4985 (654 Enterobacterales and 4331 non-fermenters) MEM non-susceptible (based on CLSI breakpoints) strains were used for the current analysis.

Results. The minimum inhibitory concentration (MIC) range and MIC_{90} for CFDC and comparators for each MBL-producing organism group are shown in the Table. Against NDM-producing Enterobacterales, of which 42% and 33% were isolated in Turkey and Russia, respectively, CFDC inhibited the growth of 84% of isolates tested at ≤4 µg/mL. CFDC MIC_{90} was 4 µg/mL for VIM-producing Enterobacterales (41% and 31% isolated in Greece and Italy, respectively), 1 µg/mL for VIM-producing *P. aeruginosa* (50% isolated in Russia), and 4 µg/mL for IMP-producing *P. aeruginosa* (88% isolated in Czech Republic). Other comparators (except for CST) were not active against these MBL producers.

Table. MIC range and MIC90 (µg/mL) for CFDC and comparators of MBL-producing organisms

Table. MIC range and MIC_{90} (µg/mL) for CFDC and comparators of MBL-producing organisms

	NDM-producing Enterobacterales (N=45)		VIM-producing Enterobacterales (N=75)		NDM-producing A. baumannii (N=5)		VIM-producing P. aeruginosa (N=134)		IMP-producing P. aeruginosa (N=16)	
Compounds	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}
CFDC	0.25–8	8	0.12–4	4	1–8	NC	0.008–4	1	0.12–4	4
CZA	1–>64	>64	4–>64	>64	>64	NC	2–>64	>64	>64	>64
C/T	>64	>64	32–>64	>64	>64	NC	0.5–>64	>64	>64	>64
MEM	4–>64	>64	2–>64	64	64–>64	NC	4–>64	>64	8–>64	>64
FEP	32–>64	>64	0.25–>64	>64	>64	NC	8–>64	>64	>64	>64
CST	≤0.25–8	1	≤0.25–>8	>8	≤0.25–0.5	NC	≤0.25–4	2	1–2	2
CIP	2–>8	>8	≤0.12–>8	>8	≤0.12–>8	NC	0.25–>8	>8	>8	>8

NC: MIC_{90} values were not calculated because the number of isolates was ≤10. IMP: imipenemase metallo-β-lactamase; NDM: New Delhi metallo-β-lactamase; VIM: Verona integron-encoded metallo-β-lactamase.

Conclusion. CFDC inhibited the growth of 100% of MBL-positive GNB at ≤8 mg/mL and showed MIC_{90} of 4 µg/mL against all 275 MBL producers, indicating that CFDC has high potential for treating infections caused by these difficult-to-treat strains.

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1253. *In Vitro* Activity of Omadacycline against 7000 Bacterial Pathogens from the United States Stratified by Infection Type (2019)

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Session: P-58. Novel Agents

Background. Omadacycline (OMC) is a new aminomethylcycline antibacterial drug belonging to the tetracycline class, for intravenous or oral administration. It is well tolerated and has proven effective in the treatment of a variety of bacterial infections. OMC is active against bacterial strains expressing the most common clinically relevant tetracycline resistance mechanisms, namely efflux and ribosomal protection.

Methods. 7,000 clinical isolates were collected during 2019 in the SENTRY Surveillance Program from 31 medical centers in the United States (US). Isolates were obtained from bloodstream infection (23.8%), skin and skin structure infection (21.6%), pneumonia in hospitalized patients (22.7%), urinary tract infection (14.5%), intraabdominal infection (6.2%), community acquired respiratory tract infection (10.3%) and other infection types (0.9%). Identifications were confirmed by MALDI-TOF. One isolate/patient/infection episode was tested. Broth microdilution susceptibility testing was conducted according to CLSI M07 (2018) and M100 (2020) guidelines. Results were interpreted using US FDA and CLSI breakpoint criteria.

Results. OMC demonstrated potent *in vitro* activity against *Staphylococcus aureus* isolates representing multiple infection types (MIC_{90}, 0.12-0.25 mg/L; 94.7%-99.0% susceptible [S]) including MRSA (MIC_{90}, 0.25 mg/L; 96.5% S) (Table). All *S. lugdunensis* (MIC_{90}, 0.06 mg/L), *Enterococcus faecalis* (MIC_{90}, 0.12-0.25 mg/L), and *Haemophilus influenzae* (MIC_{90}, 1 mg/L) isolates were S to OMC. OMC was active against *Streptococcus pyogenes* isolates from SSSI (MIC_{90}, 0.12 mg/L; 93.3%-98.5%S) including macrolide-resistant (R) strains. Similarly, *S. pneumoniae* isolates from RTI were S to OMC (MIC_{90}, 0.06-0.12 mg/L; 98.8%-100%S) regardless of resistance to tetracycline or penicillin. Overall, 90.2%-93.6% of *Enterobacter cloacae* (MIC_{90}, 4 mg/L) and 89.7%-94.7% of *Klebsiella pneumoniae* (MIC_{90}, 4-8 mg/L) isolates from multiple infection types were S to OMC.

