1580. Colistin Potentiates the *In Vitro* Activity of Meropenem–Vaborbactam (M/V) Against Some, but not All KPC-producing *Klebsiella pneumoniae* (KPC-Kp)

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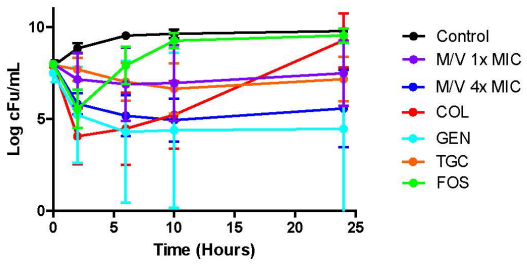
Background. M/V demonstrates potent *in vitro* activity against KPC-producing organisms. It is unclear whether the combination interacts synergistically with other active agents.

Methods. We tested isolates for responses to M/V alone (1 and 4x MIC; V fixed at 8 µg/mL), and in combination with colistin (COL; 2 µg/mL), fosfomycin (FOS; 100 µg/mL + 25 µg/mL G6P), gentamicin (GEN; 2 µg/mL), and tigecycline (TGC; 2 µg/mL) by time-kill using a starting inoculum of 1×10^8 cFu/mL. 24h was the primary endpoint.

Results. 16 KPC-Kp isolates were studied (7 KPC-2 and 9 KPC-3); all were M/V-susceptible (MIC range: 0.015 – 4 µg/mL). 44% harbored *ompK36* mutations (4 IS*5* promoter insertion, 2 134–135 DG duplication, and 1 premature stop codon). Median M/V MICs were higher against isolates with mutant *ompK36* (0.25 vs. 0.03; $P = 0.002$). Mean log-kills by M/V at 1x and 4x were -0.50 and -2.41, respectively; M/V was bactericidal (≥3-log kill) against 6% and 56%, respectively (Figure 1). Mean log-kills at 4× were greater against KPC-2 (-3.79) than KPC-3 (−1.33) isolates ($P = 0.09$), and among isolates with (−3.31) vs. without (−1.71) *ompK36* mutations ($P = 0.11$). GEN was the most active single agent (bactericidal against 56%, mean log-kill = −3.04). In combo with M/V, rates of synergy (>2-log kill in combo) with COL, FOS, GEN, and TGC were 44%, 19%, 12.5%, and 12.5%, respectively (Figure 2). Corresponding rates of bactericidal activity were 44%, 25%, 69%, and 31%, respectively. Antagonism (> 1-log kill by most active single agent) was identified for each combo against 2 isolates. Mean log-kills by M/V + GEN were greater against isolates with GEN MICs ≤1 (−7.16) vs. ≥2 (−1.66; $P = 0.001$), reflecting the activity of GEN alone. Mean log-kills by M/V + COL were greater against isolates with IS*5* insertions (-6.32) compared with wild type (−2.38) or other mutations (−1.77) in *ompK36*. Responses to M/V + FOS were not dependent upon FOS MIC, but log-kills were greater against mutant (-2.13) vs. wild-type (0.01) *ompK36* ($P = 0.03$).

Conclusion. M/V + GEN is rapidly cidal if GEN MICs are ≤1, while M/V + COL resulted in highest rates of synergy against diverse KPC-Kp. Mean log-kills were highest among isolates with IS*5* promoter insertions suggesting a potential role for COL combination therapy against KPC-Kp isolates with decreased outer membrane permeability.

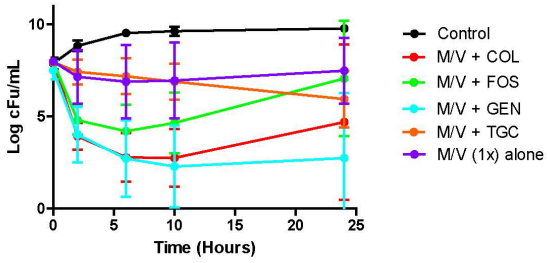
Figure 1. Mean log-kills by each agent alone against KPC-Kp (n=16)



COL = Colistin 2 µg/mL; FOS = Fosfomycin 100 µg/mL + 25 µg/mL G6P; GEN = Gentamicin 2 µg/mL; M/V = Meropenem-vaborbactam (vaborbactam fixed at 8 µg/mL); TGC = Tigecycline 2 µg/mL

Note. Error bars show the standard deviation of log-kills at each time point.

