

## Supplementary Material

### Studies Investigating In Vitro Synergisms of New Antimicrobials and Experimental Animal Models of IE

#### 1. Ceftobiprole

##### 1.1 In Vitro Synergism

BPR synergism with different antimicrobials such as aminoglycosides, plazomicin, levofloxacin, and rifampin has been evaluated in several studies [1–15]. Campanile et al. specifically studied the in vitro synergism of BPR with daptomycin, linezolid, levofloxacin, rifampin, or piperacillin/tazobactam against different 46 Gram-positive pathogens, such as *S. aureus*, CoNS, and *Enterococcus spp.*, and found that BPR exhibited synergism with daptomycin against all Gram-positive isolates and only against *Enterococcus spp.* with levofloxacin [7]; additionally, treatment with linezolid was only effective against four isolates belonging to different species. These results were consistent with the previous study by Barber et al., who demonstrated that the combination of BPR and daptomycin (DAP) was the most potent in vitro antibiotic combination against methicillin-resistant *S. aureus* (MRSA) strains with varying degrees of vancomycin (VAN) susceptibility [14]. Interestingly, BPR maintains in vitro activity against DAP- and BPR-resistant MRSA clinical isolates and even enhanced DAP binding to the cell membrane in DAP-resistant strains by altering the charge and membrane fluidity [8].

BPR also showed activity against ampicillin-sensitive *E. faecalis* [1]; however, resistance to ampicillin in *E. faecalis* and *E. faecium* correlated with reduced susceptibility and resistance to BPR, respectively [3]. The data provided by Deshpande et al, who evaluated the combination of BPR and gentamicin against *Enterococcus spp.*, is also of interest [3]. The authors showed how BPR and gentamicin exhibited synergism against 62.5% of VAN-susceptible or intermediate *E. faecium*, while this combination was indifferent in the only two (37.5%) *E. faecalis* samples tested. Arias et al. (2007) also observed synergy between BPR and aminoglycosides (streptomycin) against two strains of beta lactamase-producing *E. faecalis* and synergy between BPR and gentamicin against a strain of VAN-resistant *E. faecalis* (vanB), but not against the VanA sample they tested [15].

Aware of evidence regarding the synergistic effect of beta-lactam antibiotics and DAP against VAN-resistant *E. faecium* and *E. faecalis* (VRE), Werth et al. found that BPR and DAP were synergistic against four out of six strains of VAN-resistant *E. faecium* and *E. faecalis* with varying susceptibilities to DAP [16]. Additionally, exposure to BPR reduced the minimum inhibitory concentration (MIC) of DAP in all tested strains.

Peiffer-Smadja et al. investigated the in vitro bactericidal activity of amoxicillin combined with various cephalosporins including BPR against 10 *E. faecalis* strains isolated from patients with IE caused by the same pathogen. The authors found that the combinations of amoxicillin and BPR and ceftaroline (CPT) and amoxicillin consistently exhibited lower bactericidal activity compared to combinations with other cephalosporins such as cefazolin, cefotaxime, ceftriaxone, and cefepime [9].

##### 1.2 Animal Studies

BPR was first investigated by Enteza JM et al. in an experimental rat model of MRSA IE, showing that BPR was able to sterilize >90% of cardiac vegetation [10].

Subsequently, BPR was evaluated in a rabbit model of aortic valve IE due to methicillin-resistant and vancomycin-intermediate *S. aureus* (VISA). While BPR was as effective as VAN against the MRSA strains examined in the study, it was more effective than VAN against VISA strains [12]. Likewise, Tattevin et al. demonstrated the potency of BPR and its superiority to VAN, DAP, and linezolid in an animal model of IE caused by MRSA, showing that there were significantly fewer residual organisms in vegetation in BPR-treated rabbits than in any other treatment groups [11].

#### 2. Ceftaroline

##### 2.1 In Vitro Synergism

The association between CPT and VAN or DAP shows in vitro synergism compared with any agent alone against MRSA or daptomycin-unsusceptible (DNS) MRSA [17,18], including VISA isolates [19]. Werth et al. found that the association between DAP and CPT resulted in significantly improved killing compared to DAP or VAN alone against DNS, VISA, and MRSA strains. Although DAP reached bactericidal activity faster than CPT alone, the association of DAP and CPT was significantly faster than DAP alone against all strains [20]. While most beta-lactams, when combined with VAN, showed synergism against vancomycin-sensitive MRSA (VSSA), heterogenous VISA (hVISA), and VISA strains, VAN/CPT had the most beneficial effect in terms of its time-killing curve [21]. Eliazar et al. found that the combination DAP/CPT was more active than VAN/CPT or any agent alone against DNS MRSA and VISA bacteremia

isolates [22]. Considering DAP-resistant *S. aureus*, CPT showed synergy with DAP or VAN, which was most evident in cases of lower CPT MICs [23].