Conclusion. OMC demonstrated potent *in vitro* activity against Gram-positive and -negative bacterial pathogens from multiple infection types including SSSI and RTI and isolates displaying resistance to tetracycline, macrolides, and penicillin.

Table 1

		Omadacycline		Tetracycline	
Organism (no. of isolates)	Infection Type[a]	MIC_{90} (mg/L)	%S / %R[b]	MIC_{90} (mg/L)	%S / %R[c]
S. aureus (1,623)	ALL	0.25	98.3 / 0.2	≤0.5	95.0 / 4.0
S. aureus (736)	SSSI	0.12	99.0 / 0.1	≤0.5	94.3 / 4.3
S. aureus (396)	RTI	0.12	94.7 / 2.5[d]	≤0.5	94.9 / 5.1
MRSA (684)	ALL	0.25	96.5 / 0.4[e]	1	94.7 / 4.7
S. lugdunensis (26)	ALL	0.06	100 / 0.0[e]	≤0.5	96.2 / 0.0
E. faecalis (229)	ALL	0.25	100 / 0.0[e]	>16	29.3 / 70.7
E. faecalis (60)	SSSI	0.12	100 / 0.0	>16	21.7 / 78.3
S. pyogenes (68)	SSSI	0.12	98.5 / 0.0	>4	79.4 / 20.6
macrolide-R (15)	SSSI	0.12	93.3 / 0.0	>4	40.0 / 60.0
S. pneumoniae (380)	RTI	0.06	99.7 / 0.0	>4	77.1 / 22.6
tetracycline-R (86)	RTI	0.12	98.8 / 0.0	>4	0.0 / 100
penicillin-R (41)	RTI	0.06	100 / 0.0	>4	61.0 / 39.0
H. influenzae (291)	RTI	1	100 / 0.0	0.5	99.0 / 1.0
E. cloacae (219)	ALL	4	93.6 / 2.8[e]	16	85.4 / 11.4
E. cloacae (41)	SSSI	4	90.2 / 4.9	>16	83.3 / 11.9
K. pneumoniae (511)	ALL	4	93.2 / 3.5[f]	>16	78.9 / 18.6
K. pneumoniae (39)	SSSI	8	89.7 / 5.1	>16	66.7 / 30.8
K. pneumoniae (136)	RTI	4	90.4 / 5.1	>16	77.2 / 19.9
K. pneumoniae (113)	UTI	4	94.7 / 1.8[f]	>16	79.6 / 17.7

[a] ALL; all infection types, SSSI; skin and skin structure infection, RTI; respiratory tract infection, UTI; urinary tract infection.
[b] % susceptible (S) and % resistant (R) using US FDA breakpoint interpretive criteria.
[c] % S and % R using CLSI breakpoint interpretive criteria.
[d] US FDA breakpoints for CABP (MSSA only) applied for all *S. aureus*.
[e] US FDA breakpoint for ABSSSI applied.
[f] US FDA breakpoint for ABSSSI and CABP applied.

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1254. *In vitro* activity of sulbactam-durlobactam against recent global clinical *Acinetobacter baumannii-calcoaceticus* complex isolates

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Session: P-58. Novel Agents

Background. *Acinetobacter baumannii-calcoaceticus* complex (ABC) causes severe infections that are difficult to treat due to increasing resistance to antibacterial therapy. Sulbactam (SUL) has intrinsic antibacterial activity against ABC, but its clinical utility has been compromised by the prevalence of serine β-lactamases. Durlobactam (DUR, previously ETX2514) is a diazabicyclooctenone β-lactamase inhibitor with potent activity against Ambler classes A, C and D serine β-lactamases that effectively restores SUL activity against ABC isolates. SUL-DUR is an antibiotic designed to treat serious infections caused by *Acinetobacter*, including multidrug-resistant strains, which is currently in Phase 3 clinical testing. The potency of SUL-DUR against geographically diverse ABC isolates collected in 2018 was measured.