Figure 2. Mean log-kills by each M/V combination regimen against KPC-Kp (n=16)



COL = Colistin 2 µg/mL; FOS = Fosfomycin 100 µg/mL + 25 µg/mL G6P; GEN = Gentamicin 2 µg/mL; M/V = Meropenem-vaborbactam (vaborbactam fixed at 8 µg/mL); TGC = Tigecycline 2 µg/mL

Note. Error bars show the standard deviation of log-kills at each time point.

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1581. Comparative *In Vitro* Activity of Ceftolozane/tazobactam and Comparator Agents Against *Enterobacteriaceae* and *Pseudomonas Aeruginosa* Clinical Isolates in Colombia

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Background. Multidrug-resistant Enterobacteriaceae (Ent) and Pseudomonas aeruginosa (Pae) are involved in a considerable number of healthcare-associated infections, thus representing a therapeutic challenge. Ceftolozane–tazobactam (C/T) is a combination of a novel cephalosporin with a known β-lactamase inhibitor. Ceftolozane has high affinity for penicillin-binding proteins, improved outer membrane permeability, increased stability against efflux and enhanced stability against chromosomal AmpC β-lactamases compared with other β-lactam antibiotics. This agent is not active against carbapenemases. We evaluated the in vitro activity of C/T against clinical isolates of Ent and Pae collected from 2016- 2017 and compared it to the activity of broad-spectrum antimicrobial agents.

Methods. 1.644 Ent and Pae non-duplicate clinical isolates were collected in 13 medical centers located in 12 Colombian cities. Minimum inhibitory concentrations (MIC) were performed by broth microdilution and interpreted according to current CLSI guidelines. Isolates tested included 813 *Escherichia coli* (Eco), 441 *Klebsiella pneumoniae* (Kpn), 82 *Enterobacter* spp., (Enb); 60 *Serratia marcescens* (Sma) and 248 Pae. Comparator agents were ceftriaxone (CRO), cefotaxime (CTX), ceftazidime (CAZ), cefepime (FEP), piperacillin/tazobactam (TZP), ertapenem (ETP), imipenem (IMI), meropenem (MEM).

Results. Susceptibilities to C/T and comparators of 4 Ent species and Pae are shown in Table 1. Compared with other β-lactams such as CRO, CAZ, TZP, and FEP, C/T had considerably higher susceptibility rates against ESBL, non-carbapenem-resistant (CR) Eco and Kpn isolates. C/T MIC50/90 were: Eco (≤1/≤1); Kpn (≤1/128); Enb (≤1/64); Sma (≤1/≥256); Pae (≤1/≥256). In the case of P.aeruginosa despite the high resistance rates observed in the study, C/T had the best susceptibility, even higher than the carbapenems.

Conclusion. Overall, C/T demonstrated higher in vitro activity than currently available cephalosporins and TZP when tested against Ent and Pae. C/T provides an important treatment option against infections caused by non-carbapenemase producing Gram-negative pathogens. Further studies are warranted to identify an emerging mechanism of resistance in Colombia.

Table 1. Susceptibility rates of C/T and comparators agents against 1644 *Enterobacteriacea* and *P. aeruginosa* clinical isolates from Colombia [a]

Organisms	C/T%S	CRO%S	CTX%S	CAZ%S	TZP%S	FEP%S	ETP%S	IMI%S	MEM%S
Eco (813)	94	72	72	79	84	82	91	95	95
Eco ESBL-non-CR (156)	97	0	2	33	42	92	100	100	100
Kpn (441)	70	50	51	52	62	57	69	74	76
Kpn ESBL-non-CR (83)	82	0	6	20	25	54	100	98	100
Sma (60)	68	-	-	62	63	63	70	67	73
Sma ETP *susceptible* (39)	92	-	-	92	95	87	100	92	100
Ent (82)	60	-	-	48	48	57	59	70	74
Ent ETP-*susceptible* (48)	88	-	-	73	73	83	100	100	100
Pae (248)	66	-	-	55	59	57	-	30	47
Pae MEM-*susceptible* (117)	97	-	-	86	88	91	-	63	100
Pae MEM-*non-susceptible* (131)	39	-	-	27	29	30	-	1	0

