxacin resistant | 0% | 0% | in vitro (TK); in vivo (Guinea pigs, cage infection) | TK: 0%; in vivo: 0% | TK: 100%; in vivo: 0% | 0% | - | - | - | [73] |
| E. coli | 2011, Greece | Samonis | 20 | ESBL (100%) | 0% | 1 (5%) | in vitro (ET) | 5 (25%) | - | 15 (75%) | 0% | - | - | - | [86] |
| | 2019, China | Huang | 30 | KPC (100%) | 19 (63%) | 11 (36%) | in vitro (ET, CB) | ET: 5 (16%); CK: 4 (13%) | ET: 9 (30%); CK: 11 (36%) | ET: 16/15 (50%); CK: 15/15 (50%) | 0% | ET: 14/19 (73%); CK: 6/55 (40%); ET: 5/11 (45%); CK: 7/13 (53%) | - | - | - | [88] |
| K. pneumoniae | 2019, Greece | Papoutsaki | 11 | KPC (100%) | 35% | 96% | in vitro (ET, TK) | ET: 16/33 (48%); TKA: 1/22 (4%) | ET: 17/33 (51%); TKA: 2/22 (9%) | 0% | 0% | - | - | ET performed three times with different methods: a) Elisa/Agar method, b) Cross formation method, c) MIC/MIC ratio method. TK was performed two times: a) TIG 1,3 mg/L + FOS 0,5xMIC and b) TIG 1,3 mg/L + FOS 30 mg/L. [87] |
| | 2017, China | Yu | 136 | KPC (100%) | 78 (57%) | 25 (18%) | in vitro (CB, TK) | CK: 2 (1%); TKA: 0% | CK: 113 (85%); TKA: 5 (7%) | CK: 19 (14%); TKA: 2 (2%) | CK: 2 (1%); TKA: 0% | - | - | Only 4 strains were tested with TK. [89] |
| | 2013, Turkey | Evren | 12 | OXA-48 (100%) | 11 (92%) | 5 (41%) | in vitro (CB) | 4 (33%) | 6 (50%) | 2 (18%) | 0% | - | - | Authors considered Indistinguishable effect for FICI between 0.5 and 4. In vivo experiment: bacterial count using FOS + TIG combination was reduced ≥ 2 log over single antimicrobials. [74] |
| | 2011, Greece | Samonis | 63 | Serine-KPC (77%); MBL (1%); ESBL (21%) | 1 (1%) | 10 (15%) | in vitro (ET) | 18 (27%) | - | 47 (72%) | 0% | - | - | - | [86] |
Table 12. Cont.

| Strain         | Year and Country | Author                  | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Tigecycline-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Tigecycline Susceptibility Restoration (%) | Comments | Reference |
|----------------|------------------|-------------------------|--------------------|-----------------------------------------------|------------------|--------------------------|-------------------------------------------------|-----------------------|---------------------|---------------------|--------------------------|------------------------------------------|------------------------------------------|----------|-----------|
| P. aeruginosa  | 2011, Greece     | Samonis                 | 15                 | MDR (100%)                                    | 1 (6%)           | 15 (100%)                | in vitro (ET)                                | 2 (13%)               | -                   | 13 (86%)            | 0%                       | -                                        | -                                         | Authors considered Indifferent effect for FICI between 0.5 and 4. In vivo experiment: bacterial count using FOS + TIG combination was reduced ≥ 2 log over single antimicrobials | [86]     |
| A. baumannii   | 2019, USA        | Flamm                   | 5                  | 7/50 MDR strains (A. baumannii, Enterobacterales e P. aeruginosa) | -                | -                        | in vitro (CB)                                | 0%                   | 4 (80%)             | 1 (20%)             | 0%                       | -                                        | -                                         | Authors considered Partial Synergy when FICI was between 0.5–1 and Additive effect for FICI = 1. Any synergistic effect was reported. Additive, Indifferent and antagonistic effect were not evaluated. | [38]     |
|                | 2016, Netherlands| Leite                   | 20                 | Colistin-Resistant (60%)                       | 20 (100%)        | 5%                       | in vitro (CB, 2-Well Method)                  | 0%                   | -                   | -                   | -                        | -                                         | -                                         |                      |           |
|                | 2018, Italy      | Simonetti               | 15                 | MRSA (100%)                                   | 0                | 0%                       | in vitro (CB); in vivo (mice, wound infection) | 12 (80%)              | -                   | 3 (20%)             | 0%                       | -                                        | -                                         | Authors considered Indifferent effect for FICI between 0.5 and 4. In vivo experiment: bacterial count using FOS + TIG combination was reduced ≥ 2 log over single antimicrobials. Only 8 strains were tested with Time-kill Assay. Biofilm cultures were 100% TIG resistant and 94% FOS resistant. No FICI were reported by authors, no synergistic effect was seen on any strains. | [80]     |
|                | 2012, Taiwan     | Tang                    | 33 (8 TK)          | MRSA (100%)                                   | 6%               | 0%                       | in vitro (TK, Biofilm Model)                  | 0%                   | -                   | 100%                | 0%                       | -                                        | -                                         | Authors considered Indifferent effect for FICI between 0.5 and 4. In vivo experiment: bacterial count using FOS + TIG combination was reduced ≥ 2 log over single antimicrobials. | [66]     |
|                | 2019, Thailand   | Hemapampairoa           | 12                 | VRE (100%)                                     | 12 (100%)        | 3 (25%)                  | in vitro (CB)                                | 1 (8%)                | 9 (79%)             | 2 (18%)             | 0%                       | -                                        | -                                         | Authors considered Indifferent effect for FICI between 0.5 and 4. In vivo experiment: bacterial count using FOS + TIG combination was reduced ≥ 2 log over single antimicrobials. Additive, Indifferent and antagonistic effect were not evaluated. | [55]     |
| E. faecium     | 2018, Italy      | Simonetti               | 15                 | -                                              | 0%               | 0%                       | in vitro (CB); in vivo (mice, wound infection) | 12 (80%)              | -                   | 3 (20%)             | 0%                       | -                                        | -                                         | Authors considered Indifferent effect for FICI between 0.5 and 4. In vivo experiment: bacterial count using FOS + TIG combination was reduced ≥ 2 log over single antimicrobials. Additive, Indifferent and antagonistic effect were not evaluated. | [90]     |
