Fosfomycin as Partner Drug

Subjects: Others
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Fosfomycin is being increasingly prescribed intravenously for multidrug-resistant bacterial infections, usually administered as a partner drug. 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.

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1. Introduction

Fosfomycin (FOS) is being increasingly prescribed for multidrug-resistant bacterial infections. In patients with systemic involvement, intravenous FOS is usually administered as a partner drug, as part of an antibiotic regimen. Hence, the knowledge of FOS pharmacodynamic interactions (synergistic, additive, indifferent and antagonistic effect) is fundamental for a proper clinical management of severe bacterial infections.

Full text and Tables can be found in the systematic review: https://www.mdpi.com/2079-6382/9/8/500

2. Synergistic Interactions

2.1. Penicillins

Twenty-eight papers evaluating FOS in combination with penicillins, penicillins + β-lactamase inhibitors, penicillinase-resistant penicillins were reviewed. Breakpoints for penicillins were inferred from EUCAST breakpoints [1]. 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. [2] 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 [3] and against 6 biofilm-producer *E.*

faecalis isolates with the combination FOS + ampicillin [4]. *In vivo* experiments showed 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.

2.2. Cephalosporins

Forty-one papers evaluating FOS in combination with cephalosporins and cephalosporins + β-lactamase inhibitors were reviewed. Breakpoints for cephalosporins were inferred from EUCAST breakpoints. 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. [5][6] and *Enterobacterales* isolates [2][7][8]. Antagonistic effect was observed against 4 *P. aeruginosa* isolates with the combination FOS + ceftazidime [9], 1 *S. aureus* and 1 *S. epidermidis* isolates with the combination FOS + ceftriaxone [6]. 9 *in vivo* studies [10][11][12][13][14][15][16][17][18] performed with different strains (*E. coli*, *P. aeruginosa*, *S. aureus*, *S. pneumoniae*, *S. sanguis*) confirmed results obtained *in vitro* or resulted in higher synergistic effect (additive effect only against 3 *S. aureus* isolates).

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 [2]), while the combination ceftazidime/avibactam + FOS was synergistic in 28.8% of cases (66 isolates tested [2][19][20]). Against *P. aeruginosa*, the combination ceftolozane/tazobactam + FOS resulted synergistic in 71.1% of cases, while the combination ceftazidime/avibactam + FOS was synergistic in 31.6% of cases.

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

2.3. Carbapenems

Forty-four papers evaluating FOS in combination with carbapenems were reviewed. 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.

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*. [9] and in 1 isolate of *S. aureus* in the study by Quentin *et al.* [21]. 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 [16][22] the results in vivo were concordant with those found *in vitro*, while in the third study the combination *in vivo* resulted less effective [23].

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

2.4. Monobactams

Five papers evaluating FOS in combination with aztreonam (ATM) were reviewed. 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.

The largest study evaluating FOS in combination with ATM on Enterobacterales isolates [24] reported an indifferent effect on most (64.6%) isolates. The combination was reported to have an additive effect on most isolates of *P. aeruginosa*, sometimes leading to ATM susceptibility restoration [24][25]. There were no in vivo studies evaluating this combination.

2.5. Quinolones

Twenty-nine papers evaluating FOS in combination with quinolones were reviewed. Quinolones are bactericidal antibiotics that directly inhibit bacterial DNA synthesis. Breakpoints for quinolones were inferred from EUCAST breakpoints. Synergism rates were not unanimous on all studies for isolates of *P. aeruginosa.* For *E. coli* isolates there was a weak synergism. In a recent *in vitro* study there was complete FOS and ciprofloxacin susceptibility restoration [26]. The combinations showed different synergistic rates for *Staphylococcus* spp. isolates with 100% synergistic rate in 1 *in vitro* study [27] and in 1 *in vivo* study [28]. 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* [29]. The combination with levofloxacin showed mainly an additive effect in *P. aeruginosa* [30][25][31] and in *Acinetobacter* spp. [30] isolates.

In summary good additive/synergistic effect rates are reported when quinolones + FOS are used against *S. aureus* and *P. aeruginosa* isolates.

2.6 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. 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 [32]. Overall, 41 papers evaluating FOS in combinations with AMG were reviewed. Due to the peculiarity of possible AMG therapeutic use (e.g. inhaled formulation in CF), 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 [33]: 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 CF 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 [3] and in 2005 by Pruekprasert *et al.* in 27% of 22 *P. aeruginosa* strains [9].

Focusing on different bacterial strains, generally a synergistic or additive effect of FOS + AMG was demonstrated on KPC-producing *K. pneumoniae* [34][35][36]; however, Souli *et al.* observed an indifferent effect of FOS + gentamycin combination in all of their tested KPC+ strains [37].

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 *N. gonorrhoeae* (both, gentamicin) in two studies [38][7]: 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) [39].

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

2.7 Macrolides

Six papers evaluating FOS in combination with macrolides, in particular with erythromycin (ERY), azithromycin (AZT), clarithromycin (CLT), or midecamycin (MDM), were reviewed.