Several in vitro studies showed a superior synergic effect of CPT combined with ampicillin (AMP) against *E. faecalis* isolates if compared with AMP alone or AMP/gentamicin [24,25]. Likewise, CPT/AMP was more active against *E. faecalis* than AMP/ceftriaxone (CRO) [24]. Cusumano et al. described an in vitro synergism of ertapenem (ERT) or meropenem (MEM) in combination with CPT against *E. faecalis* isolates: the combination of MEM/CPT in vitro was as active as AMP and CRO [26]. Interestingly, CPT reduced the MICs of DAP in VRE strains in vitro, suggesting its potential use in vivo [27].

The most widely accepted hypothesis regarding the synergism between AMP and cephalosporins is complementary penicillin-binding protein (PBP) saturation [28]. Indeed, CPT binds PBP 2 and 3 with an increased affinity for PBP2a, while AMP binds PBP 4 and 5 [29]. Moreover, CPT increases cell membrane fluidity and decreases the cell surface charge. Interestingly, the mechanism of synergism between DAP and CPT could restore DAP sensibility in DNS *E. faecium* strains. Thus, DAP binding on cell surfaces is significantly increased by CPT in DNS *E. faecium* strains [30]. The enhanced DAP binding on cell surfaces due to CPT was also found for MRSA [18].

## 2.2 Animal Studies

The bactericidal activity of CPT has been largely demonstrated by Jaqueline and colleagues in several in vivo studies using rabbit IE models. The authors reported that in MSSA, MRSA, hGISA, and MR-GISA rabbit IE models, CPT alone showed a higher four-day bactericidal activity than all glycopeptides, DAP, and linezolid, with a higher volume of sterile vegetation in all rabbits treated with CPT [31–33]. Furthermore, CPT showed more potent activity than VAN or linezolid against vancomycin-sensitive or -resistant *E. faecalis* IE [34]. Finally, a recent study on a murine model showed that the CPT efficacy against MRSA BSI is not inferior after 24 h of treatment with VAN and DAP. The CPT effectiveness was also demonstrated in hVISA and DNS strains, showing its potential use against difficult to treat *S. aureus* bacteraemia [35].

## 3. Dalbavancin

### 3.1 In Vitro Synergism

Synergy was analyzed for dalbavancin (DAL) and nine different antimicrobials against MRSA, MSSA, VISA, methicillin-resistant *S. epidermidis* (MRSE), vancomycin-susceptible *E. faecalis*, *S. pneumoniae*, and *S. pyogenes*. The results showed no antagonism, but full synergism was present only with oxacillin (the  $\beta$ -lactam representative). Gentamycin and VAN had frequent partial synergy (60%), followed by clindamycin (40%), DAP, levofloxacin and quinopristin/dalfopristin (30% each), and rifampicin (10%). Linezolid offered the least active combination (80% indifferent) [36]. More recently, DAL combination with  $\beta$ -lactams was evaluated against different phenotypes of *S. aureus*: MRSA, VISA, hVISA, DAP non-susceptible (DNS), and linezolid-resistant. All agents reduced DAL MICs, but the time-kill curves showed that DAL with cefazolin, cefepime, and ertapenem had synergy against all isolates; DAL with ceftaroline had synergy against all strains but one MRSA strain; DAL with oxacillin was not synergic against two MRSA strains and one hVISA strain. The authors suggested that agents with PBP-1 affinity may be more effective for DAL synergism [37].

### 3.2 Animal Studies

The applicability of DAL in IE was first investigated by Candiani et al. in a rat staphylococcal IE model where, at lower dosages, it was shown to be as effective as teicoplanin and VAN in bacterial load reduction [38]. Subsequently, DAL was tested in an in vivo rabbit model of IE caused by glycopeptide-sensitive and glycopeptide-intermediate *S. aureus* (GISA) isolated from a human before and after exposure to VAN and teicoplanin, respectively. The activity was not influenced by the reduced glycopeptide susceptibility and no DAL-resistant strain was detected [39].

## 4. Oritavancin

### 4.1 In Vitro Synergism

ORI was combined with other agents against one vancomycin-susceptible *E. faecium* strain, and four VRE strains. Synergy was shown in one VRE strain treated with ORI and gentamycin, while antagonism emerged for ORI with DAP

(two VRE) and ORI with rifampicin (one VRE) [40]. Recently, the combination of ORI with fosfomycin (FOS) demonstrated synergism in eight out of ten VRE (five VanA and five VanB) isolates and showed an additive effect in the remaining two. The combination restored FOS-susceptibility in 85% of FOS-resistant isolates [41].

#### 4.2 Animal Studies

In 1998, ORI was tested on a rabbit model of MRSA left-sided IE. Compared to VAN, after a four-day treatment course, there were no significant differences in cleared bacteremia, reduced vegetation, or tissue bacterial counts [42]. In rabbit models of IE, ORI was also compared to VAN and teicoplanin against three different strains of *E. faecalis* (glycopeptide-susceptible, VanA and VanB). Its bactericidal activity was not decreased by the glycopeptide resistance, regardless of the phenotype [43]. In a similar experiment, the in vivo combination with gentamicin was synergistic and bactericidal against the three *E. faecalis* strains and prevented the emergence of mutants [44].