|                | 2013, Taiwan     | Tang                    | 9                  | VRE (100%)                                     | 56%              | 0%                       | in vitro (TK, Biofilm Model)                  | TKA: 3 (33%); BM: 5 (56%) | -                   | -                   | -                        | -                                        | -                                         |                      | [13]      |
| E. faecium     | 2019, Thailand   | Hemapampairoa           | 12                 | VRE (100%)                                     | 12 (100%)        | 3 (25%)                  | in vitro (CB)                                | 1 (8%)                | 9 (79%)             | 2 (18%)             | 0%                       | -                                        | -                                         |                       |           |
|                | 2018, Italy      | Simonetti               | 15                 | -                                              | 0%               | 0%                       | in vitro (CB)                                | 10 (66%)              | -                   | 5 (33%)             | 0%                       | -                                        | -                                         | Authors considered Indifferent effect for FICI between 0.5 and 4. In vivo experiment: bacterial count using FOS + TIG combination was reduced ≥ 2 log over single antimicrobials. Additive, Indifferent and antagonistic effect were not evaluated. | [90]     |
|                | 2013, Taiwan     | Tang                    | 10                 | VRE (100%)                                     | 70%              | 0%                       | in vitro (TK, Biofilm Model)                  | TKA: 3 (38%); BM: 1 (10%) | -                   | -                   | -                        | -                                        | -                                         |                      | [13]      |
| N. gonorrhoeae | 2015, Netherlands| Wind                    | 4                  | Amoxicillin and Clavulanic Acid Resistant (100%) | -                | -                        | in vitro (ET)                                | 0%                   | 0%                  | 4 (100%)            | -                        | -                                        | -                                         |                       |           |
Table 13. Studies on combination between fosfomycin and linezolid. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain     | Year and Country | Author            | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Linezolid-Resistant (%) | In Vitro (Methods)/In Vivo (Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Linezolid Susceptibility Restoration (%) | Comments | Reference |
|------------|------------------|-------------------|--------------------|-------------------------------------------------|-------------------|--------------------------|----------------------------------------------------------|------------------------|----------------------|------------------------|-------------------------------|---------------------------------|------------------------------------------|-----------|-----------|
| S. aureus  | 2018, China      | Chen              | 11 (3 TK)          | MRSA (50%)                                                    | 0%                | 0%                       | in vitro (CB, TK)                                          | 8 (72%); TK 3 (100%) | CK: 3 (27%); TK: 0% | CK: 0%; TK: 0%           | CK: 0%; TK: 0%               | -                               | -                                        | Only 3 strains were tested with TK. For the same 3 strains, the authors also evaluated Post-Antibiotic Effect (PAE) of LZD alone and in combination with FOS. PAE of LZD + FOS seemed to be increased with the increase in time of exposure, even if no statistically significant difference was found. Synergy was defined as a reduction > 3 log CFU/mL over antimicrobial agent alone, additive effect was defined as a reduction < 3 log CFU/mL. Synergistic effect was demonstrated only when 4 × MIC LZD + 2 × MIC FOS were used, 1 × MIC LZD + 2 × MIC FOS regimen showed Additive effect. Only 1 strain was tested with Time–kill Assay. The authors also evaluated in vitro and in vivo efficacy of LIN + FOS on MRSA biofilm (all 3 strains), demonstrating a synergistic effect only in vitro when using 1/2 MIC LZD + 1/2 MIC FOS and not with lower concentrations. The authors considered Indifferent effect for FICI between 0.5 and 4. Fosfomycin MIC range in combination was 2-32 mg/L, LZD MIC in combination was 0,125-1 mg/L. | [198]       |
| S. aureus  | 2018, Spain      | Coronado-Alvarez 2| 2                  | MRSA (100%)                                                  | -                 | -                        | in vitro (TK)                                              | 2 (100%) | 0%                   | 0%                     | 0%                           | -                               | -                                        | -                      | [63]       |
| S. aureus  | 2016, China      | Chai              | 3 (1 TK)           | MRSA (100%)                                                  | 2 (66%)           | 0%                       | in vitro (CB, TK)                                          | CK: 3 (100%); TK: 1 (100%) | CK: 0%; TK: 0% | CK: 0%; TK: 0%           | CK: 0%; TK: 0%               | 100%                            | 100%                                      | -                      | [94]       |
| S. aureus  | 2014, China      | Xu-Hong           | 102                | MRSA (100%)                                                   | 0%                | -                        | in vitro (CB)                                              | 100 (98%) | 2 (2%)               | 0%                     | 100%                          | 100%                            | -                                        | -                      | [199]      |
Table 13. Cont.