Methods. 929 ABC isolates, including 698 *A. baumannii*, 13 *A. calcoaceticus*, 54 *A. nosocomialis*, and 164 *A. pittii*, were collected in 2018 from geographically diverse medical centers in the United States, Europe, Latin America, Israel and the Asia-Pacific region. Susceptibility testing was performed according to CLSI guidelines. Data analysis was performed using CLSI and EUCAST breakpoint criteria where available. Select isolates were subjected to whole genome sequencing with an Illumina MiSeq V2 instrument and analysis using CLCBio Genomics Workbench v6.5.

Results. In surveillance of 929 global isolates from 2018, the SUL-DUR MIC_{90} was 2 mg/L compared with 64 mg/L for SUL alone. This level of potency was consistent across species, regions, source of infection and subsets of resistance phenotypes. Fifty percent of the isolates were non-susceptible to carbapenems. Only 7 isolates (0.75%) had SUL-DUR MIC values >4 mg/L. Whole genome sequencing of these 7 isolates revealed that they either encoded the metallo-β-lactamase NDM-1, which DUR does not inhibit, or single amino acid substitutions near the active site of PBP3, the primary target of SUL.

Conclusion. SUL-DUR demonstrated potent antibacterial activity against recent, geographically diverse clinical isolates of ABC, including MDR isolates. These data support the potential utility of SUL-DUR for the treatment of antibiotic-resistant infections caused by ABC.

Disclosures. Sarah McLeod, PhD, Entasis Therapeutics (Employee) Samir Moussa, PhD, Entasis Therapeutics (Employee) Alita Miller, PhD, Entasis Therapeutics (Employee)

1255. *In Vitro* Activity of Vancapticin against Methicillin-Resistant *Staphylococcus aureus* from Periprosthetic Joint Infection

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Session: P-58. Novel Agents

Background. The vancapticins are modified vancomycin derivatives developed by adding membrane targeting motifs to the *C*-terminus of vancomycin. We determined the *in vitro* activity of a lead vancapticin candidate against periprosthetic joint infection-associated methicillin-resistant *Staphylococcus aureus* (MRSA) in the planktonic and biofilm states, and the effect of adding 0.002% polysorbate 80 (P-80; Sigma-Aldrich) on vancapticin susceptibility testing.

Methods. Thirty-seven clinical isolates of MRSA collected at Mayo Clinic (Rochester, Minnesota) were studied. Vancapticin minimum inhibitory concentrations (MICs) were determined using Clinical and Laboratory Standards Institutes guidelines. Minimum biofilm bactericidal concentrations (MBBCs) were determined using a pegged lid microtiter plate assay. Vancapticin MIC and MBBC values were assessed with and without P-80. Vancapticin, vancomycin, and dalbavancin biofilm time-kill assays were performed using biofilms formed by 10 MRSA isolates on Teflon coupons.

Results. Vancapticin MICs with and without P-80 ranged from 0.015 to 0.12 μg/mL and 0.25 to 1 μg/mL, respectively. Vancapticin MBBCs with and without P-80 ranged from 0.25 to 4 μg/mL and 1 to 8 μg/mL, respectively. Reductions of biofilm bacterial densities on Teflon coupons after 8 and 24 hours of incubation with vancapticin, vancapticin with P-80, vancomycin, or dalbavancin with P-80 were less than 3-$\log_{10}$ cfu/cm^2 for all isolates tested.

Conclusion. Vancapticin has promising *in vitro* activity against planktonic MRSA and MRSA in a pegged lid biofilm assay, but was not bactericidal against biofilms on Teflon coupons. P-80 decreased vancapticin MICs and MBBCs.

Disclosures. **Mark A. Blaskovich, PhD**, **MAB Consulting** (Consultant)**The University of Queensland** (Employee, Grant/Research Support, Other Financial or Material Support, Inventor on patent) **Robin Patel, MD**, **Accelerate Diagnostics** (Grant/Research Support)**CD Diagnostics** (Grant/Research Support)**Contrafect** (Grant/Research Support)**Curetis** (Consultant)**GenMark Diagnostics** (Consultant)**Heraeus Medical** (Consultant)**Hutchison Biofilm Medical Solutions** (Grant/Research Support)**Merck** (Grant/Research Support)**Next Gen Diagnostics** (Consultant)**PathoQuest** (Consultant)**Qvella** (Consultant)**Samsung** (Other Financial or Material Support, Dr. Patel has a patent on Bordetella pertussis/parapertussis PCR issued, a patent on a device/method for sonication with royalties paid by Samsung to Mayo Clinic, and a patent on an anti-biofilm substance issued.)**Selux Dx** (Consultant)**Shionogi** (Grant/Research Support)**Specific Technologies** (Consultant)

1256. *In Vivo* Activity and Structural Characterization of a New Generation γ-Lactam Siderophore Antibiotic Against Multidrug-Resistant Gram-Negative Bacteria and *Acinetobacter* spp.

