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Background. Eravacycline (ERV) is a recently-approved, fully synthetic fluorocycline agent that demonstrates broad *in vitro* activity against multidrug-resistant pathogens. We sought to compare the activity of ERV with minocycline (MIN) and tigecycline (TGC) against diverse CRE clinical isolates, and to evaluate the performance of commercially-available susceptibility testing methods.

Methods. ERV, MIN, and TGC minimum inhibitory concentrations (MICs) were determined in triplicate by broth microdilution against previously characterized CRE isolates. ERV susceptibility was also measured by disk diffusion (20 µg disk; Mast Group) and MIC test strips (MTS; Liofilchem) according to manufacturer instructions.

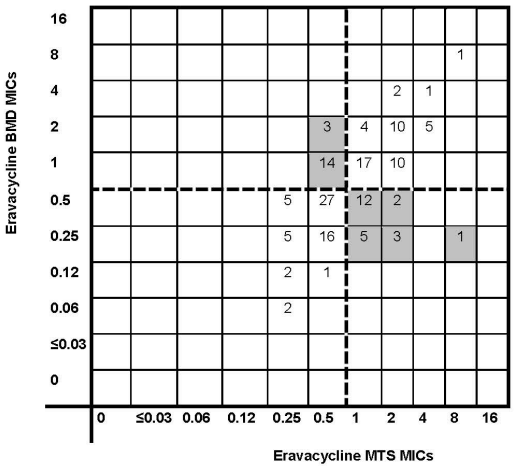
Results. 148 CRE were tested, including 92 *K. pneumoniae*, 32 *Enterobacter spp*, 11 *E. coli*, 5 *C. freundii,* 4 *K. oxytoca,* and 4 *S. marcescens.* 72% of isolates harbored bla_{KPC}, which encoded KPC-2 (n = 33), KPC-3 (n = 48), and other KPC variants (n = 22). 77% and 19% of isolates were resistant to meropenem and ceftazidime–avibactam, respectively. By BMD, the ERV, MIN, and TGC MIC range, MIC50 and MIC90 for shown in the Table. ERV MICs were ≥2-fold lower than MIN and TGC against 99% and 43% of isolates, respectively. ERV MICs did not vary by species or KPC-subtype. ERV MICs determined by BMD and MTS were well-correlated showing 89% essential agreement (MIC within one 2-fold dilution; Figure). The rate of categorical agreement (CA) was 73%. By comparison, the CA rate between BMD and disk diffusion was 78%. By both MTS and disk diffusion methods, susceptibility results clustered on either side of the susceptibility breakpoint. 50% of disk diffusion zones clustered between 14 and 16 millimeters (mm), which is 1 mm on either side of the susceptibility breakpoint (≥15 mm).

Conclusion. This study confirms the *in vitro* activity of ERV against CRE clinical isolates, which is comparable to TGC. ERV MTS demonstrated high rates of EA, but lower rates of CA. Clinicians should be aware of the nuances of ERV susceptibility testing and recognize that the modal distribution of ERV MICs against CRE lies on either side of the susceptibility breakpoint.

Table. Comparison of MICs for ERV, MIN, and TGC against CRE clinical isolates.

Agent	MIC range	MIC50	MIC90
Ceftazidime-avibactam	≤0.25 - >256	1	64
Meropenem	≤0.06 - >64	8	>64
Eravacycline (ERV)	0.06 – 8	0.5	2
Minocycline (MIN)	0.25 – 32	4	16
Tigecycline (TGC)	0.06 – 8	1	2

Figure. Correlation of ERV MICs determined by BMD and MTS



Note. ERV susceptibility breakpoint is identified by the dotted horizontal and vertical lines. Isolates with discrepant categorical interpretations are shaded in grey.

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

711. Exebacase (Lysin CF-301) Activity Against *Staphylococcus aureus* (*S. aureus*) Isolates From Bacteremic Patients Enrolled in a Phase 2 Study (CF-*301-102*)
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Background. Exebacase (CF-301) is a novel, recombinantly-produced, bacteriophage-derived lysin (cell wall hydrolase) which is the first lysin to report Phase 2 (Ph2) results which demonstrated 42.8% higher clinical responder rates with a single dose of exebacase used in addition to standard of care antibiotics (SOC) vs. SOC alone for the treatment of methicillin-resistant *S. aureus* (MRSA) bacteremia including endocarditis. We examined exebacase activity by broth microdilution (BMD) against baseline methicillin-sensitive *S. aureus* (MSSA) and MRSA isolates from each of the 116 participants in the recently complete exebacase"first in-patient' Ph2 study (NCT03163446).