| Year and Country | Author          | Number of Isolates | Strain (%) | FOS-Resistant (%) | Linezolid-Resistant (%) | In Vitro (Methods) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | Comments | Reference |
|------------------|-----------------|--------------------|------------|-------------------|-------------------------|--------------------|------------------------|---------------------|------------------------|-------------------------|----------|-----------|
| 2012, Taiwan     | Tang            | 33 (8 TK)          | MRSA (100%)| 6%                | 0%                      | in vitro (TK, Biofilm, MTT-staining method) | -                     | -                   | -                      | -                      | Only 8 strains were tested with Time–kill Assay. Biofilm cultures were 100% LZD resistant and 94% FOS resistant. Combination of FOS + LZD determined a statistically significant reduction on OD6s in biofilm cultures. | [60]     |
| 2010, Spain      | Pachón-Ibáñez  | 1                  | GISA 100%  | Gentamicin Intermediate S. aureus | -                       | -                   | -                      | -                   | -                      | -                      | In vivo experiment on mice showed a higher rate of blood culture negativization when using FOS + LZD therapy (57%) than using FOS or LZD alone (43% and 27% respectively). Synergistic effect at CB was confirmed with TK on 4 strains. The authors did not consider additive effect. They also performed Transmission Electron Microscopy, demonstrating profound morphological alteration of 2 strains when using FOS + LZD, which were not seen using FOS or LZD alone. TKAs showed synergism, but bacteriostatic effect. In vivo experiment showed statistically significant higher efficacy of high-dose LZD + FOS combination, then high dose of FOS or LZD alone, but low-dose combination had no significant differences with monotherapy or high-dose combination. | [36]     |
| 2006, Spain      | Sahuquillo Arce | 5 (4 TK)           | -          | 0%                | 0%                      | in vitro (CB, TK)    | 1 (100%)              | 0%                  | 0%                    | 0%                      | Synergistic effect at CB was confirmed with TK on 4 strains. TKAs showed synergism, but bacteriostatic effect. In vivo experiment showed statistically significant higher efficacy of high-dose LZD + FOS combination, then high dose of FOS or LZD alone, but low-dose combination had no significant differences with monotherapy or high-dose combination. | [200]    |
| 2001, Austria    | Grif            | 5 (1 TK)           | MRSA (60%) | 0%                | 0%                      | in vitro (CB, TEM)   | CK: 5 (100%); TK: 0% | -                   | -                      | -                      |                      | [43]     |
| 2018, China      | Li              | 4                  | MRSA (50%) | 0%                | 0%                      | in vitro (CB, TK); in vivo (Galleria mellonella Survival Assay) | CK: 4 (100%); TK: 0% | CK: 0%; TK: 0% | CK: 0%; TK: 0% | CK: 0%; TK: 0% |                      | [95]     |
| Strain | Year and Country | Author | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Linezolid-Resistant (%) | In Vitro (Methods)/In Vivo (Animal and Site of Infection) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Linezolid Susceptibility Restoration (%) | Comments | Reference |
|--------|-----------------|--------|-------------------|-----------------------------------------------|------------------|------------------------|-------------------------------------------------|------------------------|----------------|---------------------|---------------------|-------------------------|-------------------------------|---------|----------|
| S. epidermidis | 2001, Austria | Grif | 2 | - | 0% | 0% | in vitro (CB) | 2 (100%) | - | 0% | 0% | - | - | The authors did not consider additive effect. They also performed Transmission Electron Microscopy, demonstrating profound morphological alteration of 2 strains when using FOS + LZD, which were not seen using FOS or LZD alone. [43] |
| E. faecalis | 2013, Taiwan | Tang | 9 | VRE (100%) | 56% | 0% | in vitro (TK, Biofilm Model) | TKA: 0%; BM: 0% | - | - | - | - | - | The authors did not consider additive, indifferent or antagonistic effect. Transmission Electron Microscopy, demonstrated more morphological alterations when using FOS + LZD, than using FOS or LZD alone. [13] |
| | 2019, China | Qi | 2 | VRE (90%) | 2 (100%) | 0% | in vitro (CR, TK, TEM) | CK: 0%; TK: 0% | CK: 2 (100%); TK: 1 (50%) | CK: 0%; TK: 1 (50%) | CK: 0%; TK: 0% | 2 (100%) | 2 (100%) | Transmission Electron Microscopy, demonstrated more morphological alterations when using FOS + LZD, than using FOS or LZD alone. [201] |
| | 2012, USA | Descoutures | 32 | VRE (100%) | 9% | 3% | in vitro (TK) | See comments | See comments | 0% | 0% | - | - | The authors did not consider additive, indifferent or antagonistic effect. The authors considered MIC ≤ 64 mg/L as FOS breakpoint. FOS combined with LZD was either synergistic or additive yet bacteriostatic. Percentages of strains on which there was synergistic effect were not reported. Transmission Electron Microscopy, demonstrated more morphological alterations when using FOS + LZD, than using FOS or LZD alone. In vivo experiment showed higher survival rates of larvae when using FOS + LZD than LZD alone, but similar rates using FOS alone. [201] |
