615. Daptomycin (DAP) Synergy with β-Lactams in DAP-Resistant (DAP-R) *E. faecium* (*Efm*) Is Dependent On PBP5 Sequence and β-Lactam-binding Affinity

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Background. DAP in combination with β-lactams is a viable option to treat recalcitrant DAP-R/tolerant strains of *Efm*. Ampicillin (AMP), ceftaroline (CPT), and ertapenem (ERT) have the best synergism. Using a DAP tolerant strain (503; DAP MIC 2 μg/mL) of *Efm*, we previously showed that AMP, CPT, and ERT combined with DAP were effective in reducing bacterial loads and prevented emergence of resistance in a simulated endocardial vegetation model. However, against a DAP-R *Efm* strain (R497, DAP MIC of 16 μg/mL), CPT, ERT failed to synergize with DAP. Here, we dissect the mechanistic basis of the differing DAP plus β-lactam synergistic effect.

Methods. We performed comparative transcriptional profiling of *pbp* genes in *Efm* 503 vs. R497 using qRT–PCR. PBP5 protein levels were assessed by immunoblotting. The β-lactam-binding affinity of PBPs was quantified with bocillin-FL staining and SDS–PAGE. PBP5 sequences of *Efm* Com15 (AMP and DAP-susceptible strain) and clinical strains S447, 503 and R497 (all with AMP MIC > 256 μg/mL) were compared *in silico* to identify amino acid (AA) differences in key protein sites which were verified with sequencing

Results. *Pbp* gene transcripts and PBP5 amounts were similar between 503 vs. R497. Interestingly, bocillin SDS–PAGE showed increased β-lactam binding affinity in PBP5 of 503 compared with that of R497 and S447. PBP5 sequences of S447 and R497 were identical. All three clinical strains had classic mutations (M485A and 466'S) important for high-level AMP-R. However, 503 had additional substitutions in the transpeptidase domain (H408Q, A462V, T546N, T558A, S582G, V586L) and penicillin-binding domain (Q632K, L642P) compared with R497 and S447. The latter AA sequences in 503 are common to AMP-susceptible *Efm* strains

Conclusion. We uncovered that a "hybrid" *pbp5* allele of 503 (DAP-tolerant) correlated with synergism of DAP plus AMP, CPT or ERT and was associated with increased PBP5 β-lactam binding affinity. Lack of synergism of DAP plus CPT or ERT is associated with specific PBP amino acids in the transpeptidase and penicillin-binding domains. Thus, *pbp5* alleles are major determinants of the DAP plus β-lactam synergistic effect and could be used as a diagnostic tool to guide therapy in recalcitrant *Efm* infections

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616. Evaluation of *In Vitro* Susceptibility to Ceftazidime/Avibactam of Clinical Isolates of Carbapenem Nonsusceptible Gram-Negative Bacilli from Colombia

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Background. Ceftazidime/avibactam (CZA) is a combination of a third-generation cephalosporin and a diazabicyclooctane β-lactamase inhibitor, which is active against a broad range of class A, C and D β-lactamases. In Colombia, high rates of multidrug-resistant *Enterobacteriaceae* (*Ent*)and *P. aeruginosa* (*Pae*) have been reported. Of special concern are KPC enzymes endemic in *Ent* and found in *Pae,* which are associated with higher mortality and healthcare costs, as well as limited therapeutic options. Herein, we evaluate the susceptibility of clinical isolates of carbapenem nonsusceptible *Ent* (CNS-E) and *Pae* (CNS-P) to CZA with the aim of understanding its role as a therapeutic option for these bacteria.

Methods. Three hundred ninety-nine nonduplicate clinical isolates of carbapenem nonsusceptible Gram-negative bacilli were collected in 13 medical centers from 12 Colombian cities, from January 2016 to October 2017 (137 *K. pneumoniae* [*Kpn*], 76 *E. coli*, 34 *Enterobacter* spp., 21 *S. marcescens* [*Sma*] and 131 *Pae*). CNS-E was defined as minimum inhibitory concentrations (MIC) ≥1 mg/L for ertapenem and CNS-P was defined as MIC ≥4 mg/L for meropenem. MIC were determined by broth microdilution and interpreted according to current CLSI guidelines. CZA MIC were determined using double dilutions of ceftazidime and a fixed concentration of avibactam of 4 mg/L. Comparator agents were ceftazidime, cefepime, piperacillin/tazobactam, imipenem, meropenem, tigecycline (TGC), and fosfomycin (FOS).

Results. Antimicrobial activity of CZA and comparators is shown in Table 1. CZA susceptibility ranged from 69% in *Kpn* to 81% in *Sma,* whereas 49% of CNS-P were susceptible to CZA. In both, CNS-E and CNS-P, CZA was superior to all other tested β-lactam compounds. Notably, in CNS-E CZA susceptibility was comparable to FOS and TGC (except for TGC in *Sma*).

Conclusion. CZA is the most active β-lactam against CNS-E and CNS-P. CZA nonsusceptibility suggests the presence of other resistance mechanisms, such as class B β-lactamases that are not inhibited by avibactam, and which are more frequently reported in CNS-P. Our results highlight the key role of new agents such as CZA in KPC endemic countries and the need for surveillance studies to determine the nature of resistance mechanisms.

