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1037. Efficacy of Germinants and Omadacycline for Preventing *Clostridioides difficile* Relapse in a Murine Model

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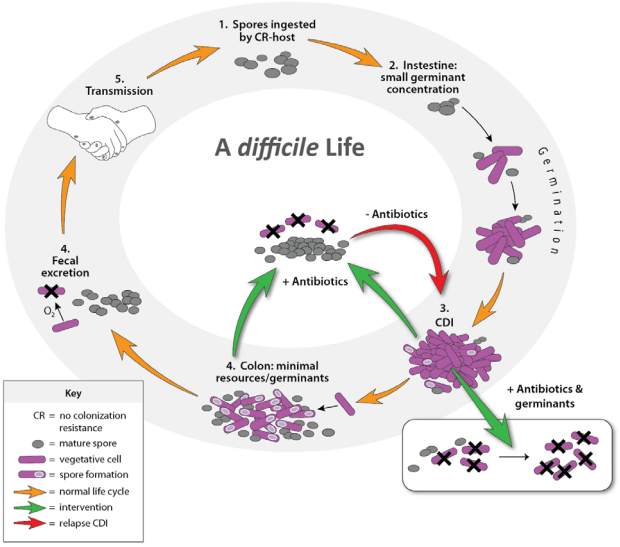
Session: P-59. New Drug Development

Background. *Clostridioides difficile* is labeled one of five urgent pathogens by the CDC. The urgency is related to the high burden of disease, limited effective antimicrobials, and recurrent *C. difficile* infections (rCDI) from residual spores (Fig. 1). Impervious to antibiotics, *C. difficile* spores could be induced into vegetative cells by germinants, namely taurocholate, for antibiotic targeting. This study aims to evaluate spore reservoir eradication through applying germinants with antibiotics.

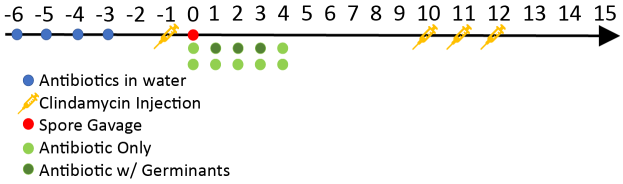
Figure 1. Schematic of the infectious life cycle of C. difficile and treatment opportunities



Noah Budi, Nasia Safdar, Warren E Rose, Treatment issues in recurrent Clostridioides difficile infections and the possible role of germinants, FEMS Microbes, Volume 1, Issue 1, September 2020, xtaa001, https://doi.org/10.1093/femsmc/xtaa001

Methods. A published murine model of rCDI using C57BL/6 mice and 1 x 10^5 *C. difficile* spores (VPI 10463) with modification was used (Fig. 2). Six hours after inoculation, mice received 1.5 mg vancomycin (VAN, n=10) or 0.25 mg omadacycline (OMC, n=10) daily by oral gavage until day 4 or either with germinant (G) solution (8 mg of sodium taurocholate, 10 mg of taurine, 0.2 mg of sodium docusate, and 1.72 mg of calcium gluconate) given concomitantly on days 1 to 3 (OMC+G, n=9 and VAN+G, n=8). As a positive control, five mice did not receive antibiotics after spores. To induce rCDI, clindamycin was given on days 10 to 12. Survival, clinical scoring (CS), and weight loss (WL) were recorded until day 15. Fecal samples were taken to measure toxin production and spore shedding. Mice that died prior to day 15, were too sick to provide samples, or had positive stool culture were considered positive for day 15 spore shedding. Fisher's exact test was used.

Figure 2: Experimental Design



Antibiotic water consisted of kanamycin 0.4 mg/ml, gentamicin 0.035 mg/mL, colistin 850 U/mL, metronidazole 0.215 mg/mL, and vancomycin 0.045 mg/mL given noon to noon on specified days. Clindamycin IP injections given as weight based dose of 10 mg/kg.

Results. Survival is summarized in Figure 3. Both OMC and VAN had 60% survival by day 15 while OMC+G and VAN+G had 100% (p=0.004). Germinant CS and WL were similar to respective antibiotic alone groups until day 8; OMC overall had less severe disease than VAN (Figure 4). Toxin production on day 10 was lower in OMC than VAN, but absent from OMC+G and VAN+G. On day 15, 100% of VAN mice were spore positive compared to 60% with OMC (p=0.087). No mice receiving germinants (OMC+G or VAN+G) were spore positive (p< 0.0001).