| E. faecium | 2012, USA | Descoutures | 32 | VRE (100%) | 9% | 3% | in vitro (CR, TK, TEM; in vivo (Cadentia Melonella Survival Assay)) | CK: 2 (50%); TK: 2 (50%) | CK: 1 (25%); TK: 1 (25%) | CK: 1 (25%); TK: 1 (25%) | 0% | 3 (75%) | 4 (100%) | - | - | The authors did not consider additive, indifferent or antagonistic effect. The authors considered MIC ≤ 64 mg/L as FOS breakpoint. FOS combined with LZD was either synergistic or additive yet bacteriostatic. Percentages of strains on which there was synergistic effect were not reported. Transmission Electron Microscopy, demonstrated more morphological alterations when using FOS + LZD, than using FOS or LZD alone. In vivo experiment showed higher survival rates of larvae when using FOS + LZD than LZD alone, but similar rates using FOS alone. [201] |
Table 14. Studies on combination between fosfomycin and rifampin. CB: checkerboard assay; TK: time–kill assay; ET: E-test.

| Strain                  | Year and Country | Author            | Number of Isolates | Known Resistance Mechanisms or Determinants (%) | FOS-Resistant (%) | Rifampin-Resistant (%) | In Vitro (Methods/In Vivo (Animal and Site of Infection)) | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | FOS Susceptibility Restoration (%) | Rifampin Susceptibility Restoration (%) | Comments | Reference |
|-------------------------|------------------|-------------------|--------------------|-------------------------------------------------|-------------------|------------------------|----------------------------------------------------------|------------------------|----------------------|------------------------|------------------------|-----------------------------|-------------------------------------|-----------|-----------|
| E. coli                 | 1978, Spain      | Olay              | 17                 | -                                               | -                 | -                      | in vitro (CB, in vivo (mouse, peritonitis))               | 1 (5.8%)               | 9 (52.9%)            | 7 (41.2%)             | 0%                     | -                           | -                                  | -         | [14]      |
| A. baumannii            | 2016, Brazil     | Leite             | 20                 | OXA-23, OXA-43 (100%)                            | (100%)            | (100%)                 | in vitro (CB, TK)                                        | 0%                     | -                    | -                      | -                      | -                           | -                                  | -         | [10]      |
| E. coli                 | 2010, Italy      | Simonetti         | 16                 | MRSA (100%)                                     | 0%                | 2 (12%)                | in vitro (ET, TK), in vivo (mouse, wound infection)     | 16 (100%)              | 0%                   | 0%                     | 0%                     | -                           | -                                  | -         | [10]      |
| A. baumannii            | 2014, Switzerland| Mihalcescu        | 1                  | MRSA (100%)                                     | 0%                | 0%                     | in vitro (ET, TK), in vivo (foreign-body infection model) | 0%                     | 0%                   | 0%                     | 0%                     | -                           | -                                  | -         | [10]      |
| S. aureus               | 2013, China      | Tang              | 8                  | MRSA (100%)                                     | 0%                | 8 (100%)               | in vitro (biofilm assay)                                 | 4 (50%)                | -                    | -                      | -                      | -                           | -                                  | -         | [11]      |
| S. aureus               | 2012, Taiwan     | Carrongos         | 1                  | MRSA (100%)                                     | -                 | -                      | in vitro (TK), in vivo (rat, tissue cage infection)      | -                      | -                    | -                      | -                      | -                           | -                                  | -         | [12]      |
| A. baumannii            | 2012, Taiwan     | Garrigos          | 35                 | MRSA (100%)                                     | 6% (planktonic) 94% (biofilm) | 0% (planktonic) 9% (biofilm) | in vitro (TK)                                        | 0%                     | -                    | -                      | -                      | -                           | -                                  | -         | [12]      |
| S. aureus               | 2001, Austria    | Gelf              | 5                  | MRSA (100%)                                     | -                 | -                      | in vitro (CB, TK)                                        | 100%                   | -                    | -                      | -                      | -                           | -                                  | -         | [10]      |
