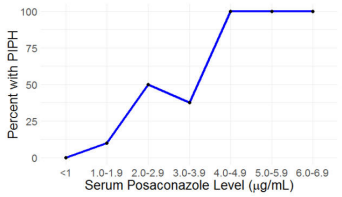
SUPPLEMENTAL FIGURE 1. Serum posaconazole levels and association with the development of posaconazole induced pseudohyperaldosteronism (PIPH).



Serum posaconazole level	#Pts without PIPH	#Pts with PIPH	Percent of patients with PIPH	Confidence interval	Fisher's Exact Test P value
<1	16	0	0%	0.0-20.6%	NA
1.0-1.9	27	3	10%	2.1-26.5%	0.54
2.0-2.9	5	5	50%	18.7-81.3%	0.004
3.0-3.9	5	3	37.50%	8.5-75.5%	0.03
4.0-4.9	0	2	100%	15.8-100%	0.007
5.0-5.9	0	2	100%	15.8-100%	0.007
6.0-6.9	0	1	100%	2.5-100%	0.06

Table 1. Differences among patients with and without posaconazole-induced pseudohyperaldosteronism (PIPH) (n=69).

Variables	PIPH(-) (n=53)	PIPH(+) (n=16)	*P* Value
Male, n (%)	25 (47.2)	8 (50.0)	.84
Age, y, median (IQR)	44.7 (34.9-57.0)	61.1 (47.3-69.6)	**.007**
Ethnicity, n (%)			.77
Caucasian	31 (58.5)	10 (62.5)	
Hispanic	13 (24.5)	3 (18.8)	
Asian	6 (11.3)	3 (18.8)	
African American	3 (5.7)	0 (0.0)	
Body mass index, kg/m², median (IQR)	24.0 (21.3-28.1)	26.2 (22.3-31.9)	.32
Diabetes mellitus, n (%)	6 (11.3)	2 (12.5)	>.99
Hypertension[a], n (%)	17 (32.1)	11 (68.8)	**.009**
Creatinine clearance, mL/min, median (IQR)	102.7 (78.0-126.6)	91.1 (66.6-113.6)	.41
Indicated for antifungal prophylaxis, n (%)[b]	40 (75.5)	6 (37.5)	**.005**
Daily dosage (mg/kg), median (IQR)	4.7 (3.9-5.4)	4.1 (3.1-4.9)	.11
Serum bicarbonate change, mmol/L, median (IQR)	-1 (-3-0)	0 (-1.5-3)	.06
Random serum posaconazole concentration (µg/mL), median (IQR)	1.2 (0.8-1.8)	3.0 (2.1-4.1)	**<.0001**

PIPH, posaconazole-induced pseudohyperaldosteronism; IQR, interquartile range.

[a]Hypertension was present prior to starting posaconazole.

[b]This variable indicates that posaconazole was prescribed for antifungal prophylaxis as opposed to treatment of an active infection.

Table 2. Differences among patients on posaconazole stratified by clinically diagnosed versus laboratory confirmed posaconazole-induced pseudohyperaldosteronism (PIPH) (n=16).

