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Response to Microbiota-Based Drug RBX2660 is Associated with Reduction in Antimicrobial Resistance Genes in Patients with Recurrent *Clostridioides difficile* Infections

REBIOTIX, INC.
kblount@rebiotix.com

Julia Garcia-Diaz MD[1], Courtney Jones[2], Hiren Karathia PhD[3], Brian Fanelli[3], Nur A Hasan PhD[3], Ken Blount PhD[2]

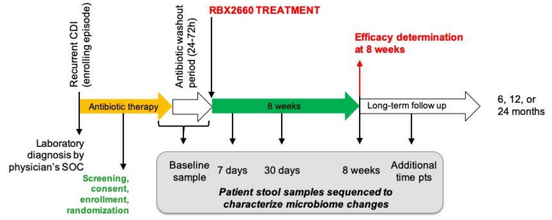
[1]Ochsner Medical Center, New Orleans, LA; [2]Rebiotix Inc. Roseville, MN; [3]CosmosID, Inc, Rockville, MD

BACKGROUND

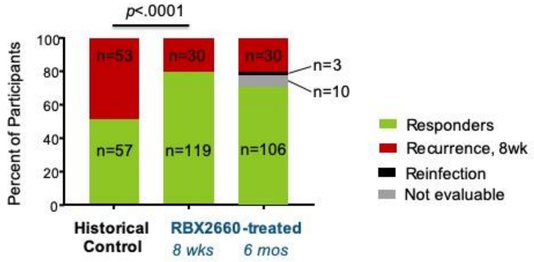
- Antibiotic microbial resistance (AMR) is a global health challenge, and is common in recurrent *Clostridioides difficile* infection (rCDI) population due to high historical exposure to antibiotics.
- The gut microbiota implicated as a reservoir of AMR bacteria.
- Therapeutic approaches that decolonize AMR gut bacteria would be valuable.
- In a previous analysis, RBX2660, an investigational standardized microbiota-restoration therapy in clinical development for preventing rCDI decreased vancomycin-resistant enterococci colonization.
- Herein, we assessed the total AMR gene profile before and after treatment in fecal samples from RBX2660 treatment responders in a Phase 2 rCDI trial.

METHODS

- PUNCH Open Label™ (NCT02589847) - prospective, multicenter, open-label Phase 2 study assessing the efficacy and safety of RBX2660 treatment of recurrent CDI.
  - *PATIENT POPULATION: multi-recurrent CDI (≥2 recurrent episodes at enrollment)*
  - *TREATMENT: two doses of RBX2660 administered 7 ± 2 days apart*
  - *EFFICACY: absence of CDI recurrence at 8 weeks after last study treatment*
  - *FAILURE: documented recurrence, including positive laboratory diagnosis for C. difficile*
  - *CONTROL GROUP: historical chart review of patients who only received antibiotic therapy for rCDI*
- Analysis included 66 longitudinally matched samples from 22 treatment responsive participants, including before treatment (BL) and 7 ± 3 and 30 ± 10 days after treatment. Sample set represents 17 trial sites from US and Canada.
- All samples were frozen without stabilizers after collection, extracted, and sequenced using a shallow shotgun method.
- Sequencing reads were compared to a proprietary database of gene sequences annotated as related to antimicrobial resistance (CosmosID)
- ≥40% sequencing coverage of an AMR gene was considered positive identification in each sample.
- AMR gene coverage for participant samples were compared to Human Microbiome Project (HMP) data for which comparable sequencing depth was simulated.