| A. baumannii            | 1997, France     | Quentin           | 6                  | -                                               | 33%               | 0%                     | in vitro (TK)                                            | 0%                     | 0%                   | 20%                    | 33%                    | -                           | -                                  | -         | [10]      |
| E. faecalis             | 2018, Italy      | Simonetti         | 16                 | -                                               | 2 (12%)           | 2 (12%)                | in vitro (CB, TK), in vivo (mouse, wound infection)     | 12 (75%)               | 0%                   | 4 (25%)               | 0%                     | -                           | -                                  | -         | [9]       |
| A. baumannii            | 2013, Taiwan     | Tang              | 9                  | VRE (100%)                                      | 56%               | 11%                    | in vitro (TK, biofilm)                                   | 12 (35%)               | 0%                   | 4 (25%)               | 0%                     | -                           | -                                  | -         | [10]      |
| S. epidermidis          | 2011, Austria    | Grif              | 2                  | MRSA (100%)                                     | -                 | -                      | in vitro (CB, TK)                                        | 0%                     | 0%                   | -                      | -                      | -                           | -                                  | -         | [10]      |
| S. epidermidis          | 1984, Germany    | Doit              | 26                 | -                                               | 0%                | 0%                     | in vitro (TK)                                            | 0%                     | 100%                 | 0%                     | -                      | -                           | -                                  | -         | [134]     |
| S. epidermidis, S.      | 2017, Germany    | Gonzalez Moreno   | 3                  | -                                               | 33%               | 0%                     | in vitro (ET)                                            | 1 (100%)               | 0%                   | -                      | -                      | -                           | -                                  | -         | [9]       |
| pyogenes S. oralis      |                   |                   |                    |                                                  |                   |                                                     |                                                          |                        |                      |                         |                        |                              |                              |           |           |
| E. faecalis             | 2018, Taiwan     | Simonetti         | 16                 | -                                               | 2 (13%)           | 2 (13%)                | in vitro (CB, TK), in vivo (mouse, wound infection)     | 11 (73%)               | 0%                   | 4 (27%)               | 0%                     | -                           | -                                  | -         | [9]       |
| A. baumannii            | 2013, Taiwan     | Tang              | 9                  | VRE (100%)                                      | 70%               | 90%                    | in vitro (TK, biofilm)                                   | 11 (73%)               | 0%                   | 4 (27%)               | 0%                     | -                           | -                                  | -         | [10]      |
| S. epidermidis          | 2011, Austria    | Grif              | 2                  | MRSA (100%)                                     | -                 | -                      | in vitro (CB, TK)                                        | 2 (100%)               | -                    | -                      | -                      | -                           | -                                  | -         | [11]      |
| A. baumannii            | 1997, France     | Quentin           | 3                  | -                                               | NA                | NA                     | in vitro (TK)                                            | 0%                     | 0%                   | 0%                     | -                      | -                           | -                                  | -         | [12]      |
| N. gonorrhoeae          | 2015, Netherlands| Wind              | 4                  | -                                               | -                 | -                      | in vitro (ET)                                            | 1 (25%)                | -                    | -                      | -                      | -                           | -                                  | -         | [14]      |

Comments: RIF antagonizes FOS. In particular, it antagonizes FOS against susceptible and intermediate isolates to RIF. The combination resulted indifferent against RIF-resistant isolates. For 2 isolates it was not possible to infer their susceptibility to RIF.
Table 15. Effect of FOS in combination with different antibiotics: overview.

