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1349. Global Surveillance of Cefiderocol Against Gram-Negative Clinical Strains Collected in North America: SIDERO-WT-2015

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Background. Cefiderocol (CFDC) is a novel parenteral siderophore cephalosporin with potent activity against a wide range of Gram-negative pathogens, including carbapenem-resistant strains. Additionally, a recently conducted *in vivo* murine-based study has demonstrated an incremental exposure-response profile over a dose range without the appearance of adaptive resistance. In this study, we evaluated the *in vitro* activity of CFDC and comparator agents against clinical isolates collected in 2015–2016 from North America from SIDERO-WT-2015 surveillance study.

Methods. A total of 3,602 isolates (2,470 *Enterobacteriaceae*, 223 *A. baumannii*, 85 *Acinetobacter* spp., 619 *P. aeruginosa*, 165 *S. maltophilia* and 17 *Burkholderia* cepacia, and 23 *Burkholderia* spp.) collected from the United States and Canada in 2015–2016 were tested. MICs were determined for CFDC, cefepime (FEP), ceftazidime–avibactam (CZA), ceftolozane–tazobactam (C/T), ciprofloxacin (CIP), colistin (CST), and meropenem (MEM) by broth microdilution and interpreted according to CLSI guidelines. As recommended by CLSI, cefiderocol was tested in iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB). Carbapenem nonsusceptible (Carb-NS) strains were defined as MEM MIC ≥2 μg/mL for *Enterobacteriaceae*, and ≥4 μg/mL for nonfermenters.

Results. CFDC exhibited potent *in vitro* activity against 3,602 strains of Gram-negative bacteria with an overall MIC_{90} of 0.5 mg/mL. As shown in the following table, MIC_{90} of CFDC against *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, and *Enterobacteriaceae* including the subset of Carb-NS isolates were 0.5, 2, 0.5 and 0.5 mg/mL, respectively. At 4 mg/mL, CFDC inhibited the growth of 99.6% of the isolates while 18.1%, 12.6%, and 13.8% showed resistance to CZA, C/T, and CST, respectively.

Conclusion. CFDC demonstrated potent *in vitro* activity against the teat isolates collected from North America with greater than 99.6% of isolates having MIC values ≤4 mg/mL, including Carb-NS isolates of *A. baumannii*, *P. aeruginosa*, and *Enterobacteriaceae*. These findings indicate that this agent has high potential for treating infections caused by these problematic organisms.

Organisms	N	CFDC	FEP	CZA	C/T	CIP	CST	MEPM
Enterobacteriaceae	2470	0.5	4	0.5	1	>8	>8	≤0.06
P. aeruginosa	619	0.5	16	8	2	>8	2	8
A. baumannii	223	2	>64	>64	>64	>8	1	>64
S. maltophilia	165	0.5	>64	64	>64	>8	8	>64

Disclosures. **M. Tsuji**, Shionogi & Co., Ltd.: Employee, Salary. **M. Hackel**, IHMA, Inc.: Employee, Salary. **Y. Yamano**, Shionogi & Co., Ltd.: Employee, Salary. **D. Sahm**, IHMA, Inc.: Employee, Salary.

1350. Therapeutic Effects of Baloxavir Marboxil against Influenza A Virus Infection in Ferrets

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Background. Baloxavir marboxil (BXM) is a novel small molecule inhibitor of cap-dependent endonuclease that is essential for influenza virus transcription and replication. In this study, pharmacokinetic profiles of BXM and baloxavir acid (BXA), an active form of BXM, were first examined in ferrets, and then the therapeutic effects of BXM against influenza A virus infection were compared with that of oseltamivir phosphate in ferrets.

Methods. The plasma exposure of BXA and BXM was examined after a single oral administration of BXM at doses of 10 and 30 mg/kg. The concentrations in plasma were determined by liquid chromatography-tandem mass spectrometry(LC/MS/MS). For efficacy study, ferrets infected intranasally with A/Kadoma/2006 (H1N1) were administrated 10 or 30 mg/kg of BXM orally twice daily for 1 day, starting at 1 day post-infection (p.i.) or administrated 10 mg/kg of BXM orally twice daily for 1 day, starting at 2 days p.i.. Oseltamivir phosphate was administered at doses of 5 mg/kg orally twice daily for 2 days as a comparison. The virus titer in the nasal washes and body temperature change were monitored during infection.