Variables	Clinically diagnosed PIPH(+) (n=8)	Laboratory confirmed only PIPH(+) (n=8)	*P* Value
Male, n (%)	3 (37.5)	5 (62.5)	.62
Age, y, median (IQR)	61.1 (46.4-70.5)	61.1 (51.1-68.0)	.92
Ethnicity, n (%)			.65
Caucasian	4 (50.0)	6 (75.0)	
Hispanic	2 (25.0)	1 (12.5)	
Asian	2 (25.0)	1 (12.5)	
Body mass index, kg/m², median (IQR)	23.8 (20.4-27.0)	29.7 (25.0-34.5)	**.046**
Diabetes mellitus, n (%)	1 (12.5)	1 (12.5)	>.99
Hypertension[a], n (%)	5 (62.5)	6 (75.0)	>.99
Creatinine clearance, mL/min, median (IQR)	86.3 (61.5-109.9)	95.9 (74.7-115.9)	.53
Indicated for antifungal prophylaxis, n (%)[b]	4 (50.0)	2 (25.0)	.61
Daily dosage, mg/kg, median (IQR)	4.6 (3.7-5.3)	3.2 (3.0-4.7)	.09
Change in SBP, mmHg, median (IQR)	32 (15-40.5)	11.5 (7- 26.5)	**.04**
Change in serum potassium, mmol/L, median (IQR)	-0.5 (-0.8- -0.4)	-0.3 (-0.4-0.2)	**.045**
Change in serum bicarbonate, mmol/L, median (IQR)	1 (-0.5-3-0)	-1 (-3.5-1.5)	.20
Plasma aldosterone, ng/dL, median (IQR)	0 (0-0)	0 (0-0)	.32
Renin activity, ng/mL/hr, median (IQR)	0.15 (0.05-1.9)	0.65 (0.15-1.2)	.56
11-deoxycortisol, ng/dL, median (IQR)	210.5 (164.5-348.5)	152.5 (79.3-616.5)	.75
Random serum posaconazole concentration	3.0 (2.0-4.3)	3.3 (2.4-4.1)	.60

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

733. Pharmacokinetic–Pharmacodynamic (PK–PD) Analyses for Alanine Aminotransferase (ALT) Using Phase 3 Data From Omadacycline (OMC)-Treated Patients

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. OMC, an aminomethylcycline structurally related to tetracycline agents, was recently approved by the US FDA for the treatment of adult patients with ABSSSI (IV-to-PO and PO regimens) and CABP (IV-to-PO regimen). To better understand exposure-related concerns for ALT increase, PK-PD relationships for ALT were evaluated using data from OMC-treated patients enrolled in three Phase 3 studies.

Methods. Repeated-measures multiple linear regression was used to evaluate factors predictive of ALT, including different OMC total-drug AUC measures prior to each ALT, with interactions and covariates selected stepwise. Using a final AIC-optimized model, predicted percent probabilities of ALT elevation >1, 1.5, 2, 3, 5, and 10 × upper limit of normal (ULN) at any time post-baseline and up to 2 days after the end of therapy were calculated among analysis patients for fixed post-baseline OMC AUC measures, and among simulated patients after IV-to-PO and PO dosing regimens.

Results. The final model, developed using data from 327 patients with PK, included increased prior cumulative AUC among males, increased baseline gamma-glutamyl transferase, and study (ABSSSI, PO only) as factors predictive of increased ALT ($P < 0.0001$). However, the model-predicted impact of OMC across fixed average daily AUC values on ALT elevation endpoints of >1, 1.5, 2, 3, 5, and 10 × ULN was minimal (Figure 1), even for males despite the interaction with AUC (Figure 2). Among all patients, the estimated increases in percent probabilities for the 90th percentile of AUC relative to zero AUC were 5.81, 5.20, 1.53, 0.61, 0.31, and 0%, respectively, and ≤11.5, 7.76, 8.33, 1.31, 1.31, and 0%, respectively, across single variable patient subsets. Percent probabilities of ALT elevation endpoints were within 2.84% when comparing simulated and observed patients after administration of OMC IV-to-PO and PO dosing regimens (Figure 3).

Conclusion. A statistically significant relationship between an increase in ALT and increase in OMC AUC for males in the presence of other factors was found. However, increases in model-predicted ALT elevation endpoints across fixed OMC AUC values, or among simulated patients after administration of OMC IV-to-PO and PO dosing regimens relative to observed patients, were minimal.

