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1060. Pritelivir in Immunocompromised Patients with Mucocutaneous Acyclovir-Resistant Herpes Simplex Virus-Infections – First Case Series

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Session: P-61. Novel Agents

Background. HSV recurrences are usually managed effectively with existing antiviral drugs (nucleoside analogs such as acyclovir). However, in immunocompromised patients (e.g., malignancy, HIV, transplant), if lesions persist or recur while receiving antiviral treatment, acyclovir resistance should be suspected. In this population, there are limited treatment options. The helicase-primase inhibitor pritelivir is a novel oral antiviral, with a new mode of action and is active against both HSV-1 and HSV-2, including acyclovir and foscarnet-resistant strains. In this case series, we report the first clinical experiences with pritelivir in the treatment of immunocompromised patients with acyclovir resistant HSV infection.

Methods. All patient reported in this case series received pritelivir in a Phase 2 study. There were treated in an open-label design with a 400 mg pritelivir oral loading dose followed by a 100 mg oral maintenance dose daily for up to 28 days.

Results. Of the 23 patients, 11 had HIV infection and 12 had malignancy, transplant or an autoimmune disease. Of this cohort, 19 patients showed full resolution of their HSV-related lesions during the 28 day treatment period, while in 4 subjects lesions improved but did not completely heal during the observation period. Pritelivir was well tolerated without significant adverse effects.Reasons for incomplete lesion resolution during the 28 day treatment period, were extensive lesions in one patient, one patient with resistance development, and one patient with lesions in the oral cavity. Three patients subsequently experienced full resolution, while one patient required foscarnet due to CMV reactivation, necessitating early discontinuation.

Conclusion. Pritelivir is a promising novel treatment option for patients with severe mucocutaneous HSV-1/2 infections that are resistant to acyclovir and foscarnet. An international Phase 3 study is underway to evaluate pritelivir efficacy in immunocompromised patients.

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1061. Clinical Phage Microbiology: Evaluating Phages for Biofilm-associated Prosthetic Valve Endocarditis

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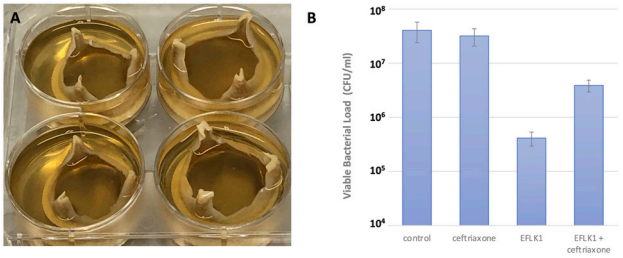
Session: P-61. Novel Agents

Background. **Prosthetic valve endocarditis (PVE)** is a major treatment challenge associated with biofilm formation. It requires intensive infectious diseases consultations and prolonged therapy. Nevertheless, high mortality rates are reported even with timely diagnosis and optimal management. *Bacteriophage (phage) therapy*, the use of bacterial viruses as antimicrobial agents, has been suggested as a potential adjunctive treatment for PVE. This is due to the ability of lytic phages to synergize with antibiotics and to destroy biofilms. However, due to their high specificity, it is crucial to match the phages by *in-vitro* evaluations that simulate the clinical settings.

Methods. In this study we demonstrate this matching using an *in-vitro* PVE model of vancomycin-resistant *Enterococcus faecalis* (VRE). We have looked at the ability of the phage EFLK1, alone or in combination with antibiotics, to destroy mature biofilms from a commonly used bioprosthetic valve. In addition, we tried to predict these effects using several *in-vitro* phage susceptibility assays.

Results. We found that the phage EFLK1 presents a significant inhibitory effect against planktonic cultures of VRE, both alone or in combination with ampicillin or ceftriaxone. We then tested the effect of these combinations on mature biofilm grown on a standard 96-well plates. We found that the phage, or its combination with ceftriaxone, led to a two-log reduction in the bacterial viability. In contrast, the addition of ampicillin to the phage caused interference with this antibacterial effect. When tested against biofilm grown on a pericardial patch, the combination of EFLK1 and ceftriaxone was found most efficient. Finally, when tested on the whole bioprosthetic aortic valve, we found that the phage EFLK1 alone was even more efficient than its combination with ceftriaxone.

Biofilm Eradication from Bioprosthetic Aortic Valve



(A) Representation of E. faecalis biofilm formation on bioprosthetic valves. (B) Following 48-hours of growth, the valves were treated for five days by the phage EFLK1,

ceftriaxone or their combination. The valves were then washed from any planktonic cells and the biofilm biomass was established by CFU enumeration.