Results. BXA was detected in ferret plasma after a single oral administration of BXM at 10 and 30 mg/kg, in more than a dose-proportional manner. When the treatment was initiated at 1 day p.i., BXM at 10 and 30 mg/kg showed reduction of virus titer to an undetectable level on day 2 p.i. and statistically significant reduction in virus titer over time from day 2 to 3 p.i. compared with vehicle and oseltamivir phosphate. Moreover, the change of body temperature over time from 8 hours after the first administration to 3 days p.i. was significantly lower in BXM at 10 and 30 mg/kg than vehicle and oseltamivir phosphate. These effects were also observed in ferrets treated with BXM at 10 mg/kg even when administered at 2 day p.i. where ferret exhibit fever that is more than 1 degree higher than on 1 day p.i..

Conclusion. Single-day oral administration of BXM had beneficial effects on viral titer and symptoms in ferrets infected with influenza A virus, which were superior to those observed with oseltamivir phosphate and vehicle.

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1351. *In vitro* Activity of Cefiderocol (S-649266), a Siderophore Cephalosporin, Against Enterobacteriaceae With Defined Extended-Spectrum B-Lactamases and Carbapenemases

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Background. Cefiderocol is a novel siderophore cephalosporin targeted for activity against carbapenem and multidrug-resistant Gram-negative species, including extended-spectrum β-lactamase (ESBL) and carbapenemase-producing strains. The Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacteriaceae (CRACKLE) is a federally funded, prospective multi-center consortium of 20 hospitals from nine US healthcare systems to track carbapenem-resistant Enterobacteriaceae.

Methods. Minimum inhibitory concentrations (MICs) of cefiderocol and meropenem were determined by broth microdilution according to current CLSI guidelines. Cefiderocol was tested in iron-depleted cation-adjusted Mueller–Hinton (MH) broth, meropenem was tested in cation-adjusted MH broth. Cefiderocol MICs were read as the first drug well in which the growth was significantly reduced (i.e., a button of <1 mm or light/faint turbidity) relative to the growth observed in the growth control well containing the same medium. Trailing endpoints were disregarded. Isolates tested included 35 *Escherichia coli*, five Enterobacter/Citrobacter group, and 794 *Klebsiella pneumoniae*. Isolates had characterized β-lactamases including TEM, SHV, and CTX-M ESBLs and KPC, NDM, and OXA carbapenemases.

Results. Cefiderocol MICs ranged from ≤0.03 to >64 mg/L, with overall MIC50 of 0.5 mg/L and MIC90 of 4 mg/L (table). MIC90 value (≤0.03 mg/L) was lowest against isolates with no ESBLs or carbapenemases. MIC90 was 1 mg/L for OXA and TEM/SHV groups, 2–4 mg/L for KPC-3 groups and 8 mg/L for NDM and KPC-2 groups.

Conclusion. Compared with isolates without ESBLs and carbapenemases, cefiderocol shows higher MICs against isolates with ESBLs, including TEM, SHV, and CTX-M and carbapenemases including KPC, NDM, and OXA. The clinical utility of cefiderocol against ESBL and carbapenemase-producing *Enterobacteriaceae* is dependent on the pharmacokinetic and pharmacodynamic properties of cefiderocol.

Table: Activity of Cefiderocol

β-Lactam Resistance	N	MIC range (mg/L)	MIC50 (mg/L)	MIC90 (mg/L)
ampC	3	0.25 to 2	NA	NA
KPC-2	255	≤0.03 to 32	0.5	8
KPC2 + Other	101	≤0.03 to 16	2	8
KPC-3	276	≤0.03 to 64	0.25	2
KPC3 + Other	106	≤0.03 to 16	0.5	4
NDM	28	0.25 to >64	2	8
OXA	8	≤0.03 to 1	0.25	1
TEM/SHV ESBL	42	≤0.03 to >64	2	1
None	15	≤0.03 to 0.12	≤0.03	≤0.03
All	834	≤0.03 to >64	0.5	4