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Session: P-58. Novel Agents

Background. Multidrug-resistant (MDR) *A. baumannii* presents a critical need for innovative antibacterial development. We have identified a new series of γ-lactam (oxopyrazole) antibiotics that target penicillin binding proteins (PBPs) and incorporate a siderophore moiety to facilitate periplasmic uptake. YU253911, an advanced iteration of this class shows potent *in vitro* activity against clinically relevant Gram-negative organisms including *Acinetobacter* spp.

Methods. Minimum inhibitory concentrations (MICs) for YU253911 were determined using broth microdilution against a 198-member panel of clinical isolates of *Acinetobacter* spp. Resistant strains were further evaluated for susceptibility to YU253911 in combination with sulbactam. The antibiotic's target protein was evaluated by binding studies with Bocillin™, a fluorescent penicillin analogue, and modeled in the PBP active site. YU253911 was evaluated *in vivo* in a mouse soft tissue infection model.

Results. MIC testing for YU253911 revealed an MIC_{50} of 0.5 μg/mL and an MIC_{90} of 16 μg/mL, which compared favorably to all tested β-lactam antibiotics including penicillins, cephalosporins, monobactams and carbapenems (MIC_{50} = 2 to > 16 μg/mL). Combination with sulbactam augmented the activity of the agent. There was no apparent correlation between YU253911-resistance and the presence of specific β-lactamase genes, and incubation with representative β-lactamase proteins (KPC-2, OXA-23, OXA-24, PER-2, PDC-3, NDM-1, VIM-2, and IMP-1) showed negligible hydrolysis of the agent. YU253911 showed promising preclinical pharmacokinetics in mice with a 15 h half-life from intravenous administration and demonstrated a dose-dependent reduction in colony forming units from 50 and 100 mg/kg q6h dosing in a mouse thigh infection model using *P. aeruginosa*.

Conclusion. YU253911, a new generation γ-lactam antibiotic effective against MDR *A. baumannii* demonstrated promising in *in vitro* potency and favorable pharmacokinetics which correlated with *in vivo* efficacy.

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1257. A phase II Prospective Randomized Study to Assess Ceftolozane-Tazobactam in the Management of Febrile Neutropenia in Patients with Hematological Malignancies

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Session: P-58. Novel Agents

Background. Despite the implementation of successful antibiotic stewardship programs, antibiotic resistance continue to emerge particularly against gram-negative bacteria. With the increase use of antibiotics in high risk patients with hematological malignancies, the empiric therapy with standard antibiotic could be inappropriate. New antibiotics may be useful to cover potential resistant pathogens. We evaluated the role of a new cephalosporin /β-lactamase inhibitor ceftolozane-tazobactam (C/T) in comparison to standard of care (SOC) antibiotics in the empiric treatment of febrile neutropenic cancer patients with hematological malignancies.

Methods. We conducted a prospective randomized open label comparative study to evaluate the safety and efficacy of C/T vs SOC antibiotics consisting of cefepime, piperacillin-tazobactam or meropenem when used in combination with gram positive antibacterial agents. Between May 2018 and March 2020, we enrolled 88 febrile neutropenic patients with hematological malignancies who presented to our emergency center. Patients received at least 72 hours of intravenous study drugs and were followed through end of IV therapy and for up to 42 days.

Results. A total of 88 patients were analyzed of whom 42 received C/T and 46 SOC antimicrobial agents. The rate of documented bloodstream infections was similar in both groups (CE-TZ 21% vs SOC 26%, p=0.61). Favorable clinical response at end of IV therapy was significantly better in the C/T arm compared to SOC therapy (88% vs 72%, p=0.039), at test of cure (21 days), and last follow-up (42 days). In patients with documented infections, the rate of microbiological eradication was similar in both groups. Drug-related adverse events that led to drug discontinuation was similar in both groups (7%). Similarly overall mortality was similar in both groups.

Conclusion. The empiric use of C/T to cover gram negative organisms in high risk febrile neutropenic patients with hematological malignancies is safe and associated with better clinical outcome than SOC antimicrobial agents. The emergence of resistant pathogens should be further evaluated.

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1258. Activity of a Series of Investigational Compounds Tested Against Invasive Fungal Isolates

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