Methods. Patients with complicated bacteremia or endocarditis caused by *S. aureus* were enrolled into Study CF-301-102 at study centers in the United States, EU, Latin America, Israel, and Russia from 2017 and 2018. Baseline isolates from blood cultures were collected prior to administration of exebacase. Exebacase MICs against 117 isolates of MSSA (n = 74) and MRSA (n = 43) were determined at a central laboratory using a modified BMD approved by the CLSI for exebacase AST.

Results. The exebacase MICs of baseline patient isolates from the Ph2 study ranged from 0.125 – 2 µg/mL and the $MIC_{50/90}$ values for all MSSA and MRSA isolates were 0.5/1 µg/mL. Exebacase MICs reported in a recent surveillance study were similar, with $MIC_{50/90}$ values of 0.5/1 µg/mL. Of the 6 total subjects with EXE MICs of 2, 3 were clinical responders, 2 were indeterminate (not available for assessment), and 1 was a clinical nonresponder at Day 14.

Conclusion. Exebacase was highly active against all baseline *S. aureus* isolates from blood cultures obtained from bacteremic patients enrolled in the Ph2 study. Based on data from previously presented exposure target attainment animal studies, PK/PD modeling and preliminary nonclinical breakpoint assessments, we expected that strains with MIC values of ≤2 µg/mL will have been susceptible to the Ph2 clinical exebacase dose determined based on target attainment studies under study in Ph2.

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

712. Activity of Exebacase (CF-301) Against Methicillin-Resistant Staphylococcus aureus (MRSA) Biofilms on Orthopedic Kirschner Wires
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Background. Orthopedic foreign body-associated infection can be difficult to treat due to the formation of biofilms protecting microorganisms from both antimicrobials and the immune system. Exebacase (EXE) is a phage-derived lysin which acts as a direct lytic agent by hydrolyzing the peptidoglycan cell wall of *Staphylococcus aureus*. In this study, the activity of EXE was evaluated in comparison to daptomycin against MRSA biofilms on orthopedic Kirschner wires (K-wires).

Methods. MRSA strain IDRL-6169 was studied; it has a MIC of 0.5 µg/mL for both daptomycin (DAP) and EXE. Biofilms were formed in 1 mL of 10^6 cfu/mL tryptic soy broth on 0.5x0.1 mm threaded stainless steel K-wires for 10 hours, after which the wires were removed from the media and placed into 0.04 mL of either DAP or EXE at 0 (vehicle only), 0.098, 0.98, or 9.8 mg/mL. DAP+EXE was also tested, each at 0.098 mg/mL. Bacteria were quantified after 0, 2, 4, 8, and 12 hours of incubation at 37°C. Testing was performed in triplicate. Results were reported as $\log_{10}$ cfu/K-wire reduction relative to vehicle alone. A 3-$\log_{10}$ cfu/K-wire reduction was considered bactericidal. P-values were calculated using Kruskal–Wallis.

Results. The bacterial burden of vehicle alone ranged from 5.49- to 6.33-$\log_{10}$ cfu/K-wire at all time points. Bacterial reductions for each treatment compared with carrier solution are shown in the table. DAP showed no bactericidal activity. EXE showed bactericidal activity at all concentrations at all time points studied except 0.098 mg/mL at 8 hours. There was no significant difference between EXE at 0.098 and 0.98 mg/mL at any time point but EXE at 9.8 mg/mL did show superiority over the lower concentrations. DAP+EXE 0.098 mg/mL was bactericidal at all time points.

Conclusion. EXE showed a rapid effect against MRSA biofilms on orthopedic K-wires apparent within the first 2 hours of exposure and was more active than daptomycin alone at the same concentrations.

Table 1. Mean log10 cfu/K-wire reduction compared to carrier solution

	Daptomycin			Exebacase			Daptomycin + Exebacase
Duration of Treatment	0.098 mg/ml	0.98 mg/ml	9.8 mg/ml	0.098 mg/ml	0.98 mg/ml	9.8 mg/ml	0.098 mg/ml
2 h	0.23	0.06	0.46	**5.12**	**4.83**	**5.68**	**5.29**
4 h	0.48	1.21	0.68	**3.60**	**3.20**	**5.52**	**3.24**
8 h	0.39	0.39	0.31	2.24	**3.67**	**5.78**	**4.34**
12 h	0.38	0.61	0.81	**3.05**	**4.41**	**4.76**	**3.50**

Bold values considered bactericidal

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

713. Preventive Administration of MEDI6389, a Combination of Monoclonal Antibodies (mAbs) Targeting Alpha-Toxin (AT), Panton-Valentine Leukocidin (PVL), Leukocidin ED (LukED), Gamma-Hemolysin and Clumping Factor A (ClfA), in a Rabbit Model of USA300 MRSA Prosthetic Joint Infection (PJI)
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Background. mAbs targeting staphylococcal virulence factors could represent an interesting preventive strategy in PJI. We evaluate here MEDI6389 compared with isotype-matched control IgG (c-IgG) in a rabbit model of USA300 MRSA PJI.