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. Only one *in vitro* study evaluated FOS + ERY combination against *Enterobacterales* (87 strains of *E. cloacae*, *E. coli*, *Proteus* spp. and *K. pneumoniae*), reporting synergistic effect against 52% of isolates and additive effect against 30% [7]; 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 [7]. 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 [7]. Some studies evaluated FOS + AZT combination, reporting indifferent effect in 100% of cases, either when tested against *N. gonorrhoeae*

(2 studies) [38][40] or against *S. epidermidis* (1 study) [41]. 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 [42][43]. 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.

2.8 Glycopeptides

Eighteen articles evaluating FOS in combination with glycopeptides (vancomycin and teicoplanin) have been reviewed. 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

Synergism 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 synergism was detected in one heterogeneous glycopeptide-intermediate *S. 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* [12][22][44][45][46].

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.

2.9 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.

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. Almost all studies evaluated *in vitro* FOS + MIN combination against different bacterial species. When evaluated against *Enterobacterales* (20 strains), FOS + MIN proved to have additive effect most of the time (65% of isolate), but only in few cases synergistic effect [30]. Similar results were observed when it was tested against multidrug-resistant *P. aeruginosa* [30] and *A. baumannii* isolates; furthermore, in the last case, complete restoration of susceptibility of MIN was reported [47]. Only one study evaluated FOS + TEC combination against *Enterobacterales* (100 isolates), observing indifference in almost 100% of cases [48]. 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. 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. Finally, when FOS + MIN was tested against MRSA proved to have synergistic effect in numerous cases [49][50]. No study reported any case of antagonism.

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

2.10 Polymyxins

Thirty-two papers evaluating FOS in combination with polymyxins were reviewed.

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. Synergism rates were not unanimous on all studies but was reported in 23/29 papers. Synergisms rate were 100% in 2 *in vitro* studies against *K. pneumoniae* [34][51] and 2 *in vivo* studies respectively against *A. baumannii* and *E.coli* [52][53]. The overall effect was indifferent on most isolates of *P. aeruginosa* and *Enterobacterales*. Antagonism was reported *in vitro* against *K. pneumoniae* and *A. baumannii* [54].

Four papers evaluated polymyxin B. Synergism was observed in 100% of *in vitro* isolates of CP *K. pneumoniae* according to Bulman *et al.* [55]. FOS + polymyxin had a prevalent addictive effect *in vitro* against *Pseudomonas* spp. [56] and *A. baumannii* [47]. In a study there was a complete polymyxin B susceptibility restoration [47]. 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.

2.11 Daptomycin

Thirteen papers evaluating FOS in combination with daptomycin (DAP) were reviewed. DAP is a cyclic lipopeptide administered intravenously for Gram-positive infections, acting through bacterial membrane depolarization.

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 [46][57][58][59] and 2 *in vivo* studies [23][57]). DAP showed excellent synergistic activity in association with FOS against *Enterococcus* spp. 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 [23] or less [60] 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.

2.12 Tigecycline

Fourteen papers evaluating FOS in combination with tigecycline (TIG) were reviewed. TIG is the first glycylcycline 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.

When evaluated *in vitro* against *Enterobacterales* or *A. baumannii* FOS + TIG had synergistic effect approximately in 17% of cases and additive effect in the 43%, while indifference was reported for all remaining cases [61][62][63].

Mostly indifference was observed when it was tested against *N. gonorrhoeae* or *P. aeruginosa*[38][64]. When tested against 61 isolates of Enterococcus spp. (3 studies) many cases of synergistic effect was reported *in vitro* (about 40% of cases) [65][66][39] and *in vivo* against E. faecalis [65]. In all *in vitro* studies only 2 cases of antagonism were reported, against *K. pneumoniae* [63].

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

2.12 Linezolid

Thirteen papers evaluating FOS in combination with linezolid (LZD) were reviewed.

LZD is a synthetic antibiotic which binds rRNA on both 30S and 50S ribosomal subunits, inhibiting bacterial proteins synthesis. It is used for Gram-positive infections treatment, including MRSA and *E. faecium* vancomycin-resistant (VREF) infections.

When evaluated against *S. aureus* isolates, combination FOS + LZD had a synergistic effect in vitro approximately in 95% of cases [27][46][67][68] and even against staphylococcal biofilm cultures [49]; furthermore, the only 2 *in vivo* studies performed proved FOS + LZD

combination to have higher efficacy than FOS or LZD alone [22][68]. In no case was reported synergistic effect against *E. faecalis*.

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*.

2.14 Rifampin

Fourteen papers evaluating FOS in combinations with rifampin were reviewed.

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 showed

synergistic activity in association with FOS against *Enterococcus* spp., resulting in synergistic effect in

20−100% of cases [65]. When evaluated

against *S. aureus* isolates, the combination FOS + rifampin had a synergistic effect *in vitro* against

34−100% of isolates [65][69]. Antagonistic effect was

observed in 33% of isolates in the study by Quentin *et al.* [21] 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.

2.15 Miscellanea

Two papers evaluating FOS in combination with metronidazole (MTZ) were reviewed. 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% [70]. *In vivo* study showed a significantly decrease mortality and increase cure rates if the animal treated with MTZ + FOS [71].