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1352. A Computational Approach for Exploring the Binding Mechanism of Chebulinic Acid on Herpes Simplex Virus-2 and Its Implication on Chikungunya and Dengue

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Background. Chebulinic acid (CA), a natural compound isolated from the tree Terminalia chebula, was recently reported to have shown antiviral activity against Herpes simplex virus-2 (HSV-2). The study showed inhibition activity of CA, preventing the attachment of HSV-2 on the host cells. This activity was speculated to be due to an interaction between CA and viral surface glycoproteins, triggering alterations in its function or making virus particles inert and preventing their attachment to host cells. However, the mechanism of this inhibition was not established. The current study was designed not only to help gain insights of the mechanism of action of CA on HSV-2, but also to computationally check its binding affinity on other enveloped arboviruses, i.e., Chikungunya (ChikV) and Dengue (DenV).

Methods. The viral surface glycoproteins of HSV-2, ChikV, and DenV were subjected to molecular docking with CA using the software, AutoDock Vina. Protein–protein docking was performed with ClusPro online server to elucidate the specific site and residues involved in binding between viral protein and human host receptors. Due to unavailability of crystal structure of Prohibitin, a human receptor for ChikV, structural modeling was performed with i-Tasser server.

Results. The conformations obtained after docking showed good hydrogen bond interactions with a docking energy of −9.3, −8.1, and −8.8 kcal/mol against HSV-2, ChikV, and DenV, respectively. In all three viruses, CA was found to bind specifically at the site directly involved in host attachment, suggesting a possible mechanism of action by which CA inhibits the viral attachment that is consistent with the result obtained from the in vitro experiment on HSV-2. Hence the natural bio-molecule Chebulinic acid has the potential to inhibit the host attachment step of HSV-2, ChikV, and DenV by directly binding to their viral glycoproteins.

Conclusion. Chebulinic acid shows a good propensity as an antiviral agent, capable of acting against multiple enveloped viruses. Additionally, a more potent and specific drug can be designed on the template of CA by process of molecular modification.

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1353. *In Vitro* Activity of Lefamulin (LEF) Against Bacterial Pathogens Commonly Causing Community-Acquired Bacterial Pneumonia (CABP): 2016 SENTRY Data From the United States

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Background. LEF, the first pleuromutilin antibiotic for IV and oral use in humans, is in Phase 3 clinical trials for the treatment of CABP in adults. In the first of these to be completed, LEF demonstrated noninferiority to moxifloxacin ± linezolid. LEF inhibits bacterial translation by binding the 50S ribosomal subunit at the A- and P-sites in the peptidyl transferase center. CABP is a leading cause of infectious diseases in the United States and increasing antibacterial resistance complicates its treatment. This study investigated the *in vitro* activity of LEF and comparators against a contemporary set of bacterial respiratory pathogens collected in the United States.

Methods. Isolates (n = 1674, 1/patient) were collected from 32 medical centers in the United States as part of the SENTRY Surveillance Program. LEF and comparators were tested by CLSI broth microdilution methods, and susceptibility was determined using the CLSI (2018) breakpoints.

Results. LEF was the most active compound against *Streptococcus pneumoniae* ($MIC_{50/90}$ of 0.12/0.12 µg/mL), and its activity was not affected by resistance to other antibiotic classes. *S. pneumoniae* isolates were susceptible to levofloxacin (99.1%) and ceftriaxone (97.7%), whereas only 53.9%, 63.9%, and 80.4% of isolates were susceptible to macrolides, penicillin (oral), and tetracycline, respectively. LEF also showed potent activity against *Staphylococcus aureus* ($MIC_{50/90}$ of 0.06/0.12 µg/mL), including methicillin-resistant (MRSA) isolates ($MIC_{50/90}$ of 0.06/0.12 µg/mL, 87.1% resistant to erythromycin), *Haemophilus influenzae,* ($MIC_{50/90}$ of 0.5/1 µg/mL, 26.9% β-lactamase producing), and *Moraxella catarrhalis* ($MIC_{50/90}$ 0.06/0.06 µg/mL, 96.5% β-lactamase positive) (figure).

