Table 1: Clinical outcomes of standard versus extended infusions among critically ill patients requiring vasopressors

	Standard (n=39)	Extended (n=47)	P-Value
Hours on medication, median (IQR)	165 (139.5-223)	170 (120.5-240.5)	0.745
Hospital length of stay in hours, median (IQR)	1055 (494-3524)	554 (267.5-1054)	0.035
Readmission within 30 days, N (%)	10 (27)	7 (20)	0.483
Death within 30 days, N (%)	9 (23.1)	2 (5.1)	0.023
Time to blood culture clearance in hours, median (IQR)	67.9 (26.5-90.2)	28.2 (26.7-33.6)	0.391
Time to defervescence in hours, median (IQR)	62.4 (20.5-201.4)	136 (67.5-291.1)	0.100
Time to PCT normalization in hours, median (IQR)	144.4 (82.2-238.6)	118.5 (87.1-234.4)	0.660
Time to CRP normalization in hours, median (IQR)	110.6 (58.3-215.7)	230 (110-337.5)	0.059
Time to WBC normalization in hours, median (IQR)	163.1 (63-238.6)	183 (123.3-305.7)	0.276

Disclosures. **All Authors:** No reported Disclosures.

1952. Bacteriophage Treatment Improves Survival of Mice Infected with Carbapenem-Resistant Klebsiella pneumoniae

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Session: 227. Novel Antimicrobials and Approaches Against MDR Organisms
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Background. Bacteriophage (phage) therapy is being considered as a treatment option for patients with multi-drug-resistant bacterial infections. However, there is a dearth of controlled clinical data to support therapeutic phage efficacy. As a first step toward addressing this deficiency, we tested the ability of two well-characterized phages, alone and in combination, to kill carbapenem-resistant *Klebsiella pneumoniae* (ST258) in blood in vitro and rescue mice from lethal ST258 infection.

Methods. Wild-type C57BL/6J mice were infected with a lethal inoculum of ST258 by intra-peritoneal (IP) injection followed 1 hour later by IP administration of lytic phage P1, P2, or P1+P2 at a multiplicity of infection (MOI) estimated at 1. Survival of each group of mice was tracked for 10 days. In separate experiments, mice were sacrificed at 1 hour, 24 hours, and 48 hours post-phage treatment. Mouse blood and tissues were collected at each timepoint for enumeration of bacteria and phage, screening for phage resistance, and histopathology.

Results. ST258 survival in mouse blood in vitro was significantly less after 1 hour of incubation with P1 or P1+P2 (MOI 1) compared with the control group (no phage). Consistent with the *in vitro* data, none of the mice (0/15) in the control group (no phage) survived to 10 days post-infection, whereas 12/15, 14/15, and 15/15 mice survived in the P2, P1, and P1+P2-treated groups, respectively ($P < 0.0001$).

Conclusion. Prompt, systemic administration of lytic bacteriophages rescued mice from lethal ST258 infection. These data support the potential of phage therapy to effectively treat infections caused by ST258. It will be important to assess whether, for other phage-bacteria combinations, in vitro lysis in blood correlates with in vivo treatment efficacy and therefore may have predictive utility.

Disclosures. **All Authors:** No reported Disclosures.

1953. VE303, a Rationally Designed Bacterial Consortium for Prevention of Recurrent Clostridioides difficile (C. Difficile) infection (rCDI), Stably Restores the Gut Microbiota After Vancomycin (vanco)-Induced Dysbiosis in Adult Healthy Volunteers (HV)

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Background. Gut microbiota alterations and resulting changes in metabolites involved in colonization resistance and host responses, including bile acids (BA) and short-chain fatty acids (SCFA), are hallmarks of *C. difficile* infection. Reduction in rCDI was shown with fecal microbiota transplants (FMT), but FMT has limitations for routine use and carries unforeseen risks. VE303 is a first-in-class drug being developed for prevention of rCDI consisting of a rationally defined bacterial consortium manufactured under GMP conditions. VE303 comprises 8 distinct species belonging to Clostridium clusters IV, XIVa, and XVII, the commensal bacteria associated with clinical response in FMT, suppress *C. difficile* growth *in vitro* and improve survival *in vivo.*

Methods. A first-in-human Phase 1 dose-escalation study assessed safety and tolerability of VE303 in HV after vanco-induced dysbiosis. PK (strain colonization and durability) and PD (restoration of the resident microbiota, SCFA pool, and BA pool) were evaluated by metagenomic sequencing and metabolomics analysis of fecal material.

Results. HV ($N = 23$) received oral vanco 125 mg QID for 5 days followed by VE303 capsules at escalating single then multiple doses (total dose range 1.6×10^9 to 1.1×10^{11} CFU). VE303-related AEs, mostly gastrointestinal, all Grade 1 and transient, were observed in 35% of HV. Colonization with VE303 strains was abundant, durable (detected at 24 weeks), and dose-dependent. VE303 rapidly expanded 10- to 100-fold and each strain was detectable within 2 days after dosing. VE303 enhanced subjects' microbiota and metabolic recovery after vanco treatment. When compared with the vanco-only cohort ($N = 5$), VE303 led to earlier and more complete recovery of beneficial taxa (eg, Bacteroidetes, Firmicutes), reduction in inflammatory taxa (e.g., Proteobacteria) (Figure 1.), and recovery of the secondary BA and SCFA pools.