Table 1. Antimicrobial activity of ceftazidime/avibactam and comparators against 399 clinical isolates of carbapenem non-susceptible *Enterobacteriaceae* and *P. aeruginosa* from 13 Colombian hospitals

Organism	Isolates	CZA%S	CAZ%S	FEP%S	TZP%S	IMI%S	MER%S	TGC%S	FOS%S
K. pneumoniae	137	69	0	0	0	18	23	73	80[a]
E. coli	76	72	0	0	0	45	47	64	76
Enterobacter spp	34	74	12	12	21	29	38	76	71[a]
S. marcescens	21	81	5	5	19	19	24	52	81[a]
P. aeruginosa	131	45	27	29	30	1	0	-	79[b]

CZA: ceftazidime/avibactam; CAZ: ceftazidime; TZP: piperacillin/tazobactam; FEP: cefepime; IMI: imipenem; MEM: meropenem; TGC: tigecycline; FOS: fosfomycin

[a] Fosfomycin breakpoints for *Enterobacteriaceae* were extrapolated from *E. coli* breakpoint by CLSI (fosfomycin non-susceptible MIC ≥ 128 mg/L).

[b] There are no fosfomycin breakpoint for *P. aeruginosa* by EUCAST or CLSI. ECOFF of ≤ 128 μg/ml by EUCAST for *P. aeruginosa* was applied.

Carbapenem non-susceptibility was defined as MIC ≥ 1 mg/L for ertapenem in *Enterobacteriaceae* and MIC ≥ 4 mg/L for meropenem non-susceptibility in *P. aeruginosa.*

Ceftazidime non-susceptible MIC ≥ 8 mg/L for *Enterobacteriaceae* and ≥ 16 mg/L for *P. aeruginosa*.

Cefepime non-susceptible MIC > 4 mg/L for *Enterobacteriaceae* and ≥ 16 mg/L for *P. aeruginosa*.

Piperacillin/tazobactam non-susceptible MIC ≥ 32/4 mg/L for *Enterobacteriaceae* and *P. aeruginosa*.

Ceftazidime/avibactam susceptible MIC ≤ 8/4 mg/L for *Enterobacteriaceae* and *P. aeruginosa* and ceftazidime/avibactam resistant MIC ≥ 16/4 mg/L for *Enterobacteriaceae* and *P. aeruginosa*.

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617. Efficacy of Dimercaptosuccinic Acid (DMSA), a Zinc Chelator, in Combination with Imipenem Against Metallo-β-Lactamase Producing *Escherichia coli* in a Murine Peritonitis Model

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Background. A strategy used by bacterial strains to resist β-lactam antibiotics is the expression of metallo-β-lactamases (MBL) requiring zinc for activity. The use of a zinc chelator may restore carbapenem activity against MBL-producing Enterobacteriaceae. DMSA is a heavy metal chelator approved in humans with a satisfactory safety record. Our objective was to evaluate the activity of DMSA in combination with carbapenems, *in vitro* and in a fatal murine peritonitis model, against MBL-producing *Escherichia coli*.

Methods. Isogenic derivatives of wild-type *E. coli* CFT073 producing the MBL NDM-1, VIM-2, IMP-1, and the serine carbapenemases OXA-48 and KPC-3 were constructed. Minimum inhibitory concentrations (MICs) of imipenem, meropenem, and ertapenem were determined against each strain alone or in combination with DMSA. Mice were infected with *E. coli* CFT073 or NDM-1 and treated intraperitoneally for 24 hours with imipenem 100 mg/kg every 4 hours, DMSA 200 mg/kg every 4 hours, or both. Mice survival rates and bacterial counts in peritoneal fluid (PF) and spleen were assessed at 24 hours.

Results. *In vitro*, DMSA in combination with each carbapenem permitted a significant decrease of the MICs against all MBL-producing strains, in a concentration-dependent manner. The maximum effect was found for the NDM-1 strain with a 6- to 8-fold MIC reduction, depending on the carbapenem used. NDM-1 strain became susceptible to carbapenems with concentrations of DMSA ≥6 mM. Increasing zinc concentrations above 1 mg/L (average human plasma concentration) did not alter this effect. No benefit of DMSA was observed against non-MBL strains. *In vivo*, when used alone, the DMSA regimen was not toxic in uninfected mice and ineffective against NDM-1-infected mice (100% mortality). Combination of imipenem and DMSA significantly reduced bacterial counts in PF and spleen as compared with imipenem alone ($P < 0.001$), and reduced mortality, although not significantly (11% vs. 37%, respectively, $P = 0.12$). No benefit of the combination was observed against CFT073.

Conclusion. DMSA is highly effective *in vitro* in reducing carbapenems MICs against MBL-producing *E. coli* and appears as a promising strategy in combination with carbapenems for the treatment of NDM-1-related infections.

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618. Fluconazole-Resistant *Candida albicans* Vaginitis with Cross-Resistance to Azoles: A Case Report

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