[a] ESBL phenotype defined as a MIC at ≥ 2 mg/L for ceftriaxone

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1582. Delafloxacin Activity Against Drug-Resistant *Streptococcus pneumoniae*, *Haemophilus influenzae*, Haemophilus parainfluenzae, and *Moraxella catarrhalis* from US Medical Centers (2014–2018)

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Background. Delafloxacin (DLX) is an anionic fluoroquinolone (FQ) antimicrobial that was approved in 2017 by the United States (US) Food and Drug Administration for the treatment of acute bacterial skin and skin structure infections. DLX recently successfully completed a clinical trial for the treatment of community-acquired bacterial pneumonia (CABP). In the present study, *in vitro* susceptibility (S) results for DLX and comparator agents were determined for CABP pathogens including *Streptococcus pneumoniae* (SPN), *Haemophilus influenzae* (HI), *H. parainfluenzae* (HP) and *Moraxella catarrhalis (*MC) clinical isolates from US hospitals participating in the SENTRY Program during 2014–2018.

Methods. A total of 1,975 SPN, 1,128 HI, 684 MC, and 43 HP isolates were collected from community-acquired respiratory tract infections (CARTI) during 2014–2018 from US hospitals. Sites included only 1 isolate/patient/infection episode. Isolate

identifications were confirmed at JMI Laboratories. Susceptibility testing was performed according to CLSI broth microdilution methodology, and CLSI (2019) breakpoints were applied where applicable. Other antimicrobials tested included levofloxacin (LEV) and moxifloxacin (MOX; not tested in 2015). Multidrug-resistant (MDR) SPN isolates were categorized as being nonsusceptible (NS) to amoxicillin-clavulanate, erythromycin, and tetracycline; other SPN phenotypes were LEV-NS or penicillin (PEN)-NS. β-Lactamase (BL) presence was determined for HI, HP, and MC.

Results. The activities of the 3 FQs are shown in the table. The most active agent against SPN was DLX, with the lowest $MIC_{50/90}$ values of 0.015/0.03 mg/L. DLX activities were similar when tested against the MDR or PEN-NS for SPN phenotypes. LEV-NS isolates had DLX $MIC_{50/90}$ results of 0.12/0.25 mg/L. DLX was the most active FQ against HI, HP, and MC. BL presence did not affect FQ MIC values for HI or MC; only 2 HP isolates were BL-positive.

Conclusion. DLX demonstrated potent *in vitro* antibacterial activity against SPN, HI, HP, and MC. DLX was active against MDR SPN that were NS to the agents commonly used as treatments for CABP. DLX had excellent activity against LEV-NS SPN. These data support the continued study of DLX as a potential treatment for CABP.

Organism/Phenotype (n)	Delafloxacin $MIC_{50/90}$ (mg/L)	Levofloxacin $MIC_{50/90}$ (mg/L)	Moxifloxacin $MIC_{50/90}$ (mg/L, n[a])
S. pneumoniae (1,975)	0.015/0.03	1/1	≤0.12/0.25 (1,684)
MDR (84)	0.03/0.03	1/2	≤0.12/0.25 (74)
Pen-NS (745)	0.015/0.03	1/1	≤0.12/0.25 (637)
LEV-NS (16)	0.12/0.25	>4/>4	2/4 (13)
H influenzae (1,128)	≤0.001/0.002	≤0.015/0.03	0.03/0.06 (965)
BL-positive (363)	≤0.001/0.002	≤0.015/0.03	0.03/0.06 (318)
H. parainfluenzae (43)	0.008/0.015	0.03/0.12	0.12/0.25 (10)
M. catarrhalis (684)	0.004/0.008	0.03/0.06	0.06/0.06 (598)
BL-positive (589)	0.004/0.008	0.03/0.06	0.06/0.06 (585)

[a]Number of isolates shown for moxifloxacin, not tested in 2015.