| Antibiotic Class                                      | Strains | Number of Studies | Number of Isolates | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | Comments                                                                 |
|-------------------------------------------------------|---------|-------------------|--------------------|------------------------|---------------------|------------------------|------------------------|--------------------------------------------------------------------------|
| Penicillins, penicillins + β-lactamase inhibitors, penicillinase-resistant penicillins |                     |                   |                    |                        |                     |                        |                        |                                                                          |
| P. aeruginosa                                         | 6       | 235               | 13                 | 51                     | 19                  | 28                     |                        | One study [1] reported high rates of indifferent effect of FOS + PIP/TAZ against PIP/TAZ-R isolates. |
| Acinetobacter spp.                                    | 1       | 5                 | 60                 | 60                     | 20                  | 0                      | 45                     |                                                                          |
| Staphylococcus spp.                                   | 7       | 295               | 60                 | 50                     | 15                  | 33                     | 10                     |                                                                          |
| Streplococcus spp.                                    | 6       | 119               | 30                 | 30                     | 55                  | 15                     | -                      |                                                                          |
| Enterococcus spp.                                     | 4       | 60                | 25                 | 25                     | 0                   | 42                     | 10                     | Antagonistic effect observed in biofilms of some E. faecalis isolates.    |
| Cephalosporins, cephalosporins + β-lactamase inhibitors |                     |                   |                    |                        |                     |                        |                        |                                                                          |
| P. aeruginosa                                         | 13      | 318               | 36                 | 36                     | 40                  | 23                     | 1                      | Antagonistic effect against 4 P. aeruginosa isolates [22].                |
| Acinetobacter spp.                                    | 2       | 39                | 8                  | 8                      | 3                   | 3                      | 9                      | Effect of the combination indeterminate on 33 isolates.                  |
| Staphylococcus spp.                                   | 12      | 284               | 97                 | 97                     | 12                  | 8                      | 1                      | Great heterogeneity of results.                                          |
| Streplococcus spp.                                    | 6       | 63                | 33                 | 33                     | 59                  | 8                      | -                      |                                                                          |
| Enterococcus spp.                                     | 2       | 77                | 58                 | 58                     | 0                   | 32                     | -                      |                                                                          |
| N. gonorrhoeae                                         | 3       | 44                | 0                  | 0                      | 5                   | 95                     | -                      |                                                                          |
| Carbapenems                                            |                     |                   |                    |                        |                     |                        |                        |                                                                          |
| P. aeruginosa                                         | 15      | 445               | 29                 | 29                     | 25                  | 36                     | 1                      |                                                                          |
| Acinetobacter spp.                                    | 5       | 105               | 28                 | 28                     | 17                  | 22                     | -                      |                                                                          |
| Gram + cocci                                          | 23      | 542               | 43                 | 43                     | 37                  | 19                     |                        |                                                                          |
| N. gonorrhoeae                                         | 1       | 4                 | 0                  | 0                      | 75                  | 25                     | -                      |                                                                          |
| Monobactams                                            |                     |                   |                    |                        |                     |                        |                        |                                                                          |
| P. aeruginosa                                         | 3       | 138               | 25                 | 25                     | 54                  | 17                     |                        |                                                                          |
| Acinetobacter spp.                                    | 18      | 264               | 17                 | 17                     | 12                  | 69                     | -                      |                                                                          |
| Staphylococcus spp.                                   | 3       | 41                | 4                  | 4                      | 36                  | 38                     | 5                      | Synergism rates not concordant in all studies.                            |
| N. gonorrhoeae                                         | 7       | 90                | 37                 | 37                     | 9                   | 34                     | -                      |                                                                          |
| Quinolones                                             |                     |                   |                    |                        |                     |                        |                        |                                                                          |
| P. aeruginosa                                         | 18      | 263               | 42                 | 42                     | 36                  | 38                     | 5                      | Synergism rates not concordant in all studies.                            |
| Acinetobacter spp.                                    | 3       | 41                | 4                  | 4                      | 36                  | 38                     | 5                      | Synergism rates not concordant in all studies.                            |
| Staphylococcus spp.                                   | 7       | 90                | 37                 | 37                     | 9                   | 34                     | -                      |                                                                          |
| N. gonorrhoeae                                         | 1       | 4                 | 0                  | 0                      | 0                   | 100                    | -                      |                                                                          |
| Aminoglycosides                                        |                     |                   |                    |                        |                     |                        |                        |                                                                          |
| P. aeruginosa                                         | 19      | 713               | 20                 | 20                     | 31                  | 36                     |                        | Synergism rates not concordant in all studies.                            |
| Acinetobacter spp.                                    | 23      | 440               | 43                 | 43                     | 29                  | 27                     | 1                      | Synergism rates not concordant in all studies.                            |
| S. aureus                                             | 5       | 102               | 37                 | 37                     | 5                   | 18                     | -                      | Synergism rates not concordant in all studies.                            |
| Streplococcus spp.                                    | 8       | 301               | 26                 | 26                     | 4                   | 53                     | 1                      | Antagonistic effect of FOS + gentamicin against 4 isolates [12].           |
| E. faecalis                                            | 1       | 16                | 0                  | 0                      | 52                  | 48                     | -                      |                                                                          |
| N. gonorrhoeae                                         | 1       | 8                 | 62                 | 62                     | 13                  | 25                     | -                      |                                                                          |
| H. influenzae                                          | 1       | 4                 | 4                  | 4                      | 25                  | 75                     | -                      |                                                                          |
| E. faecium                                             | 1       | 1                 | 0                  | 0                      | 0                   | 100                    | -                      |                                                                          |