Figure 3. Survival Percentage

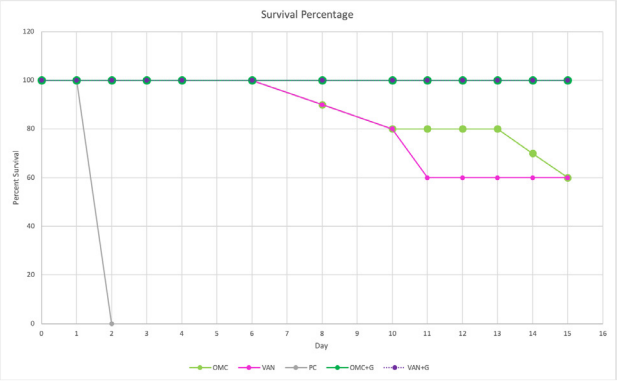
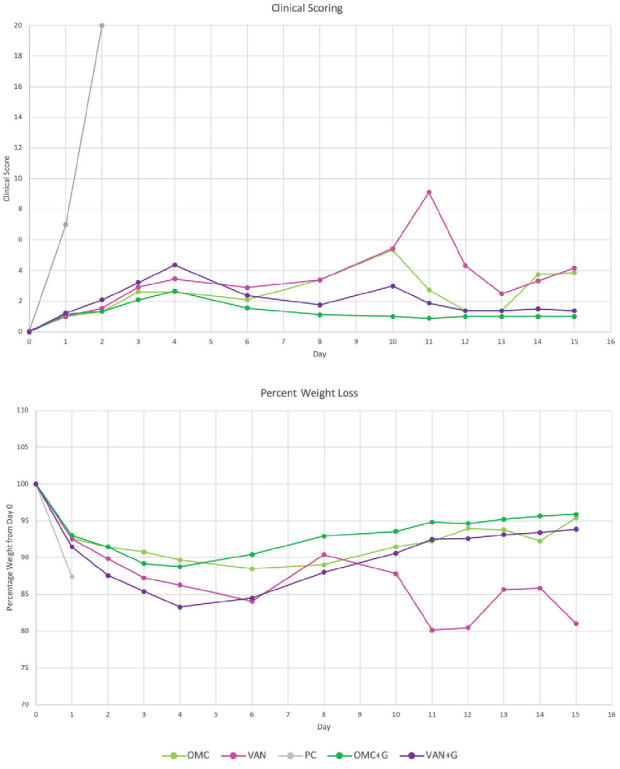


Figure 4. Clinical Scoring and Weight Loss



Conclusion. Germinant/antibiotic combinations improved survival in a rCDI mouse model compared to antibiotics alone. Germinants did not induce toxin production when combined with OMC or VAN and eliminated the spore reservoir at the end of treatment. This provides basis for further study of germinants combined with antibiotics to reduce rCDI.

Disclosures. **Warren Rose, PharmD, MPH**, **Merck** (Grant/Research Support)**Paratek** (Grant/Research Support, Advisor or Review Panel member)

1038. In Vitro Activity of Tebipenem, an Orally Available Carbapenem Agent, Against a Collection of Surveillance Gram-Positive Clinical Isolates

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Session: P-59. New Drug Development

Background. Tebipenem, an orally bioavailable carbapenem administered as a pro-drug, completed a phase 3 clinical trial for evaluating its safety and efficacy for the treatment of complicated urinary tract infection and acute pyelonephritis. The purpose of this study was to investigate the *in vitro* activity of tebipenem and comparator agents, including ertapenem and meropenem, against a recent collection of Gram-positive isolates associated with clinical infections.

Methods. The susceptibility of 580 Gram-positive organisms were tested, including: methicillin-susceptible *Staphylococcus aureus* (MSSA, 489 isolates), methicillin-susceptible *Staphylococcus epidermidis* (MSSE, 31), other methicillin-susceptible coagulase-negative staphylococci (MSCoNS, 29), and vancomycin-susceptible *Enterococcus faecalis* (31). The isolates were collected primarily from pneumonia in hospitalized patients (498 isolates; 85.9%), urinary tract infections (42 isolates; 7.2%), and bloodstream infections (38 isolates; 6.6%). Organisms were tested using reference broth microdilution methods in a central laboratory.