One paper evaluating FOS in combination with spectinomycin (SCM) was reviewed. 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 [38].

One paper evaluating FOS in combination with sulbactam (SLB) against *A. baumannii* OXA-23, showing a synergistic effect in 75% of case, and an indifferent effect in 25% of cases [72].

One paper evaluating FOS in combination with lincomycin (LNM) was reviewed. LMN is a protein synthesis inhibitor with activity against gram positive and anaerobic bacteria. When evaluated *in vitro* against *S. aureus*, combination FOS + LNM had a synergistic effect in 81% of case and an additive effect in 25% of cases [7].

One paper evaluating FOS in combination with nitroxoline (NTX) was reviewed. 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%) [48].

Two papers evaluating FOS in combination with quinupristin/dalfopristin (Synercid) were reviewed. When evaluated *in vitro* against methicillin resistant or susceptible *Staphyloccoccus* spp., combination FOS + Synercid had a synergistic effect in 100% of case [27][73].

Three papers evaluating FOS in combination with fusidic acid (FSA) were reviewed. 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 100% of cases. No antagonism was found [74][75].

Four papers evaluating FOS in combination with chloramphenicol (CHL) were reviewed. 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. When evaluated *in vitro* against either *Enterobacterales*, combination FOS + CHL had synergistic effect approximately in 40% of cases, while

additive effect in 35% and indifferent effect in the remaining cases [76][77][7][48].

Three papers evaluating FOS in combination with trimethoprim-sulfamethoxazole (TMP-SMX)

were reviewed. 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. When evaluated *in vitro*

against either *S. aureus* or *Enterobacterales*, combination FOS + TMP-SMX had indifferent effect approximately against 92% of isolates. Only in few cases, against Enterobacterales, was reported synergistic or additive effect and even antagonistic

effect was reported in 4 cases when tested against S. aureus[30][48][3].

Two papers evaluating FOS in combination with nitrofurantoin (NTF) were reviewed. NTF is a synthetic antibiotic administered orally mainly for treatment of lower urinary tract infections. When evaluated in

vitro against either vancomycin-resistant *E. faecium* or *Enterobacterales*, combination FOS + NTF had indifferent effect against 100% of isolates [48]. No synergistic, additive or antagonistic effect was observed.

2.16 Non-Antibiotic Molecules

One paper evaluating FOS in combination with auranofin (AF), an orally active gold compound for the treatment of rheumatoid arthritis, was reviewed. When evaluated *in vitro* against *Staphyloccoccus* spp., combination FOS + AF had showed a reduction of bacterial load for both MSSA and MRSA strains. *In vivo*, this combination showed a synergistically inhibition of abscess and inflammation formation. No interactions were showed against S. epidermidis MS [78].

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. 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 [79][80][81].

One paper evaluating FOS in combination with β-chloro-L-alanine (β-CLA) was reviewed. β-CLA is an amino acid analog of FOS. When evaluated in vitro against MRSA, combination FOS + β-CLA had showed a synergistic effect on biofilm production [82].

One paper evaluating FOS in combination with
plectasin NZ2114, compound capable to inhibits a cell wall biosynthesis, was reviewed. When plectasin NZ2114 evaluated in vitro against *E. faecalis*, in combination with FOS it no show a synergistic effect [83].

One paper evaluating FOS in combination with 2 quinolone derivatives (A and B) was reviewed. 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%) [84].

One paper evaluating FOS in combination with N-acetylcysteine (NAC), a mucolytic agent, was reviewed. The *in vitro* analysis against *E. coli*, had showed a capable of NAC to reduce biofilm if used in combination with FOS [85].

One paper evaluating FOS in combination with sophoraflavanone G (SFG), a phytoalexins, was reviewed. When evaluated in vitro against MRSA, combination FOS + SFG had showed a synergistic effect (100%) [86].

One paper evaluating FOS in combination with arenaemycin (ARM), also called pentalenolactones, was reviewed. When evaluated *in vitro* against *P. vulgaris* and *S. gallinarum*, combination FOS + ARM had showed a synergistic effect (100%) [87].

One paper evaluating FOS in combination with chlorogenic acid (CHA) and caffeic acid (CFA) was reviewed. When evaluated *in vitro* against resistant
L. 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 [88].

One paper evaluating FOS in combination with silver (AgNPs) and zinc oxide (ZnONPs) nanoparticles, are molecules known to affect bacterial membranes, was reviewed. When evaluated *in vitro* against *S. aureus*, *S. enterica*, and *E. coli*, combination FOS + AgNPs or ZnONPs had showed a synergistic effect (100%) [89].

3. 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, oxazolydinones, 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 in *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/avibactam and ceftolozane/tazobactam, for *Enterobacterales* and *P. aeruginosa*;
2) carbapenems for *K. pneumoniae* and *P. aeruginosa*;
3) quinolones for *P. aeruginosa*;
4) polymyxins 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 caffeic acid appeared to be good partner drugs against *L. monocytogenes*.

Our tables could act as a useful consultation tool for clinicians using FOS both as empirical or targeted antibiotic regimen.

4. 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.

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