Conclusion. VE303, a rationally designed microbial consortium, was safe, well tolerated, and efficiently restored microbiome composition after antibiotic-induced dysbiosis in a dose-dependent manner. VE303 was associated with early recovery of key PD markers of response, including microbiota composition, bile acid, and SCFA pools. A Phase 2 study of VE303 for prevention of rCDI is underway (NCT03788434).

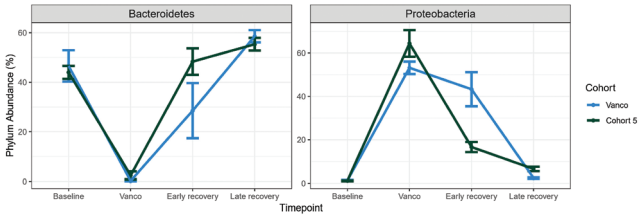

Figure 1: VE303 enhances the early recovery of the microbiota after vancomycin. The mean relative abundance (+/- SEM) of Bacteroidetes (left panel) and Proteobacteria (right panel) for HV administered vancomycin (5d QID) only (Vanco) or VE303 for 14 days (Cohort 5). The "Vanco" timepoints include samples collected during vancomycin administration +24hrs. The "Early recovery" timepoints include samples collected within the first 7 days of recovery. The "Late recovery" timepoints include samples collected after the first 7 days of recovery.

Disclosures. **All Authors:** No reported Disclosures.

1954. In vivo Efficacy of Delayed Therapy with the Novel Inositol Acyltransferase Inhibitor Fosmanogepix (APX001) in a Murine Model of Candida auris Invasive Candidiasis

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Background. *Candida auris* is an emerging pathogen associated with antifungal resistance and high mortality. The novel antifungal manogepix (APX001A) prevents glycosylphosphatidylinositol-anchored protein maturation through inhibition of the inositol acyltransferase Gwt1 enzyme, and has demonstrated *in vitro* and *in vivo* activity against numerous pathogenic fungi, including *C. auris*. We evaluated the efficacy of the prodrug fosmanogepix (APX001) following delayed initiation of therapy in a murine model of *C. auris* invasive candidiasis.

Methods. Neutropenic outbred mice (10 per cohort) were inoculated intravenously with *C. auris* (minimum inhibitory concentrations [MICs]: manogepix 0.03 mg/mL, fluconazole >64 mg/mL, caspofungin 0.25 mg/mL).Treatment with placebo, fosmanogepix (104 or 130 mg/kg by intraperitoneal injection [IP] three times daily, or 260 mg/kg IP twice daily), fluconazole (20 mg/kg/day orally), or caspofungin (10 mg/kg/day IP) began 1 day later and continued for 7 days. Mice were followed post therapy until day 21 to assess survival. Kidneys and brains were collected on day 8, on the days that mice succumbed to infection, or on day 21. Fungal burden was assessed by colony-forming units (CFU).

Results. Survival was significantly improved at each dose level of fosmanogepix (median >21 days; 90–100%) and high dose caspofungin (>21 days; 90%) compared with placebo (5 days; 10%; $P < 0.0001$). On day 8 post-inoculation, kidney and brain fungal burdens were significantly reduced in mice treated with fosmanogepix 260 mg/kg BID compared with placebo and in kidneys of mice treated with caspofungin (Table 1). In the survival arm, fungal burden in kidneys and brains was significantly lower at each dose level of fosmanogepix and with high dose caspofungin compared with placebo. In contrast, no improvements in survival or reductions in fungal burden were observed with fluconazole.

Conclusion. Fosmanogepix demonstrated potent *in vivo* activity against invasive candidiasis caused by *C. auris* even with delayed initiation of treatment. Improvements in both survival and reductions in fungal burden within the kidneys and brains were observed. These data demonstrate the potential utility of fosmanogepix against *C. auris* infections.

Table 1. Mean (standard deviation) kidney and brain fungal burden in the fungal burden (day 8 post-inoculation) and survival arms of mice infected with *C. auris* and treated with placebo, manogepix, fluconazole, or caspofungin for 7 days. *P*-values vs. placebo. The molecular weight of the methylphosphate prodrug is 1.3-fold higher than the active moiety such that doses were 80, 100 and 200 mg/kg of active moiety.

Group	Placebo	Fosmanogepix 104 mg/kg IP TID	Fosmanogepix 130 mg/kg IP TID	Fosmanogepix 260 mg/kg IP BID	Fluconazole 20 mg/kg PO QD	Caspofungin 10 mg/kg IP QD
Kidney $\log_{10}$ CFU/g Day 8	5.61 (1.86)	4.30 (0.48)	4.11 (0.98) P = 0.076	3.86 (1.59) P = 0.0273	5.88 (1.82)	3.41 (1.02) P = 0.0033
Brain $\log_{10}$ CFU/g Day 8	4.40 (1.81)	3.85 (0.42)	3.78 (0.26)	2.99 (0.96) P = 0.0088	4.91 (1.03)	4.36 (0.48)
Kidney $\log_{10}$ CFU/g Survival Arm	7.90 (1.82)	4.53 (0.52) P < 0.0001	4.55 (0.85) P < 0.0001	4.47 (0.84) P < 0.0001	8.16 (0.94)	3.27 (1.67) P < 0.0001
Brain $\log_{10}$ CFU/g Survival Arm	6.36 (1.25)	3.10 (0.90) P < 0.0001	3.27 (0.79) P < 0.0001	3.12 (0.90) P < 0.0001	6.61 (1.34)	2.70 (1.58) P < 0.0001