Results. Tebipenem had an MIC_{90} value of 0.03 mg/L against MSSA and 0.015 mg/L against MSSE isolates. Ertapenem MIC_{90} values were 8-fold higher against MSSA (MIC_{90}, 0.25 mg/L) and 32-fold higher against MSSE (MIC_{90}, 0.5 mg/L). Tebipenem displayed an MIC_{90} value of 0.03 mg/L against MSCoNS species other than *S. epidermidis*. This result was 8- and 32-fold lower than those of meropenem (MIC_{90}, 0.25 mg/L) and ertapenem (MIC_{90}, 1 mg/L), respectively. Tebipenem inhibited all *E. faecalis* isolates at ≤1 mg/L (MIC_{90}, 1 mg/L), with an MIC_{90} value at least 2-fold lower than meropenem (MIC_{90}, >1 mg/L) and 16-fold lower than ertapenem (MIC_{90}, >8 mg/L).

Conclusion. Tebipenem displayed potent activity against methicillin susceptible staphylococci, including MSSA, MSSE, and other MSCoNS. Tebipenem *in vitro* activity was greater than meropenem and ertapenem when tested against *E. faecalis*. These data indicate that tebipenem may be an option for treating urinary tract infections caused by these organisms or as an empiric option to provide broader coverage against Gram-negative and -positive organisms.

Organism	Cumulative % at tebipenem MIC of:								
(no. tested overall)	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1
Methicillin-susceptible *Staphylococcus aureus* (489)	0 0.0	9 1.8	325 68.3	151 99.2	4 100.0				
Methicillin-susceptible *Staphylococci epidermidis* (31)	1 3.2	22 74.2	8 100.0						
Other methicillin-susceptible coagulase-negative staphylococci (29)	4 13.8	4 27.6	17 86.2	4 100.0					
Enterococcus faecalis (31)						0 0.0	4 12.9	20 77.4	7 100.0

Disclosures. **S J Ryan Arends, PhD**, **AbbVie (formerly Allergan)** (Research Grant or Support)**GlaxoSmithKline, LLC** (Research Grant or Support)**Melinta Therapeutics, LLC** (Research Grant or Support)**Nabriva Therapeutics** (Research Grant or Support)**Spero Therapeutics** (Research Grant or Support) **Abby L. Klauer, n/a**, **Cidara Therapeutics, Inc.** (Research Grant or Support)**Spero Therapeutics** (Research Grant or Support) **Nicole Cotroneo**, **Spero Therapeutics** (Employee, Shareholder) **Ian A. Critchley, Ph.D.**, **Spero Therapeutics** (Employee, Shareholder) **Rodrigo E. Mendes, PhD**, **AbbVie** (Research Grant or Support)**AbbVie (formerly Allergan)** (Research Grant or Support)**Cipla Therapeutics** (Research Grant or Support)**Cipla USA Inc.** (Research Grant or Support)**ContraFect Corporation** (Research Grant or Support)**GlaxoSmithKline, LLC** (Research Grant or Support)**Melinta Therapeutics, Inc.** (Research Grant or Support)**Melinta Therapeutics, LLC** (Research Grant or Support)**Nabriva Therapeutics** (Research Grant or Support)**Pfizer, Inc.** (Research Grant or Support)**Shionogi** (Research Grant or Support)**Spero Therapeutics** (Research Grant or Support)

1039. Rapid Restoration of Bile Acid Compositions After Treatment with RBX2660 for Recurrent *Clostridioides difficile* Infection—Results from the PUNCH CD3 Phase 3 Trial

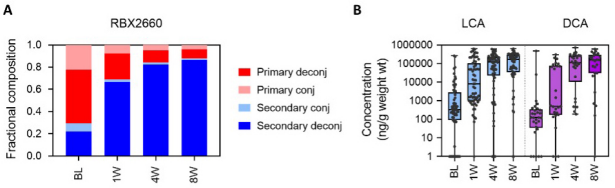
Romeo Papazyan, PhD[1]; Bryan Fuchs, PhD[1]; Ken Blount, PhD[2]; Carlos Gonzalez, MS[3]; Bill Shannon, PhD MBA[3]; [1]Ferring Research Institute, San Diego, CA; [2]Rebiotix, Inc., Roseville, Minnesota; [3]BioRankings, LLC, St. Louis, Missouri

Session: P-59. New Drug Development

Background. Microbiota-based treatments are increasingly evaluated as a strategy to reduce recurrence of *Clostridioides difficile* infection (rCDI), and their proposed mechanisms include restoration of the microbiota and microbiota-mediated functions, including bile acid metabolism. RBX2660—a broad-consortium investigational live biotherapeutic—has been evaluated in >600 participants in 6 clinical trials, with consistent reduction of rCDI recurrence. Here we report that fecal bile acid compositions were significantly restored in treatment-responsive participants in PUNCH CD3—a Phase 3 randomized, double-blinded, placebo-controlled trial of RBX2660.

