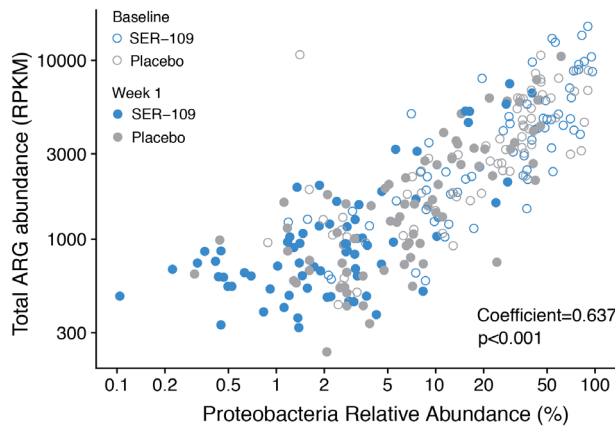


Figure 2. Total ARG abundance is associated with the relative abundance of Proteobacteria in SER-109 and placebo subjects at baseline and week 1.



RPKM (Reads per kilobase per million mapped reads), a measure of normalized gene abundance. Coefficient and p-value obtained from fitting a linear mixed model to baseline and week 1 samples, with subject as the random effect.

**Conclusion.** SER-109 was associated with significantly greater reduction of ARGs and AR bacteria abundances compared to placebo at 1 week post treatment. These findings support a potential role of microbiome therapeutics in rapid decolonization of AR bacteria with implications for infection prevention.

**Disclosures.** Timothy J. Straub, MS, Seres Therapeutics (Employee) Liyang Diao, PhD, Seres Therapeutics (Employee) Christopher Ford, PhD, Seres Therapeutics (Employee, Shareholder) Matthew Sims, MD, PhD, Astra Zeneca (Independent Contractor) Diasorin Molecular (Independent Contractor) Epigenomics Inc (Independent Contractor) Finch (Independent Contractor) Genentech (Independent Contractor) Janssen Pharmaceuticals NV (Independent Contractor) Kinevant Sciences gmbH (Independent Contractor) Leonard-Meron Biosciences (Independent Contractor) Merck and Co (Independent Contractor) OpGen (Independent Contractor) Prenosis (Independent Contractor) Regeneron Pharmaceuticals Inc (Independent Contractor) Seres Therapeutics Inc (Independent Contractor) Shire (Independent Contractor) Summit Therapeutics (Independent Contractor) Thomas J. Louie, MD, Artugen (Advisor or Review Panel member) Crestone (Consultant, Grant/Research Support) Da Volterra (Advisor or Review Panel member) Finch Therapeutics (Grant/Research Support, Advisor or Review Panel member) MGB Biopharma (Grant/Research Support, Advisor or Review Panel member) Rebiotix (Consultant, Grant/Research Support) Seres Therapeutics (Consultant, Grant/Research Support) Summit PLC (Grant/Research Support) Vedanta (Grant/Research Support, Advisor or Review Panel member) Colleen S. Kraft, MD, MSc, Rebiotix (Individual(s) Involved: Self): Advisor or Review Panel member Stuart H. Cohen, MD, Seres (Research Grant or Support) Stuart H. Cohen, MD, Nothing to disclose Mary-Jane Lombardo, PhD, Seres Therapeutics (Employee, Shareholder) Barbara McGovern, MD, Seres Therapeutics (Employee, Shareholder) Lisa von Moltke, MD, Seres Therapeutics (Employee, Shareholder) Matt Henn, PhD, Seres Therapeutics (Employee, Shareholder)

**LB16. Surveillance Rates of Cefiderocol Heteroresistance Correlate With All-cause Mortality in the APEKS-NP and CREDIBLE-CR Trials**

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**Background.** Cefiderocol is a recently FDA approved, novel siderophore beta-lactam antibiotic. Conventional antimicrobial susceptibility testing (AST) suggests that a variety of Gram-negative pathogens, including carbapenem-resistant (CR) isolates, are overwhelmingly susceptible to cefiderocol. This antibiotic performed well in the APEKS-NP trial for the treatment of nosocomial pneumonia caused largely by carbapenem susceptible isolates. However, in the CREDIBLE-CR trial involving exclusively CR Gram-negative bacteria, cefiderocol was associated with a higher rate of all-cause mortality. We hypothesized one explanation for these discrepant data might be undetected cefiderocol heteroresistance (HR).