Conclusion. This study demonstrates that a proper *in-vitro* matching is essential in the treatment of PVE with phages. As seen here, the phage-antibiotic combination intended for treatment should be drawn according to their efficacy on suitable models, simulating the clinical settings, with the specific pathogen, the valve material, and the used phages taken into consideration.

Disclosures. **Ran Nir-Paz, MD**, **BiomX** (Consultant)**Technophage** (Scientific Research Study Investigator, Advisor or Review Panel member)

1062. Analysis of Resistance to Oral Standard of Care Antibiotics for Urinary Tract Infections Caused By *Escherichia coli* and *Staphylococcus saprophyticus* Collected Worldwide between 2019-2020

S J Ryan Arends, PhD[1]; Deborah Butler, n/a[2]; Nicole Scangarella-Oman, MS[3]; Lindsey Paustian, BS (ASCP)[1]; Jennifer M. Streit, BS[1]; Rodrigo E. Mendes, PhD[1]; [1]JMI Laboratories, North Liberty, Iowa; [2]GSK, Collegeville, Pennsylvania; [3]GlaxoSmithKline Pharmaceuticals, Collegeville, Pennsylvania

Session: P-61. Novel Agents

Background. Gepotidacin (GSK2140944) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor under development for the treatment of gonorrhea and uncomplicated urinary tract infections (UTI). This study reports on the *in vitro* activity of gepotidacin and other oral antibiotics when tested against contemporary *Escherichia coli* and *Staphylococcus saprophyticus* clinical isolates collected from patients with UTIs for a gepotidacin uUTI global surveillance study as a part of the SENTRY Antimicrobial Surveillance Program.

Methods. A total of 3,562 *E. coli* and 344 *S. saprophyticus* isolates were collected between 2019 and 2020 from 92 medical centers located in 25 countries. Most isolates (68%) tested were cultured from urine specimens collected from patients seen in ambulatory, emergency, family practice, and outpatient medical services. Bacterial identifications were confirmed by MALDI-TOF. Isolates were tested for susceptibility by CLSI methods at a central laboratory (JMI Laboratories). MIC results for oral antibiotics licensed for the treatment of uUTI and drug-resistant subsets were interpreted per CLSI guidelines.

Results. Gepotidacin ($MIC_{50/90}$, 2/2 mg/L) displayed good activity against 3,562 *E. coli* isolates, with 98.0% of all observed gepotidacin MICs ≤4 mg/L (Table). Susceptibility (S) rates for the other oral agents tested against these isolates were: amoxicillin-clavulanate (79.6% S), ampicillin (45.6% S), ciprofloxacin (72.5%S), fosfomycin (99.0% S), mecillinam (94.1%S), nitrofurantoin (97.3% S), and trimethoprim-sulfamethoxazole (68.2% S). When tested against the drug-resistant subsets, gepotidacin maintained similar $MIC_{50/90}$ values (2/4 mg/L), except against isolates resistant to fosfomycin (2/8 mg/L). Against *S. saprophyticus* isolates, gepotidacin ($MIC_{50/90}$, 0.06/0.12 mg/L) inhibited all isolates at ≤0.25 mg/L. Most oral agents showed S results of >97% against *S. saprophyticus* isolates, except for penicillin (3.5%S).

Conclusion. Gepotidacin demonstrated potent *in vitro* activity against contemporary *E. coli* and *S. saprophyticus* urine isolates. This activity was largely unaffected among isolates demonstrating drug-resistance to other oral standard of care antibiotics.

Table

Organism (No. isolates)	No. and cumulative % of isolates inhibited at a gepotidacin MIC (mg/L) of:								Gepotidacin	
Drug-resistant	≤0.25	0.5	1	2	4	8	16	32	MIC_{50}	MIC_{90}
E. coli (3,562)	47	190	1218	1780	255	48	19	5	2	2
	1.3	6.7	40.8	90.8	98.0	99.3	99.9	100		
AMX-CLA-R (202)	3	12	50	95	31	4	5	2	2	4
	1.5	7.4	32.2	79.2	94.6	96.5	99.0	100		
AMP-R (1,914)	29	135	682	852	160	33	18	5	2	4
	1.5	8.6	44.2	88.7	97.1	98.8	99.7	100		
FQ-R (902)	34	100	311	338	92	16	8	3	2	4
	3.8	14.9	49.3	86.8	97.0	98.8	99.7	100		
FOS-R (25)	0	3	7	7	4	3	1		2	8
	0.0	12.0	40.0	68.0	84.0	96.0	100			
MEC-R (151)	4	8	39	78	17	3	2		2	4
	2.6	7.9	33.8	85.4	96.7	98.7	100			
NIT-R (46)	1	1	11	24	7	1	0	1	2	4
	2.2	4.3	28.3	80.4	95.7	97.8	97.8	100		
TMP-SMX-R (1,130)	19	87	421	468	91	31	9	4	2	4
	1.7	9.4	46.6	88.1	96.1	98.8	99.6	100		

Abbreviations: -R, resistant per CLSI 2021; AMX-CLA, amoxicillin-clavulanate; AMP, ampicillin; FQ, fluoroquinolones; FOS, fosfomycin; MEC, mecillinam; NIT, nitrofurantoin; and TMP-SMX, trimethoprim-sulfamethoxazole.

