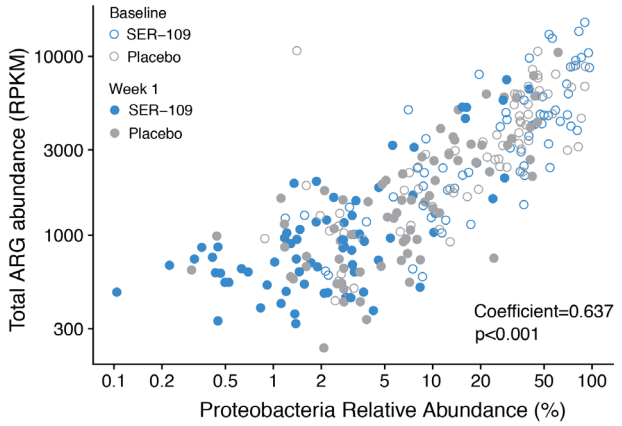
Figure 2. Total ARG abundance is associated with the relative abundance of Proteobacteria in SER-109 and placebo subjects at baseline and week 1.



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.

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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

		Acinetobacter	*Klebsiella*	*Pseudomonas*	Total
Hetero-resistance GA, USA	Susceptible (S)[A]	11% [4/35]	0% [0/50]	5% [1/20]	5% [5/105]
	Cephalosporin-resistant[B]	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[C]	22% [5/23]	10% [5/48]	8% [2/24]	13% [12/95]
	CREDIBLE-CR[C]	49% [19/39]	21% [6/28]	18% [2/11]	35% [27/78]

[A]These isolates are susceptible to meropenem, cefepime, ceftazidime, and ceftriaxone by clinical antimicrobial susceptibility testing.
[B]These isolates are carbapenem (meropenem) susceptible but resistant to at least one of the extended spectrum cephalosporins cefepime, ceftazidime, and ceftriaxone by clinical antimicrobial susceptibility testing.
[C]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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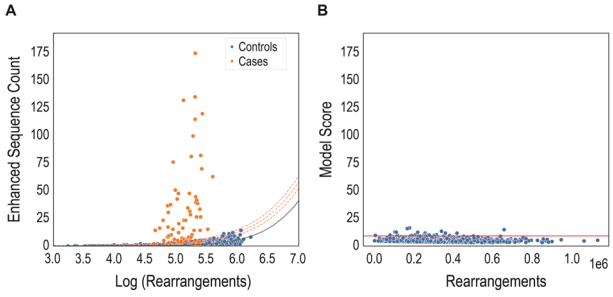
Background. Changing climate and demographic trends have led to recent increases in the incidence of tick-borne illnesses. Early diagnosis of Lyme disease (LD) is critical for initiation of antibiotics to mitigate symptoms and prevent late manifestations. In patients not presenting with a typical erythema 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).



Results. In early LD, TCR testing demonstrated a 1.9-fold increase in sensitivity compared to STTT (56% vs 30%), with a 3.1-fold increase ≤4 days from the onset of symptoms (44% vs 14%). TCR positivity predicted subsequent seroconversion in 37% of initially STTT-negative patients, suggesting the T-cell response is detectable before the humoral response. While positivity for both tests declined following treatment, greater declines in posttreatment sensitivity were observed for STTT compared to TCR testing. Higher TCR scores were associated with measures of disease severity, including abnormal liver function tests, disseminated rash, and number of symptoms. A subset of LD-associated TCRs mapped to *B. burgdorferi* antigens, demonstrating the high specificity of a TCR immunosequencing approach.

Table 1. TCR classifier sensitivity stratified by serostatus.

	Sensitivity	n
All JHU	0.56 (0.49–0.62)	118/211
STTT Positive	0.92 (0.84–0.98)	59/64
STTT Post-Treatment Seroconverter	0.58 (0.45–0.74)	22/38
Persistent STTT Negative	0.34 (0.27–0.43)	37/109

Figure 2. Validation of the TCR classifier in the JHU cohort and other holdout endemic controls. Distribution of model scores (A) and assay sensitivity (B). Model scores (C) and ROC (D) curves by serostatus.