### Table 15. Cont.

| Antibiotic Class | Strains               | Number of Studies | Number of Isolates | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | Comments |
|------------------|-----------------------|-------------------|--------------------|------------------------|---------------------|------------------------|-------------------------|----------|
| **Glycopeptides** | A. baumannii          | 1                 | 20                 | 0                      | 0                   | 100                    | -                       |          |
| **Staphylococcus spp.** | 12                 | 229               | 17                 | 16                     | 0                   | 65                     | 2                       | In 2 studies [69,176] VAN exhibited higher synergistic rates than TEC. Antagonistic effect with FOS + VAN against 5 isolates of S. aureus [12,43]. |
| Enterococcus spp. | 2                    | 55                | 25                 | 22                     | 0                   | 24                     | -                       |          |
| S. pneumoniae    | 2                    | 28                | 4                  | 4                      | 92                  | -                      | -                       |          |
| **Enterobacteriales** | 1                 | 87                | 53                 | 34                     | 14                  | -                      | -                       |          |
| N. gonorrhoeae    | 2                    | 12                | 0                  | 11                     | 84                  | -                      | -                       |          |
| P. aeruginos      | 2                    | 31                | 19                 | 79                     | 2                   | -                      | -                       | -        |
| S. aureus         | 1                    | 34                | 26                 | 68                     | 8                   | -                      | -                       | -        |
| S. epidermidis    | 1                    | 11                | 0                  | 0                      | 100                 | -                      | -                       |          |
| S. pseudintermedius | 1                  | 8                 | 62                 | 25                     | 12                  | -                      | -                       |          |
| Streptococcus spp. | 1                  | 26                | 15                 | 27                     | 58                  | -                      | -                       |          |
| **Macrolides**    | Enterobacteriales    | 2                 | 120               | 5                      | 11                  | 84                     | -                       | Indifferent effect when tetracycline was tested, but one study showed additive or synergistic effect when using minocycline + FOS combination [38]. |
| N. gonorrhoeae    | 1                    | 5                 | 40                 | 60                     | 0                   | -                      | -                       |          |
| P. aeruginos      | 2                    | 12                | 12                 | 56                     | 32                  | -                      | -                       |          |
| **Tetracyclines** | Acinetobacter spp.   | 1                 | 25                 | 12                     | 56                  | 32                     | -                       | In all experiment minocycline susceptibility restoration was observed [65]. |
| S. aureus         | 3                    | 152               | 72                 | 1                      | 27                  | -                      | -                       |          |
| Enterococcus spp. | 3                    | 75                | 24                 | 10                     | 20                  | -                      | -                       |          |
| N. gonorrhoeae    | 1                    | 4                 | 0                  | 0                      | 100                 | -                      | -                       |          |
| **Polymyxins**    | Enterobacteriales    | 18                | 381               | 26                     | 35                  | 35                     | 4                       | Antagonistic effect of FOS + colistin observed against 14 isolates of K. pneumoniae. |
| P. aeruginos      | 4                    | 111               | 27                 | 41                     | 31                  | -                      | -                       |          |
| Acinetobacter spp. | 12                 | 206               | 19                 | 15                     | 32                  | -                      | -                       | Antagonistic effect of FOS + colistin observed against 3 isolates of A. baumannii. |
| N. gonorrhoeae    | 1                    | 4                 | 0                  | 0                      | 100                 | -                      | -                       |          |
| **Daptomycin**    | Staphylococcus spp.  | 13                | 186               | 56                     | 31                  | 14                     | -                       |          |
| Enterococcus spp. | 5                    | 49                | 97                 | 0                      | 3                   | -                      | -                       |          |
| Antibiotic Class | Strains | Number of Studies | Number of Isolates | Synergistic Effect (%) | Additive Effect (%) | Indifferent Effect (%) | Antagonistic Effect (%) | Comments |
|------------------|---------|------------------|-------------------|-----------------------|--------------------|-----------------------|------------------------|----------|
| Tigecycline      |         |                  |                   |                       |                    |                       |                        |          |
| Enterobacterales | 9       | 313              | 17                | 17                    | 44                 | 34                    | 1                      | One in vivo study observed indifferent effect in 100% of cases against *E. coli* [73] and one in vitro study reported 2 cases of antagonistic effect against *K. pneumoniae* isolates [10]. |
| *P. aeruginosa*  | 1       | 15               | 13                | 13                    | 0                  | 87                    | -                      |          |
| *Acinetobacter spp.* | 2 | 25              | 21                | 21                    | 0                  | 79                    | -                      |          |
| *S. aureus*      | 2       | 48               | 0                 | 16                    | 0                  | 3                     | -                      |          |
| *Entenococcus spp.* | 3 | 61              | 61                | 0                     | 0                  | 9                     | -                      |          |