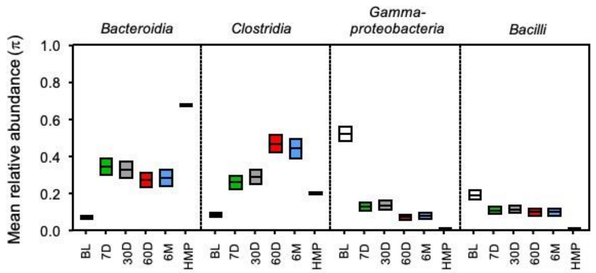


RBX2660 IS EFFICACIOUS & DURABLE



- 119 of 149 RBX2660-treated participants (80%) were responders at 8 weeks after treatment
- 57 of 110 patients (52%) in the historical control group were recurrence-free 8 weeks after antibiotic treatment
- Only 3 of 109 evaluable primary RBX2660 responders reported reinfection at 6 months
- 97% of RBX2660-treated 8-week responders who were evaluable at 6 months remained recurrence-free
- Follow up ongoing to 24 months

RBX2660 SHIFTS MICROBIOME COMPOSITION

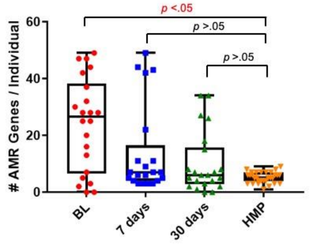


- Participants were dysbiotic at study entry, with decreased *Bacteroidia* and *Clostridia* and overabundance of *Gammaproteobacteria* and *Bacilli*
- *Bacteroidia*, *Clostridia* increased and *Gammaproteobacteria*, *Bacilli* decreased after treatment; durable to 6 months after treatment
- Based on shallow-shotgun sequencing data

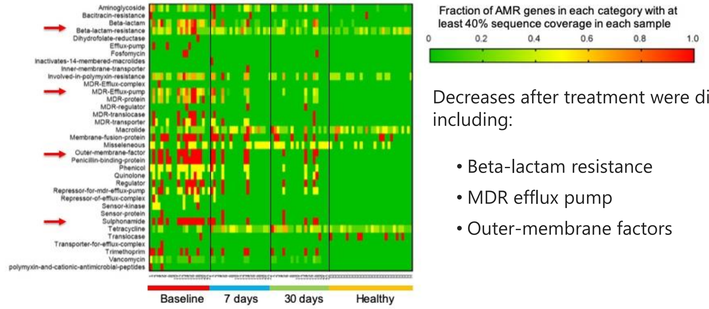
ANTIMICROBIAL RESISTANCE GENES (AMR) ANALYSIS

ANTIMICROBIAL RESISTANCE GENES WERE DECREASED POST-RBX2660 AMONG TREATMENT RESPONDERS

- Prior to treatment (BL) rCDI participants had significantly higher abundance of antimicrobial resistance (AMR) genes than the HMP healthy population
- After treatment (7 and 30 days), participants' had decreased AMR gene abundance, not significantly different from HMP



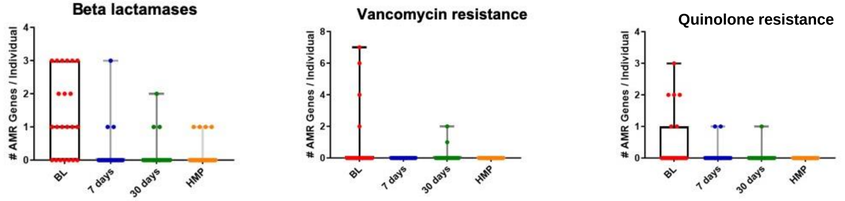
AMR GENE DECREASES WERE IN BROAD FUNCTIONAL CLASSES



Decreases after treatment were distributed among AMR gene classes, including:

- Beta-lactam resistance
- MDR efflux pump
- Outer-membrane factors
- Penicillin-binding proteins
- Sulphonamide resistance
- Vancomycin resistance

KEY AMR CLASSES IDENTIFIED BEFORE BUT NOT AFTER RBX2660 TREATMENT



CONCLUSIONS

- In a Phase 2 open-label trial, RBX2660 was 80% effective for preventing rCDI, with durable response to at least 6 months.
- Responding participants' microbiomes resolved toward a healthier composition after treatment .
- In a 22-participant subgroup analysis, there was a significant decrease in antimicrobial resistance genes from before to after successful response to RBX2660.

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