Methods. Rabbits were randomized for prophylaxis with either c-IgG (n = 13; 30 mg/kg; controls) or MEDI6389 (n = 13; 30 mg/kg of each mAb) administered intravenously 12h before infection. A cemented screw and ultrahigh-molecular-weight polyethylene washer were placed intraarticularly in the external femoral condyle. After suturing the joint capsule and musculocutaneous layers, 300 µL of a standardized bacterial inoculum containing 5×10^5 CFU of a USA300 MRSA clinical isolate were injected intraarticularly. Animals were euthanized on day 8 and the knee joint was harvested for bacteriological analysis (synovial bacterial counts, and enumeration of screw-adherent bacteria after sonication) and histology (conventional pathology, and transmission electron microscopy [TEM] for neutrophils analysis). *In vivo* observations made on neutrophils were confirmed by TEM analysis of human neutrophils incubated *in vitro* with purified PVL, LukED, and gamma-hemolysin with or without the corresponding mAb.

Results. In comparison with the control group, the average amount of pus (1.7 ± 1.8 vs. 3.1 ± 1.2 g, P = 0.026) and the number of bacteria in the synovial pus (5.9±1.5 vs. 7.2±1.4 log10 CFU, P = 0.031) and on the screw (2.7 ± 1.5 vs. 4.1 ± 1.6 log10 CFU, P = 0.035) were decreased in animals pretreated by MEDI6389. Conventional pathological examination showed a marked reduction in synovitis of MEDI6389-pretreated animals. TEM of synovitis harvested from infected knee joints of control animals showed significant greater number of abnormal neutrophils that appeared rounded, with condensed nucleus and no granules, compared with those pretreated with MEDI6389 (P = 0.002). This classical leukocidin-induced neutrophilic killing phenotype could be neutralized with anti-leukocidin mAbs using *ex vivo* human neutrophils incubated with PVL, LukED, HlgAB, or HlgCB.

Conclusion. The preventive administration of MEDI6389 allows a reduction of local inflammation and bacterial burden in this USA300 MRSA rabbit PJI model.

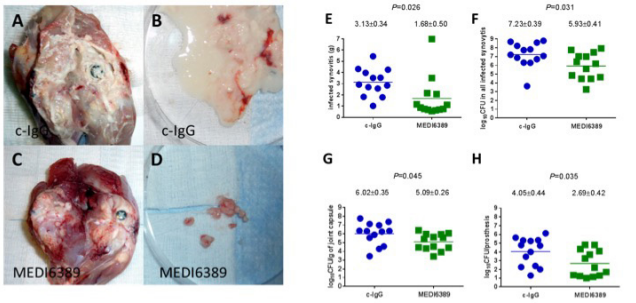

Fig. 1 – Gross aspect (A-D), amount of pus (E) and bacterial counts in the synovial fluid (F), the joint capsule tissue (G) and against the screw (H) of rabbits preventively treated by MEDI6389 and controls (IgG)

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

714. Analysis of the Effect of Urine on the *In Vitro* Activity of Gepotidacin and Levofloxacin Against *Escherichia coli, Staphylococcus epidermidis,* and *Staphylococcus saprophyticus*

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Background. Gepotidacin (GSK2140944) is a first in class novel triazaacenaphthylene bacterial type II topoisomerase inhibitor in clinical development for the treatment of gonorrhea and uncomplicated UTI (acute cystitis). Gepotidacin selectively inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism not utilized by any currently approved therapeutic agent and demonstrates *in vitro* activity against most target pathogens resistant to established antibacterials, including fluoroquinolones. This study was undertaken to determine the effect of various urine parameters on the *in vitro* activity of gepotidacin and a comparative agent, levofloxacin, against a variety of bacteria.

Methods. Study strains were tested according to the reference CLSI broth microdilution method using cation-adjusted Mueller–Hinton broth (CAMHB) and the following method variations: CAMHB with 25%, 50%, and 100% urine (not pH adjusted) and 100% urine (pH adjusted to 7.2–7.4, and 8). Quality control strains were concurrently tested each day.