### 5. Old Antibiotic With a Renewed Interest: Fosfomycin

#### 5.1 In Vitro Synergism

A recent systematic review comprising a total of 1087 Gram-positive isolates investigated the rate of synergism of DAP-containing regimens using in vitro and in vivo studies. A total of 14 studies evaluating the DAP and FOS combination were evaluated. The authors found that the combination was synergistic against most *S. aureus* isolates (55.4%). In particular, the combination was synergistic against all the MSSA isolates [45]. Likewise, DAP and FOS was bactericidal against the majority of MRSA strains at both standard and high bacterial inocula (106 and 108 CFU/mL, respectively) [46]. Less recently, Debbia et al. showed a synergism rate of 80-90% of FOS and DAP against a collection of 50 staphylococcal strains, including MRSE [47]. This synergistic activity may be explained by the PBP-1 inhibition exerted by FOS and by fosfomycin's ability to modify cell wall protein compositions [46,48–50]. The combination of DAP and FOS has also been shown to be synergistically active against a DAP-resistant strain in an in vitro and in vivo model of MRSA IE [49].

Five in vitro studies evaluated DAP and FOS against 22 isolates of *Enterococcus spp.* (fourteen *E. faecalis*, eight *E. faecium*): the most frequent interaction was synergism (63.6%), which was slightly higher for VAN-resistant than for susceptible strains. Fosfomycin and DAP also exhibited a greater efficacy against *E. faecalis* biofilm formation than the single drugs alone [45,51].

Conflicting results concerning the effect of FOS in combination with cephalosporins against clinical isolates of *Staphylococcus spp.* have been reported, with synergism rates ranging from 16% to 100% [51]; in particular, a study reported that results were different between FOS and ceftriaxone against *S. epidermidis* if checkerboard or killing studies were used (16% and 83.3%, respectively) [52]. However, a large number of available reports of in vitro and in vivo studies showed synergistic activity of FOS and different beta-lactams against MRSA, in particular with regard to imipenem–FOS, which was found to be the most active combination against MRSA and one GISA strain [53–57]. Likewise, meropenem and imipenem showed a synergism of 90–100% against *S. epidermidis* [55,57]. The mechanism of synergy between FOS and beta-lactams is not well understood. However, molecular studies showed that FOS and imipenem significantly decreased PBP1, PBP2 (but not PBP2a), and PBP3 synthesis, thus increasing the effect of imipenem on MRSA and GISA strains [55].

The combination of ceftriaxone and FOS showed a high in vitro synergistic effect against a collection of *E. faecalis* strains isolated from patients with IE, with a synergy rate of 55.6% [58]. Descorouez et al. (2013) showed full synergism of amoxicillin and FOS against four strains of VRE, while antagonistic effects were found against six biofilm-producer *E. faecalis* isolates with the combination of FOS and ampicillin [59,60].

As for *Streptococcus spp.*, less data is described; however, Gonzalez Moreno et al., in an in vitro biofilm model with microcalorimetry, showed a delay of 8 h in the production of heat if FOS was added to benzylpenicillin against *S. anginosus*, *S. agalactiae*, or *S. oralis* compared with untreated controls, while less recent studies showed a synergistic rate of 23% and 32% in in vitro experiments with FOS combined with penicillin G and ampicillin, respectively [58,59,61–63].

#### 5.2 Animal Studies

Experimental animal models of IE with FOS have been described for many years, showing encouraging results [46,47,62,64]. Likewise, FOS's anti-biofilm activity has been shown in several models of infections [65–67].

In an experimental model of rabbit MRSA IE, DAP and FOS significantly improved the efficacy of DAP monotherapy at 6 mg/kg/day in terms of both the proportion of sterile vegetation and a decrease in the density of bacteria within the vegetation. Interestingly, DAP and FOS was as effective as DAP monotherapy at 10 mg/kg/day [46]. The same authors in a rabbit model of MSSA IE showed that adding FOS or cloxacillin to DAP significantly improved the efficacy of DAP

in sterilizing vegetation and showed better activity than cloxacillin alone. No recovered isolates showed increased DAP MIC [47].

Rice et al. evaluated the combination of DAP and FOS against a strain of *E. faecalis* with high-level gentamicin resistance in a rat IE model; the authors found an absence of superiority of the combination therapy over the monotherapy. No antagonism was found when considering *Enterococcus spp.* models [63].

Del Rio et al. showed that the combination of imipenem and FOS was highly synergistic against MRSA in an experimental model of IE, with a percentage of sterile vegetation of 73% in the combination group compared to 0% and 7% in cases using FOS or imipenem alone, respectively [56]. Notably, the combined regimen avoided the development of resistance to FOS, which was, in contrast, observed in 42% of isolates recovered from the FOS monotherapy arm. Vicente et al. (1981) showed a 100% rate of synergistic interaction between FOS and cefoxitim in an experimental model of IE due to *S. sanguis*, with a significant reduction in log<sub>10</sub> CFU per gram of vegetation in the combination group compared to each drug alone [62].

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