Figure 1. Model-predicted percent probabilities of achieving ALT elevation endpoints among all patients across a range of average daily omadacycline AUC values

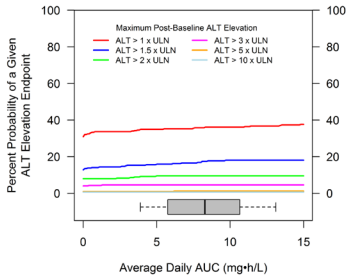


Figure 2. Model-predicted percent probabilities of achieving ALT elevation endpoints among male patients across a range of average daily omadacycline AUC values

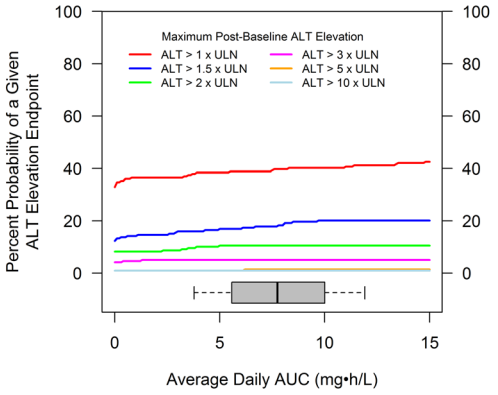
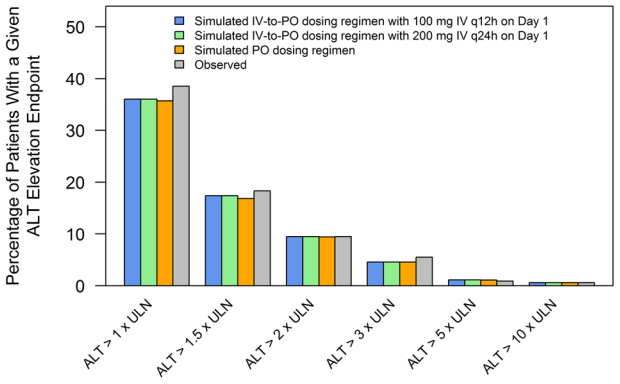


Figure 3. Percentage of ALT elevation endpoints among simulated and observed patients after administration of omadacycline IV-to-PO and PO dosing regimens



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

734. Modeling the Pharmacokinetics and Pharmacodynamics of Intravenous and Oral Omadacycline with and without a Loading Dose

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Omadacycline (OMC) is an intravenous (IV) and oral aminomethylcycline antibiotic in the tetracycline class approved in the United States to treat acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) in adults. The approved dosing regimens of OMC include a loading dose designed to achieve steady-state exposures early in the course of therapy. We assessed the impact on OMC exposure and subsequent pharmacodynamics (PD) on Day 2 and at steady state (Day 5) in the situation where a loading dose may not be given.

Methods. Phase 1 pharmacokinetic (PK) data were used to determine OMC exposure on Day 2 and at steady state (Day 5) for the following: IV regimens 100 mg IV q12h on Day 1 then 100 mg IV QD (load), 100 mg IV QD (no load); and oral regimens 450 mg oral QD on Days 1 and 2 then 300 mg QD (load) and 300 mg oral QD (no load). AUCs on Day 2 and Day 5 for no-load regimens were compared with the regimens with loading doses. Additionally, AUC:MIC ratios were calculated using OMC MIC_{90} for two main pathogens of interest in ABSSSI and CABP, respectively, *Staphylococcus aureus* (0.25 mg/L) and *Streptococcus pneumoniae* (0.12 mg/L). *In vivo* AUC:MIC targets for stasis and 1-log kill used were 21.9 and 57.7 (*S. aureus*) and 31.2 and 65.8 (*S. pneumoniae*).

Results. Day 2 and 5 AUCs are shown in the Figure. AUCs on Day 2 were lower for the two regimens without loading doses and were 72% (IV) and 73% (oral) of those with a loading dose. However, at steady state on Day 5, no-load regimen AUCs were essentially the same at 98% for both the IV and oral regimens. Despite lower AUCs on Day 2 for the no-load regimens, the AUC:MIC ratio would still be expected to exceed the stasis threshold for both pathogens and the 1-log kill threshold for *S. pneumoniae* (figure). This same pattern was also noted on Day 5.

Conclusion. Exposure as assessed using AUC was lower early on in therapy on Day 2 for both IV and oral regimens. However, exposures were not different on Day 5 at steady state. Despite lower exposure on Day 2, OMC would still be expected to meet or exceed PK/PD thresholds associated with stasis for *S. aureus* and *S. pneumoniae.* The 1-log kill threshold was exceeded for *S. pneumoniae*. Further studies are needed to confirm any clinical impact of the omission of OMC loading doses.