Methods. PUNCH CD3 participants received a single dose of RBX2660 or placebo between 24 to 72 hours after completing rCDI antibiotic treatment. Clinical response was the absence of CDI recurrence at eight weeks after treatment. Participants voluntarily submitted stool samples prior to blinded study treatment (baseline), 1, 4 and 8 weeks, 3 and 6 months after receiving study treatment. A liquid chromatography tandem mass spectrometry method was developed to extract and quantify 33 bile acids from all participant fecal samples received up to the 8-week time point. Mean bile acid compositions were fit to a Dirichlet multinomial distribution and compared across time points and between RBX2660- and placebo-treated participants.

Results. Clinically, RBX2660 demonstrated superior efficacy versus placebo (70.4% versus 58.1%). RBX2660-treated clinical responders' bile acid compositions shifted significantly from before to after treatment. Specifically, primary bile acids predominated before treatment, whereas secondary bile acids predominated after treatment (Figure 1A). These changes trended higher among RBX2660 responders compared to placebo responders. Importantly, median levels of lithocholic acid (LCA) and deoxycholic acid (DCA) showed large, significant increases after treatment (Figure 1B).



A. Bile acid compositions before (BL) and up to 8 weeks after RBX2660 treatment among treatment responders. Compositions are shown as the fraction of total bile acids classified as primary or secondary conjugated or deconjugated bile acids. B. Concentrations of lithocholic acid (LCA) and deoxycholic acid (DCA) among RBX2660 treatment responders, shown with individual samples and time point group median with interquartile ranges.

Conclusion. Among PUNCH CD3 clinical responders, RBX2660 significantly restored bile acids from less to more healthy compositions. These clinically correlated bile acid shifts are highly consistent with results from a prior trial of RBX2660.

Disclosures. **Romeo Papazyan, PhD**, **Ferring Research Institute** (Employee) **Bryan Fuchs, PhD**, **Ferring Pharmaceuticals** (Employee) **Ken Blount, PhD**, **Rebiotix Inc., a Ferring Company** (Employee)

1040. Knee Explant Analysis (KnEA) Using PLG0206 in Periprosthetic Joint Infection (KnEA Study)

David Huang, MD, PhD[1]; Dana Parker, BS[2]; Nicholas Pachuda, DPM[1]; Despina Dobbins, BS[1]; Jonathan Steckbeck, PhD[1]; Kenneth Urish, MD, PhD[2]; [1]Peptilogics, Houston, Texas; [2]University of Pittsburgh, Pittsburgh, Pennsylvania

Session: P-59. New Drug Development

Background. PLG0206 is a novel engineered cationic antimicrobial peptide being evaluated for treatment of prosthetic joint infections (PJI). This study evaluated the rapid bactericidal activity of PLG0206 to decrease biofilm and planktonic bacteria on *ex vivo* infected prosthesis following removal from patients with chronic PJI.

Methods. De-identified infected prosthetics were removed from nine patients with PJI, despite chronic suppressive oral antibiotics, during a 2-stage revision procedure. Removed prosthetics were then submersed *ex vivo* to an expected clinical exposure of PLG0206, 1 mg/mL, for ~15 minutes. Upon completion of the 15-minute exposure, the treated explant was placed into buffer and sonicated. The sonication solution was then plated for bacterial analysis including colony forming unit (CFU) enumeration. Remaining explanted implants from the same patient served as a control and was processed similarly but without exposure to PLG0206.

Results. As shown in the Table, both Gram-positive and Gram-negative bacteria were identified from removed prosthetics during a 2-stage revision procedure of chronic PJI. Eight of ten infected prosthetics treated *ex vivo* to PLG0206 1 mg/mL were sterilized (No. 1-5, 8-10). Of the two infected prosthetics that were not sterilized (No. 6 and 7), one was polymicrobial (No. 6) and the other was monomicrobial (No. 7). Collectively, infected prosthetics exposed to PLG0206 demonstrated a mean 4log10 reduction (range 2 to 7).

Summary of culture and CFU log reduction among infected prosthetics exposed and not exposed to PLG0206