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1583. Eight Years of Sustained Potency and Activity of Oritavancin against Gram-Positive Isolates Causing Bacteremia and Endocarditis in the USA, Including Enterococcal Infections Requiring an Optimized Dosing Strategy for Daptomycin

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Background. Oritavancin (ORI) is a potent lipoglycopeptide with desirable PK/PD parameters for treating serious gram-positive infections. This study assessed the activity of ORI against *Staphylococcus aureus* (SA), *Enterococcus faecalis* (EF), and *E. faecium* (EFM) causing bloodstream infection (BSI), including infective endocarditis (IE) and daptomycin (DAP)- susceptible dose-dependent (SDD) vancomycin-resistant (VRE) subsets. We also evaluated the longitudinal activity of ORI.

Methods. A total of 5,469 SA, 1,157 EF, and 721 EFM were recovered from BSI in 35 US sites (2011–2018). Subsets of SA isolates causing IE (84) and EFM displaying DAP-SDD-VRE phenotypes (230) were included. Identification was confirmed by MALDI-TOF MS and isolates were tested for susceptibility (S) according to CLSI.

Results. Overall, ORI showed similar MIC_{50} (0.03 mg/L) and MIC_{90} results (0.06 mg/L) against MRSA and MSSA (figure) and the SA EC subset (41.7% MRSA; data not shown). Similar findings were noted for ORI tested against EF DAP-S ($MIC_{50/90}$, 0.015/0.06 mg/L) and DAP-SDD ($MIC_{50/90}$, 0.015/0.06 mg/L). ORI MIC values against DAP- and VAN-S EFM ($MIC_{50/90}$, ≤0.008/0.015 mg/L) were at least 8-fold lower than those from DAP-SDD-VRE isolates ($MIC_{50/90}$, 0.06/0.12 mg/L; 31.9% of all EFM), and all EFM were inhibited by ORI at ≤0.25 mg/L. The longitudinal analysis showed MRSA rates varying from 39.7% (2017) to 46.8% (2011), while the annual ORI MIC_{50} and MIC_{90} results were 0.015–0.06 mg/L and 0.03–0.12 mg/L, respectively, against MRSA during the 8-year period. ORI yearly MIC_{50} and MIC_{90} results were 0.015–0.03 mg/L and 0.03–0.12 mg/L against EF, respectively. MIC_{50} and MIC_{90} results of 0.008–0.03 mg/L and 0.03–0.12 mg/L, respectively, were obtained for ORI against the DAP-SDD EF subset each year. ORI MIC_{50} and MIC_{90} results of 0.03–0.06 and 0.06–0.12 mg/L were obtained annually against DAP-SDD-VRE (EFM), respectively.

Conclusion. ORI showed a potent activity against this collection of isolates causing BSI and IE in the USA, including resistant subsets requiring higher dosage regimens when treating serious infections. In addition, ORI maintained a stable potency throughout the 8-year study period with no apparent temporal trends.

Organism / Phenotype	Cumulative % inhibited by oritavancin at:							$MIC_{50/90}$
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	
S. aureus								
MSSA	4.2	40.1	79	95.9	100			0.03/0.06
MRSA	3.6	39.7	77.4	95	99.9	100		0.03/0.06
E. faecalis								
DAP-S	27.5	68.4	88.9	94.4	97.8	99.6	100	0.015/0.06
DAP-SDD	28.9	61.4	77.1	92.8	98.8	100		0.015/0.06
E. faecium								
DAP-S-VSE	85.6	99	100					≤0.008/0.015
DAP-SDD-VRE	4.3	18.3	49.6	82.2	97	100		0.06/0.12

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; DAP-S, daptomycin susceptible; DAP-SDD, daptomycin susceptible-dose dependent; VSE, vancomycin-susceptible enterococci; VRE, vancomycin-resistant enterococci.

Disclosures. **All authors:** No reported disclosures.