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1063. ARGONAUT-V: Susceptibility of Multidrug-Resistant (MDR) *Pseudomonas aeruginosa* to Cefepime-Taniborbactam

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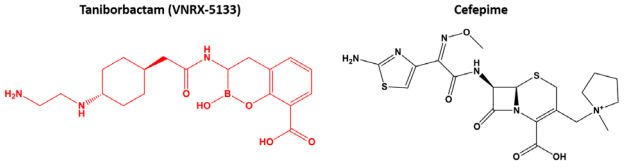
Session: P-61. Novel Agents

Background. *P. aeruginosa* is a Gram-negative pathogen responsible for many serious infections. MDR, both intrinsic and acquired, presents major clinical challenges. Taniborbactam (formerly VNRX-5133; Fig 1) is a β-lactamase inhibitor (BLI) characterized as a bicyclic boronate, uniquely possessing activity toward all four Ambler classes of β-lactamases, both serine and metallo, with the exception of class B IMP β-lactamases. The β-lactam-BLI (BL-BLI) combination cefepime-taniborbactam (FTB; Fig 1) is currently in phase 3 clinical trials.



Structures of taniborbactam and cefepime. The β-lactamase inhibitor is in red and the β-lactam antibiotic is in black.

Methods. The activity of FTB was tested against 197 well-characterized clinical *P. aeruginosa* isolates that were part of PRIMERS (Platforms for Rapid Identification of MDR-Gram-negative bacteria and Evaluation of Resistance Studies). Nearly 58% of these strains were reported as carbapenem-non-susceptible. Porin changes, efflux pumps, and/or the presence of acquired class A or class B carbapenemases were previously reported. Broth microdilution minimum inhibitory concentrations (MICs) were determined by CLSI M07 Ed. 11 methods with custom Sensititre frozen panels and interpreted using CLSI M100 Ed. 30 breakpoints. American Type Culture Collection strains were used for quality control. FEP breakpoints were provisionally used for FTB, where taniborbactam was fixed at 4 μg/mL.

Results. Percent susceptibility to BL agents alone was 45.2% for imipenem (IPM), 55.8% for meropenem (MEM), 60.9% for ceftazidime (CAZ), and 67.0% for FEP. The addition of BLI to BL increased % susceptibility for MEM-vaborbactam (MVB), 56.9%; ceftolozane-tazobactam (C/T), 77.7%, CAZ-avibactam (CZA), 79.7%, and FTB, 82.7%. MIC_{50}s were in the susceptible range for all drugs except IPM, which was intermediate, and all MIC_{90}s were in the resistant range (Table 1). Taniborbactam reduced FEP MIC by 2-fold in 32% of isolates and ≥ 4-fold in 13% of isolates. Against carbapenem-non-susceptible strains, % susceptibilities were: FTB, 68.5%, CZA, 63.0%, C/T, 59.3%; and MVB, 21.3% (Table 2).

	AMK	ATM	C/T	CAZ	CZA	FEP	FTB	IPM	MEM	MVB	TZP	TOB
CLSI Susceptible Breakpoint	≤16	≤8	≤4/4	≤8	≤8/4	≤8	≤8*	≤2	≤2	*	≤16/4	≤4
MIC_{50}	4	8	0.5	4	2	4	4	4	1	1	8	0.5
MIC_{90}	>32	>16	>8	>16	>8	>16	>8	>4	>4	>4	>64	>8
%S	87.3	53.8	77.7	60.9	79.7	67.0	82.7*	45.2	55.8	56.9	56.9	78.7

MIC_{50} and MIC_{90} values (μg/mL) and percent susceptibility (%S) for all P. aeruginosa strains (n=197). AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime-avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem-vaborbactam; TZP, piperacillin-tazobactam; TOB, tobramycin. *The breakpoints for FEP and MEM alone were provisionally applied to FTB and MVB, respectively. Tazobactam, avibactam, and taniborbactam were fixed at 4 μg/mL, while vaborbactam was fixed at 8 μg/mL. Breakpoints from CLSI M100, 31st ed, 2021.

MIC50 and MIC90 values (μg/mL) and percent susceptibility (%S) for all P. aeruginosa strains (n=197). AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime-avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem-vaborbactam; TZP, piperacillin-tazobactam; TOB, tobramycin. *The breakpoints for FEP and MEM