Figure 2

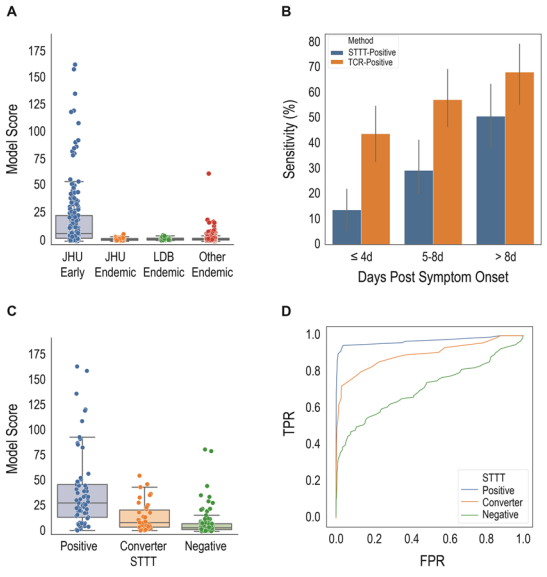
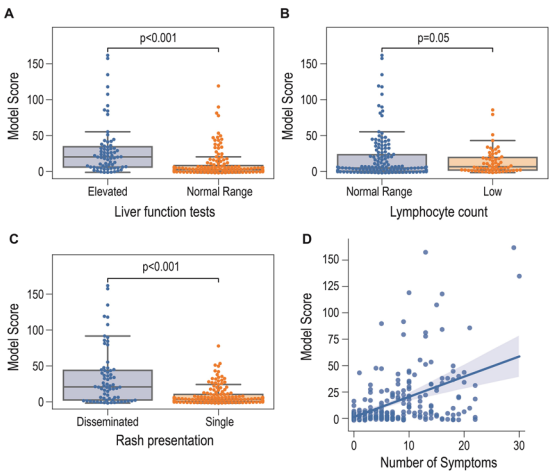


Figure 3. Clinical correlates of TCR scoring. (A) Liver function test; (B) lymphocyte count, (C) rash presentation, (D) number of symptoms.

Figure 3



Conclusion. T-cell-based testing has potential clinical utility as a sensitive and specific diagnostic for early LD, particularly in the initial days of illness.

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LB18. Healthcare Utilization for Acute Respiratory Illness by Race/Ethnicity across Ambulatory, Emergency, and Hospital Settings

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Background. Given the disproportionate impact of COVID-19 among racial/ethnic minority groups across the United States on emergency visits, hospitalizations, and deaths, we examined healthcare utilization more broadly for acute respiratory illness (ARI across healthcare settings by racial/ethnic group.

Methods. Using data on 33,992,254 unique nonpharmacy healthcare encounters from the IBM Explorys Electronic Health Record database from January 1, 2020–May 1, 2021, across healthcare settings (ambulatory care or telehealth, emergency department, and hospitalizations) with nonmissing bridged racial/ethnic data. Encounters were classified as ARI based on ICD-10 and SNOMED codes and aggregated by month and US Census region. We estimated the population denominator as the total number of persons by bridged racial/ethnic group with encounters recorded during 2019. We both estimated the rate of ARI visits per 100,000 persons across healthcare settings and the rate ratio of ARI visits to non-ARI visits. We performed comparisons of these values by race/ethnicity, taking White persons as referent, using Poisson generalized estimating equations clustered within geographic regions.

Results. A total of 244,137 (6.5% of 3,745,135) hospitalizations, 237,873 (18% of 1,305,474) emergency visits, and 1,636,383 (5.7% of 28,941,645) ambulatory visits were associated with ARIs. We observed similar rates of ARI visits across race/ethnicity groups in all settings combined and in ambulatory settings, but higher rates of ARI hospitalization among Hispanic persons (IRR [95% CI]: 2.5 [1.7–3.7]) and higher rates of ARI emergency department visits among Black persons (2.5 [1.9–3.2]) (Figure). We also observed differences in the relative proportion of care received for ARI vs. other visits types by setting, for example with Black persons utilizing higher rates of hospital visits for ARI vs non-ARI care (2.2 [1.7–2.7]) but lower rates of ambulatory care for ARI (0.9 [0.7–0.96]).

ARI Visits Per 100k Persons