Dosing Regimen	Day 2	Day 5	*S. aureus* AUC/MIC		*S. pneumoniae* AUC/MIC	
	$AUC_{(0\text{-}24)}$ (h*ng/mL)	$AUC_{(0\text{-}24)}$ (h*ng/mL)	Day 2	Day 5	Day 2	Day 5
IV load 100 mg q12h Day 1, then 100 mg QD	11,888	9,902	48	40	99	83
Oral load 450 mg QD Days 1 and 2, then 300 mg QD	12,140	10,089	49	40	101	84
IV no load 100 mg QD	8,610	9,735	34	39	72	81
Oral no load 300 mg QD	8,863	9,908	35	40	74	83

$AUC_{(0\text{-}24)}$ = area under the concentration-time curve from time 0 to 24h; IV = intravenous; MIC = minimum inhibitory concentration; q12h = every 12 hours; QD = once per day

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

735. Bacteriophage Therapy Improves Survival of *Galleria mellonella* Larvae Injected with Vancomycin-Resistant *Enterococcus faecium*

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Vancomycin-resistant *Enterococcus faecium* (VRE) is a major multidrug-resistant organism which may cause infection or colonization in hematopoietic cell transplant (HCT) patients. The use of VRE-specific bacteriophages (phages) may potentially help eradicate VRE colonization and subsequent infections. To test the efficacy and safety of phages against VRE *in vivo*, a cocktail combining four phages was used in a VRE-infected larva model.

Methods. The pre-screening model Greater Wax *Galleria mellonella* larva was used in this study. Larvae were infected with VRE by injecting a VRE strain isolated from stools of a VRE-colonized HCT patient at a concentration of 10^7 colony-forming units/10 µL. A single phage (MDA1) or a phage cocktail (MDA1, MDA2, MDA3, and MDA4) were also injected at a concentration of 10^6 colony-forming units/10 µL. Two model groups were tested; a prevention group (PG) and a treatment group (TG). For the PG, phages were administered 1 hour before bacterial injection whereas the TG were injected with phages 1 hour post bacterial injection. Control groups included larvae injected with bacteria alone, phages alone (to measure toxicity due to phage administration), sterile media (to measure any lethal effects due to physical trauma from the injection), or without any manipulation. Every group was composed of 5 larvae. The insect's health state was observed and scored after 8 hours of incubation at 37°C using a published health index scoring system.

Results. Phages improved survival of VRE-infected larvae (table). Only 32% of the VRE-infected larvae survived after 8 hours of infection whereas more than 80% survived when adding phages, whether phages were administered before or after VRE infection. The phage cocktail was shown to be more effective than the single phage MDA1 in improving survival (66% vs. 82% survival). Injecting larvae with phages alone was safe as the same survival rate was observed when compared with those injected with sterile media or those without manipulation.

Conclusion. The use of larva model *G. mellonella* allows for rapid and efficient screening of the bacterial virulence and phage efficacy and safety. Such results highlight the feasibility and the potential impact of phage therapy on VRE colonization and infections.

Table. Efficacy of phages (MDA1 or phage cocktail MDA1, MDA2, MDA3 and MDA4) to improve survival of VRE-infected larvae.

	% of larvae survival	Median
Control	88	90
Sterile media	84	90
VRE	32	0
MDA1 alone	88	90
Phage cocktail alone	88	90
VRE+MDA1 (TG)	84	90
VRE+Phage cocktail (TG)	86	90
MDA1+VRE (PG)	66	80
phage cocktail+VRE (PG)	82	90

Abbreviations: VRE, Vancomycin-resistant *Enterococcus faecium; TG, treatment group; PG, prevention group.*

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736. The Use of Bacteriophages to Inhibit Different Strains of Vancomycin-Resistant or Susceptible Enterococci

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Background. Vancomycin-resistant Enterococci (VRE) is a well-known infectious complication among immunocompromised patients, especially hematopoietic