

multidimensional scaling (NDMS) ordination shows high interpatient dissimilarity (Bray-Curtis) for most samples, the post-ABX inpatient dissimilarity varies by ABX. The AZ group exhibited chronic alterations in taxa dissimilarity and the CF group had increases in dissimilarity directly post-ABX. The CF+AZ group displayed both acute and persistent perturbations (Figure 1). Although there was no significant change in ARG richness post-ABX, there was a significant increase in overall ARG abundance across all samples ( $P < 0.003$ ). Within each ABX, there were unique changes in ARG abundance, and groups with CF had increases in ARG abundance (Figure 2).

**Conclusion.** ABX used to treat CAP can cause acute microbiome disruptions, as evidenced by decreased microbiome species diversity and richness, and an increase in ARG abundance post-ABX. The duration of this impact is variable. To prevent microbiome disruptions, measures to prevent inappropriate ABX use via ABX stewardship are necessary.

**Figure 1. NDMS ordination plots of species composition for patient samples show drug specific increases in acute and chronic dissimilarity.**

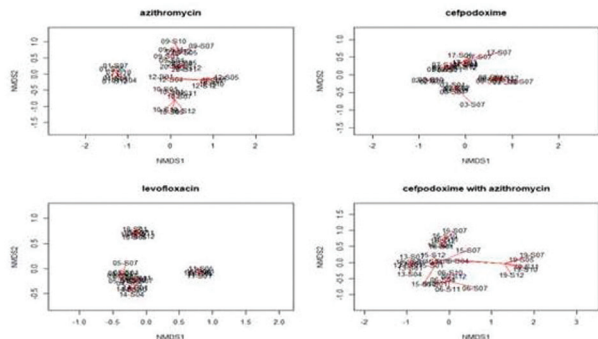
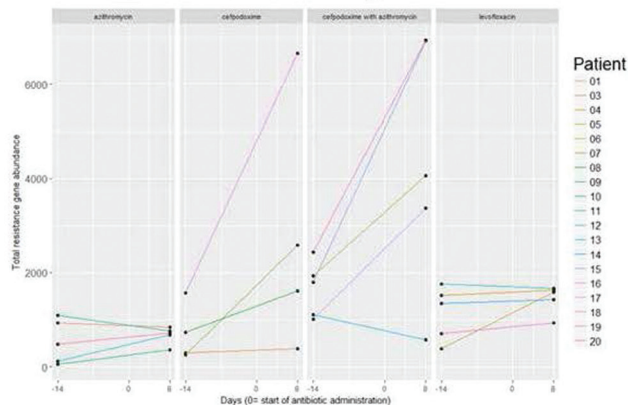


Figure 1. Plot of first two NDMS axes of metagenomic sample species abundance dissimilarity measured by Bray-Curtis.

**Figure 2. ARG abundance (RPKM) pre (0) and post (1.00) antibiotic for each patient**

**Resistance Gene Abundance Changes After Antibiotics**



Gene counts for resistance genes in Reads  $\times$  Kilobase of transcript, per Million mapped reads (RPKM) for each patient (ID).

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**1774. Ridinilazole (RDZ) for Clostridium difficile infection (CDI): Correlation of In Vitro Spectrum of Activity with Human Gut Microbiome Profiles from a Phase 2 Clinical Trial**

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**Session:** 215. Translating Microbiome Science into Practice  
Saturday, October 6, 2018: 10:30 AM

**Background.** Recurrence of CDI (rCDI) is associated with perturbation of the gut microbiome during treatment with vancomycin (VAN) or metronidazole (MTZ). RDZ is a novel, targeted spectrum antibacterial under investigation to treat CDI and reduce rCDI. Here correlation of *in vitro* spectrum of activity with preservation of the human gut microbiome and clinical outcomes is presented.

**Methods.** Susceptibility testing was to CLSI standards with VAN, MTZ, and fidaxomicin (FDX) comparators. The Phase 2 clinical trial was a double-blind, randomized

study of 100 patients assigned 1:1 to 10 days RDZ 200 mg BID or VAN 125 mg QID treatment. Primary endpoint was sustained clinical response (SCR), defined as cure at end of therapy (EOT), and no rCDI for the next 30 days. Relative effects of RDZ and VAN on the gut microbiome were examined by sequencing 16S rDNA amplicons from stool collected at baseline, days 5, 10, 25, and end of study. Bioinformatic analyses were performed in QIIME.