| *N. gonorrhoea*  | 1       | 4                | 0                 | 0                     | 0                  | 100                   | -                      |          |
| Linezolid        |         |                  |                   |                       |                    |                       |                        |          |
| *Entenococcus spp.* | 4 | 69              | 69                | 29                    | 17                 | 6                     | -                      | Synergistic effect was never observed for *E. faecalis* (2 studies) [13,201]. |
| *S. aureus*      | 9       | 166              | 74                | 74                    | 0                  | 2                     | 2                      |          |
| *S. epidermidis* | 1       | 2                | 100               | 100                   | 0                  | 100                   | -                      |          |
| Rifampin         |         |                  |                   |                       |                    |                       |                        |          |
| *E. coli*        | 1       | 17               | 6                 | 6                     | 10                | -                     | -                      |          |
| *A. baumannii*   | 1       | 0                | 0                 | 0                     | 100               | -                     | -                      |          |
| *S. aureus*      | 9       | 114              | 35                | 35                    | 21                 | 4                     | 3                      | Antibiotic effect of FO8 + RIF against 3 isolates [35,37]. |
| *S. epidermidis* | 2       | 5                | 40                | 40                    | 0                  | 40                    | -                      |          |
| *Streptococcus spp.* | 2 | 29              | 3                 | 3                     | 0                  | 97                    | -                      |          |
| *Entenococcus spp.* | 2 | 50              | 50                | 99                    | 0                  | 12                    | -                      |          |
| *N. gonorrhoea*  | 1       | 4                | 25                | 25                    | 0                  | 75                    | -                      |          |
| Metronidazole    |         |                  |                   |                       |                    |                       |                        |          |
| Intestinal bacteria (not specified) | 1 | NA              | -                 | -                     | -                  | -                     | -                      |          |
| *H. pylori*      | 1       | 24               | 0                 | 0                     | 21                 | 80                    | -                      |          |
| Spectinomycin    |         |                  |                   |                       |                    |                       |                        |          |
| *N. gonorrhoea*  | 1       | 4                | 0                 | 0                     | 100                | -                     | -                      |          |
| Sulbactam        |         |                  |                   |                       |                    |                       |                        |          |
| *A. baumannii*   | 1       | 8                | 8                 | 8                     | 0                  | 25                    | -                      |          |
| Lincocycin       |         |                  |                   |                       |                    |                       |                        |          |
| *S. aureus*      | 1       | 37               | 37                | 37                    | 19                 | 10                    | -                      |          |
| Nitrofurantoin   |         |                  |                   |                       |                    |                       |                        |          |
| *P. aeruginosa*  | 1       | 4                | 12                | 12                    | 0                  | 88                    | -                      |          |
| *S. aureus*      | 1       | 8                | 8                 | 8                     | 0                  | 88                    | -                      |          |
| Diallopristin-Quinupristin | 2 | 12             | 100               | 100                   | 0                  | 0                     | -                      |          |
| Fusidic acid     |         |                  |                   |                       |                    |                       |                        |          |
| *S. aureus*      | 3       | 239              | 63                | 63                    | 4                  | 33                    | -                      |          |
| Chloramphenicol  |         |                  |                   |                       |                    |                       |                        |          |
| Enterobacterales | 4       | 468              | 39                | 39                    | 34                 | 25                    | -                      |          |
| *P. aeruginosa*  | 1       | 19               | 19                | 19                    | 33                 | 10                    | -                      |          |
| *S. aureus*      | 1       | 46               | 46                | 46                    | 37                 | 19                    | -                      |          |
| Nitrofurantoin   |         |                  |                   |                       |                    |                       |                        |          |
| Enterobacterales | 1       | 100              | 0                 | 0                     | 100                | -                     | -                      |          |
| *Entenococcus spp.* | 1 | 32              | 0                 | 0                     | 100                | -                     | -                      |          |
| Trimethoprim-Sulfamethoxazole |         |                  |                   |                       |                    |                       |                        |          |
| Enterobacterales | 2       | 120              | 2                 | 2                     | 5                  | 99                    | -                      |          |
| *S. aureus*      | 1       | 148              | 3                 | 3                     | 0                  | 95                    | -                      | Antagonistic effect was reported for 4 isolates [12]. |
Supplementary Materials: The following are available online at http://www.mdpi.com/2079-6382/9/8/500/s1, Table S1: Studies on combination between fosfomycin and different antibiotics. CB: checkerboard assay; TK: time–kill assay; ET: E-test. Table S2: Studies on combination between fosfomycin and molecules other than antibiotics. CB: checkerboard assay; TK: time–kill assay.

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