Results. MIC endpoints in the reference method and in 100% urine were easily determined (i.e., clear buttons of growth up to the first well of no growth). Gepotidacin MIC results are summarized in the table. For E. coli and S. saprophyticus, there was a trend for higher gepotidacin MIC results with the addition of increasing amounts of urine. However, the increase was minimal such that mean dilution differences were ≤ 1.54. Against S. epidermidis, gepotidacin MICs were not significantly impacted by the addition of urine as 100% of urine condition MICs were within ±1 doubling dilution of the reference method MIC. The gepotidacin results for E. coli indicate that the average 1–2 dilution MIC increase observed in the unadjusted 100% pooled urine MIC may be associated with lower pH. A similar increase in levofloxacin MIC results for E. coli were also associated with pH, but at the higher pH of 8.0. In contrast, the increase in MIC observed in both the gepotidacin and levofloxacin S. saprophyticus results in 100% pooled urine do not appear to be a function of pH.

Conclusion. Overall, the effect of urine on the gepotidacin and levofloxacin MICs was minimal and not inclusive of all strains tested.

Results Table: Summary of gepotidacin MIC results with and without the addition of urine

Condition	*E. coli* (n=10)			*S. epidermidis* (n=4)			*S. saprophyticus* (n=6)		
	Mean MIC	Mean dil difference [a]	N(%) ±1 dil [b]	Mean MIC	Mean dil difference [a]	N(%) ±1 dil [b]	Mean MIC	Mean dil difference [a]	N(%) ±1 dil [b]
CAMHB (reference method, pH 7.2)	2.46	-	-	0.42	-	-	0.11	-	-
25% Urine (pH 7.09)	3.73	0.60	9 (90%)	0.25	-0.75	4 (100%)	0.11	0.00	6 (100%)
50% Urine (pH 6.99)	4.29	0.80	8 (80%)	0.21	-1.01	4 (100%)	0.11	0.00	6 (100%)
100% Urine (pH 6.42)	6.96	1.50	5 (50%)	0.35	-0.26	4 (100%)	0.24	1.18	4 (66.7%)
100% Urine (adjusted pH 7.31)	4.00	0.70	8 (80%)	0.50	0.25	4 (100%)	0.31	1.54	3 (50%)
100% Urine (adjusted pH 8.07)	4.29	0.80	8 (80%)	0.42	0.00	4 (100%)	0.28	1.36	3 (50%)

[a]Dilution (dil) differences were calculated for each urine condition MIC by subtracting the $\log_2$ urine condition MIC from the $\log_2$ reference method MIC. The mean dilution difference was then calculated for each urine condition.
[b]N/Percentage of urine condition MICs within ±1 doubling dilution of the reference method MIC

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

715. Bulgecin A lowers Imipenem MICs in Clinical MDR *Acinetobacter baumannii* (ACB) Strains

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Background. Genetic screening of ACB has revealed genes that confer increased susceptibility to β-lactams when these genes are disrupted suggesting novel drug targets. One such target is lytic transglycosylase, LT. Bulgecin A (BlgA) is a natural product of *Paraburkholderia acidophila* and an LT inhibitor that potentiates the activity of β-lactams.

Methods. Broth microdilution MICs were performed using carbapenem-resistant (CR)-colisitin susceptible (ColS) and CR-ColR clinical ACB strains, with a variety of resistance mechanisms, previously studied via whole-genome sequencing. A fixed concentration of pure BlgA at 100 µg/mL was combined with varying concentrations of imipenem. Sequences of the putative LTs in ACB strains were analyzed to look for amino-acid substitutions and correlated with the MIC lowering effect of BlgA. Homology models of the LTs of AB0057 ACB strain were generated.

Results. ACB MltE most resembles soluble LTs of other species with 22.39% sequence identity and 92% query coverage to Slt70 of *E. coli*. MIC results and amino-acid sequence variations in MltE LT of ACB are shown. There were no clear amino-acid substitution patterns to account for differences in BlgA effect. The mutations are distal to the BlgA binding site at residue E506.

Conclusion. These are the first MICs reported for BlgA in combination with a carbapenem demonstrating reduction in the MIC by four-fold for several MDR ACB clinical strains. Mutations in MltE Lt do not account for variations in the MICs observed. Changes in the MICs may be related to other factors such as drug penetration and alterations in PBP expression. Additional studies are underway to examine these factors.

Strain	Category	CR-genes	IMI	IMI + BlgA	Amino acid (a.a.) 6	a.a. 173	a.a. 200	a.a. 368
AB0057	CR-Col?	OXA-23	8	4	A	T	G	T
UH83	CR-ColS	OXA-24/40	32	8	A	T	G	S
UHAB420	CR-ColS	OXA-23/72	64	32	A	A	G	S
UHAB642	CR-ColS	OXA-24/65	64	64	A	T	G	S
AB046	CR-ColS	OXA-58	16	4	A	T	G	S
NDM-Col	CR-ColR	OXA-94 , NDM-1	64	64	A	T	S	S
UHAB154	CR-ColR	OXA-82	4	2	A	A	G	S
UHAB491	CR-ColR	OXA-23/66	16	4	A	A	G	S

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