HR is a form of antibiotic resistance in which an isolate harbors a minority resistant subpopulation of cells co-existing with a majority susceptible population, and is often undetected by standard AST. Isolates exhibiting undetected HR, with as low as 1 in 1 million resistant cells, can cause treatment failure in *in vivo* models.

**Methods.** We quantified HR to cefiderocol by population analysis profile (PAP) of 161 *Acinetobacter*, 180 *Klebsiella*, and 108 *Pseudomonas* isolates collected in Georgia, USA.

**Results.** We observed CR isolates exhibited a high frequency of HR, which was largely undetected by standard AST, and correlated with all-cause mortality in the CREDIBLE-CR study (Table). Carbapenem-susceptible isolates exhibited no or low rates of cefiderocol HR (Table). Cephalosporin-resistant bacteria mostly exhibited increased rates of cefiderocol HR, but below those of CR strains. These differences in rates of cefiderocol HR correlated with the mortality data from the APEKS-NP and CREDIBLE-CR trials, across the bacterial species tested (Table).

Table: Surveillance rates of cefiderocol heteroresistance correlate with all-cause mortality in the APEKS-NP and CREDIBLE-CR trials

		<i>Acinetobacter</i>	<i>Klebsiella</i>	<i>Pseudomonas</i>	Total
Hetero-resistance GA, USA	Susceptible (S) <sup>A</sup>	11% [4/35]	0% [0/50]	5% [1/20]	5% [5/105]
	Cephalosporin-resistant <sup>B</sup>	44% [8/18]	12% [5/41]	5% [1/19]	18% [14/78]
	Carbapenem-resistant (CR)	59% [64/108]	30% [27/89]	9% [6/69]	36% [97/266]
All-cause mortality	APEKS-NP <sup>C</sup>	22% [5/23]	10% [5/48]	8% [2/24]	13% [12/95]
	CREDIBLE-CR <sup>C</sup>	49% [19/39]	21% [6/28]	18% [2/11]	35% [27/78]

<sup>A</sup>These isolates are susceptible to meropenem, cefepime, ceftazidime, and ceftioxone by clinical antimicrobial susceptibility testing.

<sup>B</sup>These isolates are carbapenem (meropenem) susceptible but resistant to at least one of the extended spectrum cephalosporins cefepime, ceftazidime, and ceftioxone by clinical antimicrobial susceptibility testing.

<sup>C</sup>APEKS-NP involved only pneumonia patients while CREDIBLE-CR enrolled patients with pneumonia, bloodstream infections or urinary tract infections.

**Conclusion.** These data suggest that the lower rates of cefiderocol HR in carbapenem-susceptible isolates that predominated the APEKS-NP trial may explain the enhanced efficacy of the drug in that study as compared to the CREDIBLE-CR trial. Importantly, the widespread, undetected cefiderocol HR observed among CR pathogens may explain the discordance between this drug's excellent *in vitro* susceptibility profile and increased patient mortality in the CREDIBLE-CR trial.

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

**LB17. Immunosequencing of the T-Cell Receptor Repertoire Reveals Signatures Specific for Diagnosis and Characterization of Early Lyme Disease**

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**Background.** Changing climate and demographic trends have led to recent increases in the incidence of tick-borne illnesses. Early diagnosis of Lyme disease (LD) is critical for initiation of antibiotics to mitigate symptoms and prevent late manifestations. In patients not presenting with a typical erythema migrans rash, 2-tiered serologic testing is recommended to support a diagnosis of LD. However, 2-tiered testing is limited by ambiguity in interpretation and low sensitivity in early disease, highlighting an unmet clinical need for alternative diagnostic approaches. We identified a clinical signal for early LD based on evaluation of the T-cell response to *B. burgdorferi* infection.

**Methods.** We immunosequenced T-cell receptor (TCR) repertoires in blood samples from 3 independent cohorts of patients with laboratory-confirmed or clinically diagnosed early LD and endemic/non-endemic controls to identify 251 public, LD-associated TCRs. These TCRs were used to train a classifier that identified early LD with 99% specificity. Classifier sensitivity was evaluated in 211 LD cases and 2631 endemic controls and compared to that of standard 2-tiered testing (STTT). Biologic specificity was assessed by correlating TCR assay scores with clinical measures and by mapping the antigen specificity of Lyme-associated TCRs to *B. burgdorferi* antigens.

Figure 1. LD-associated TCRs distinguish cases (orange) from controls (blue) in training cohorts. (A) Logistic-growth curve used to define a scoring function. (B) Positive-call threshold (99th percentile in endemic controls).