**Results.** RDZ *C. difficile* (N = 50) MIC range was 0.125–0.25  $\mu$ g/mL. *Clostridium* spp. showed varied RDZ susceptibility; *C. innocuum* MIC<sub>90</sub> 1  $\mu$ g/mL, *C. ramosum* and *C. perfringens* MIC<sub>90</sub> >512  $\mu$ g/mL. VAN showed potent to moderate growth inhibition of all *Clostridium* spp. (MIC range 1–16  $\mu$ g/mL). Limited RDZ activity was observed for Gram-positive anaerobes, including *Bifidobacteria*, *eggerthella*, *Finogoldia*, and *Peptostreptococcus* (MIC<sub>90</sub> >512, >512, 64, and 64  $\mu$ g/mL) compared with VAN (MIC<sub>90</sub> 1, 4, 0.5, and 0.5  $\mu$ g/mL). *Bacteroides fragilis* MIC<sub>90</sub> for RDZ and VAN were >512 and 64  $\mu$ g/mL, respectively. These *in vitro* data correlate closely with human microbiome profiles. RDZ reduced *C. difficile* to below detection with other reductions in abundance observed in only 2 families from the *Clostridia*. VAN at EOT resulted in significant losses, often below detection, in 4 Firmicutes families, Actinobacteria, and Bacteroidetes and a 25-fold increase in Proteobacteria abundance. The preservation of the microbiome by RDZ likely accounted for reduced rCDI compared with VAN with RDZ shown to be superior on SCR to VAN with rates of 66.7% and 42.4%, respectively (pre-specified 90% CI 3.1, 39.1).

**Conclusion.** These data demonstrate strong translation of *in vitro* spectrum to human gut microbiome preservation during therapy and support further clinical development of RDZ.

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**1775. Microbiome-Based Classifiers Accurately Differentiate Infectious Diarrhea From Functional Gastrointestinal Disorders and Provide Population-Scale Confidence Measures of Fecal Microbiota Restoration in Recurrent C. Difficile Infection**

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**Background.** Fecal microbiota therapy is being actively pursued as treatment for recurrent *C. difficile* infection (rCDI), as well as for other GI disease indications associated with dysbiosis, for example, irritable bowel syndrome (IBS). RBX2660 is a microbiota-based drug designed to restore a healthier microbiome and has demonstrated clinical efficacy for preventing rCDI. Despite this and other treatment successes, our understanding of functional microbiota reconstitution at the population scale is still evolving, as is the ability to distinguish IBS from CDI recurrence. Herein we describe development of a Random Forest classifier for CDI diagnosis, and we evaluate microbiome restoration in participants of the Phase 2 trial of RBX2660.

**Methods.** Fecal 16S rDNA sequences from 2,129 subjects enrolled in diverse multi-center cohorts were analyzed (1,235 adults and 447 children with CDI, AAD, IBS, or controls). Technical variations due to different DNA extraction, primer region coverage, and sequencing platforms were addressed using closed-reference OTU picking with UCLUST. The RDP classifier and SILVA database assigned taxonomy for each OTU sequence. Stratified random sampling with 50 repeated tests of microbiota training sets was performed for supervised learning. Microbiota signatures of patients in the RBX2660 PUNCH CD2 trial were then assessed using classifiers built to predict CDI treatment outcomes and IBS misdiagnosis.

**Results.** Random Forest built the best classifiers accurately predicting 97.7% of CDI cases, and confidently distinguished CDI from IBS patients based on their microbiome signatures (figure). RBX2660 treatment significantly restored microbiota community composition in rCDI cases compared with placebo controls.

**Conclusion.** Random Forest classifiers built on a population-scale study of microbiota composition in patients with GI disease provide a highly accurate predictor of CDI cases versus potential IBS misdiagnosis in adults and children. RBX2660 significantly reduced disease classification scores in rCDI patients with a healthy-like microbiota reconstitution markedly accelerating after 30 days of treatment.

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