1584. Minocycline Activity Against *Stenotrophomonas maltophilia* Isolated From Patients in US Hospitals

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Background. *Stenotrophomonas maltophilia* (SM) has emerged as a common hospital-associated opportunistic pathogen found in immunocompromised and immunocompetent patients. SM is intrinsically resistant to many common drug classes, including carbapenems, cephalosporins, and aminoglycosides. Only 4 antibiotics have CLSI breakpoints for SM: minocycline (MIN), ceftazidime (CAZ), levofloxacin (LVX) and trimethoprim-sulfamethoxazole (TMP-SMX). Minocycline is frequently used to treat SM infections. In this study, we analyzed susceptibilities of SM isolates collected as part of the SENTRY Program. We also examined the frequency of SM isolation from pneumonia in hospitalized patients (PIHP) among all Gram-negative (GN) species.

Methods. From 2014 to 2018, 990 SM isolates were collected from hospitalized patients in 32 US hospitals. Hospitals submitted 1 isolate per patient per infection episode that met local criteria for being the likely causative pathogen and submitted consecutive isolates from pneumonia. Isolates were tested for MIN susceptibility (S) using the CLSI broth microdilution method at JMI Laboratories. Other antimicrobials tested were CAZ, LVX, and TMP-SMX. TMP-SMX was tested 3 of 5 years. All infection types were included in the susceptibility analysis. The prevalence of SM isolates in PIHP during this period was also analyzed.

Results. There were 9,120 GN pathogens isolated from PIHP. The most commonly isolated species was *P. aeruginosa* (34.7%), followed by *Klebsiella pneumoniae* (12.6%), *Escherichia coli* (10.1%), and SM (7.9%). Among the 990 infections caused by SM, PIHP was the most common at 72.4%, followed by bloodstream infections (14.4%) and skin/skin structure infections (6.9%). The %S and $MIC_{50/90}$ values of the 4 antimicrobials tested in this study are shown in the table.

Conclusion. SM was the fourth most frequent cause of GN PIHP in US medical centers. MIN was the most active drug tested against SM with 99.5%S, followed by TMP-SMX (94.7%), and CAZ was the least active with 28.5%S. This study suggests that MIN may be a consideration as a treatment for infections caused by SM, with a very low resistance rate based on CLSI breakpoints.

Table. Activities of MIN and comparator agents when tested against 990 *S. maltophilia* isolates

Antimicrobial agent	No. of isolates	MIC_{50}	MIC_{90}	Range	CLSI[a]		
					%S	%I	%R
Minocycline	990	0.5	2	≤0.06 to >8	99.5	0.3	0.2
Ceftazidime	990	32	>32	0.25 to >32	28.5	10.2	61.3
Levofloxacin	990	1	>4	≤0.12 to >4	77.8	8.9	13.3
Trimethoprim-sulfamethoxazole	609	≤0.5	1	≤0.5 to >4	94.7		5.3

[a] CLSI (2019).

Disclosures. **All authors:** No reported disclosures.

1585. Isavuconazonium Sulfate plus Micafungin Improves Survival in an Immunocompromised Murine Model of Disseminated Fusariosis

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Background. Disseminated fusariosis in patients with hematological malignancies is a frequently fatal and emerging invasive mycosis. *Fusarium* spp. are often resistant to safely achievable concentrations of mould active triazoles and amphotericin B. We aimed to determine the efficacy of isavuconazonium sulfate (ISA) alone or in combination with micafungin (MICA) in a murine model of disseminated fusariosis caused by *Fusarium solani.*

Methods. Groups of five 5-week-old Swiss Webster female mice, 20–22 g, were rendered neutropenic by intraperitoneal (IP) injection of cyclophosphamide at 200 mg/kg on day −2 and 150 mg/kg on day +3. Mice were infected with $5 \times 10E^5$ CFU *F. solani* intravenously (IV) via the lateral tail vein on day 0. To prevent bacterial infection, ceftazidime was administered 50 mg/kg/day IP. Therapy began 18 h post-challenge for 6 days. MICA was given at dosages of 10, 5, 2.5 and 1.25 mg/kg IP Q12h combined with ISA 14 mg/kg/day IP. Six groups of mice received ISA orogastrically (OG) Q8h, Q12h and Q24h at 224 mg/kg alone or combined with MICA at 10 mg/kg Q12h IP. Kaplan–Meier survival analysis was performed.

Results. ISA at 14 mg/kg Q12h combined with 10 mg/kg MICA doses resulted in improved survival but with no significant reduction of residual fungal burden compared with monotherapy or other ISA/MICA dose combinations. Improved survival