Conclusion. LEF displayed potent *in vitro* activity against a contemporary collection of respiratory pathogens from the United States. LEF was active regardless of resistance phenotype to other antibiotic classes including β-lactams, tetracyclines, or macrolides. These results further support the clinical development of lefamulin for the treatment of CABP or other respiratory tract infections.

$MIC_{50/90}$ of Lefamulin and Comparators

Organism (n)	$MIC_{50/90}$ (µg/mL)				
	Lefamulin	Amoxicillin/ Clavulanic acid	Azithromycin	Ceftaroline/ Ceftriaxone*	Moxifloxacin	Tetracycline
S. pneumoniae (815)	0.12 / 0.12	≤0.03 / 2	0.12 / >32	0.03 / 1	1 / 1	≤0.25 / >8
Penicillin susceptible† (790)	0.12 / 0.12	≤0.03 / 2	0.12 / >32	0.03 / 1	0.12 / 0.25	≤0.25 / >8
Penicillin nonsusceptible† (25)	0.06 / 0.12	4 / >4	>32 / >32	2 / >2	0.25 / 0.25	>8 / >8
S. aureus (550)	0.06 / 0.12	ND	32 / >32	0.25 / 1	≤0.06 / >4	ND
MRSA (233)	0.06 / 0.12	ND	>32 / >32	0.5 / 1	1 / >4	ND
H. influenzae (223)	0.5 / 1	1 / 2	1 / 1	0.004 / 0.015	0.03 / 0.06	0.5 / 1
M. catarrhalis (86)	0.06 / 0.06	0.12 / 0.25	0.01 5/ 0.03	0.25 / 1	0.06 / 0.06	0.25 / 0.5

MRSA=methicillin-resistant *Staphylococcus aureus*; ND=not determined.
*Ceftaroline for *S. aureus*; ceftriaxone for *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*; †Penicillin MIC≤2 µg/mL; ‡Penicillin MIC≥4 µg/mL for the nonmeningitis breakpoint.

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1354. Novel Formulation SUBA-Itraconazole in Fed and Fasted Healthy Volunteers: Expanding the Clinical Utility of the Established Mold Active Agent

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Background. Itraconazole has been established as an effective mold active agent; however, wide interpatient variability in bioavailability and poor gastrointestinal tolerability have made using the agent challenging. A novel formulation, SUBA-Itraconazole (SUperBioAvailable) has been developed by Mayne Pharma to alleviate these negative properties.

Methods. An open-label, randomized, cross-over study of SUBA–Itraconazole capsules 65 mg (2 × 65 mg BID) in healthy adults under fasting and fed conditions was assessed for steady-state levels. Subjects (n = 20) were administered two capsules of SUBA–Itraconazole twice daily on Days 1–14 and once on the morning of Day 15, either on an empty stomach or with a meal. Safety was monitored by vital signs measurements, electrocardiogram measurements, clinical safety laboratory tests (liver and kidney function tests), and physical examination.

Results. Overall, SUBA–Itraconazole demonstrated similar concentrations at the end of the dosing interval (trough), with modestly lower total and peak exposure when administered under fed conditions compared with the fasted state (fed/fasted ratios of 78.09% for AUC_{tau} [14,183.2 vs. 18,479.8] 73.05% for $C_{max,ss}$ [1,519.1 vs. 2,085.2] and 91.53% for C_{trough}[1,071.5 vs. 1,218.5]); see Figures 1 and 2. The administration of SUBA–Itraconazole 65 mg capsules was well-tolerated by the healthy subjects participating in this study.

Conclusion. The results demonstrate a promising clinical utility for SUBA–Itraconazole in practice. Unlike the conventional capsule formulation which requires a high fat meal for absorption, or the oral solution formulation which requires a fasted administration, SUBA–Itraconazole reached a therapeutic steady state in both fasted and fed states. The similar trough level, however higher peak with fasted state, likely represents a more gradual absorption of drug in the fed state. The slightly higher bioavailability in a fasted state, without gastrointestinal intolerability, is particularly promising for the clinical use of SUBA–Itraconazole in patients unable to have a high fat content meal due to chemotherapy or post-surgery such as hematology patients and transplant recipients.

Figure 1. Mean pre-dose plasma itraconazole concentrations.