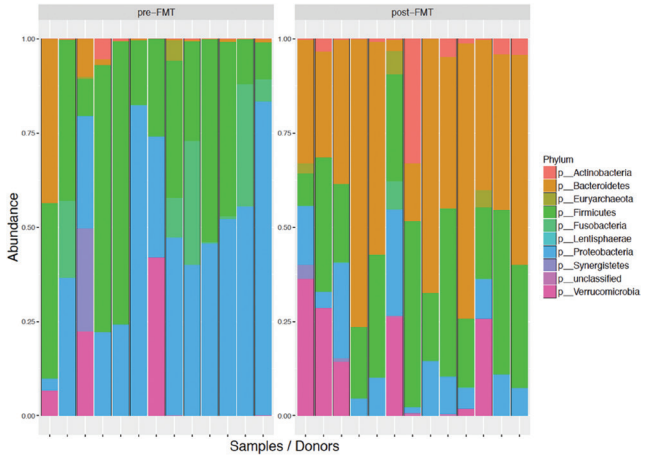
Figure 2: Relative abundance of taxa at Phylum level.



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

619. Intestinal Microbiome Changes Associated with Immune Status and *Clostridium difficile* Colonization in Hospitalized Children

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Background. The intestinal microbiome modulates local and systemic immune responses and may impact clinical outcomes. However, there are few studies in pediatric patients. We conducted a cross-sectional study of fecal microbiomes in hospitalized children on a single inpatient unit at Children's Hospital at Montefiore, Bronx, New York in 2016–2017 to test the hypothesis that "high-risk" children with chronic illnesses (cancer, transplant and sickle cell disease [SCD]) have decreased microbial diversity and higher rates of asymptomatic colonization with *C. difficile* compared with children hospitalized on the same ward but without similar risk factors.

Methods. Stool was collected within 72 hours of admission from patients who provided consent and assayed for *C. difficile* colonization by glutamate dehydrogenase (GDH); microbiome analysis was performed by 16S rRNA sequencing. Clinical and demographic data were obtained from the EMR.

Results. One hundred and six unique patients provided a sample for analysis. Sixty-nine were categorized as high-risk, including 32 SCD patients. *C. difficile* colonization rates were 22% and 19% in the high-risk and low-risk groups, respectively, but highest in the subset of SCD patients on penicillin prophylaxis (33%). The high-risk group had a trend toward lower microbial diversity than controls, and SCD patients exhibited a diversity index greater than other high-risk patients. Antibiotic use in the last 3 months and PPI use were associated with decreased microbial diversity across the entire study population ($P = 0.004$, $P = 0.007$, respectively). Among children with SCD, those on penicillin prophylaxis had a trend toward decreased alpha diversity while folic acid was associated with increased diversity ($P = 0.02$). SCD patients had greater quantities of *Bacteroides* and *Parabacteroides* and fewer *Escherichia* and *Shigella* than the other cohorts.

Conclusion. SCD and penicillin prophylaxis might be risk factors for *C. difficile* colonization and intestinal dysbiosis. The implications of these findings require further, longitudinal study.

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

620. Oral β-Lactamase Therapies Prevent Microbiome Damage and Attenuate Antibiotic Resistance From IV and Oral Antibiotics in Large Animal Models of Antibiotic-Mediated Gut Dysbiosis

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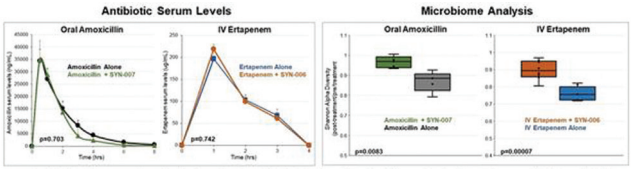
Background. Antibiotics can damage the gut microbiome leading to overgrowth of pathogens and provide selective pressure for emergence of antibiotic resistance. SYN-004 (ribaxamase) is a clinical-stage β-lactamase formulated for oral delivery intended to degrade certain β-lactam antibiotics in the GI tract to preserve the gut microbiome. Ribaxamase was evaluated in a phase 2b clinical study that met its primary endpoint of significantly reducing *C. difficile* infection in patients treated with IV ceftriaxone and demonstrated protection of the gut microbiome with reduced emergence of antibiotic resistance. Ribaxamase is intended for use with IV penicillins and cephalosporins, but does not degrade carbapenems. B-lactamase-mediated microbiome protection was expanded to include oral and carbapenem antibiotics.

Methods. For use with oral β-lactams, a ribaxamase formulation, SYN-007, was engineered for release in the lower small intestine, distal to the site of antibiotic absorption. For use with IV carbapenems, SYN-006, a novel metallo-β-lactamase, was formulated for oral delivery. SYN-007 (10 mg, PO, TID) was evaluated in dogs treated with oral amoxicillin (40 mg/kg, PO, TID) for 5 days. SYN-006 (50 mg, PO, QID) was evaluated in pigs treated with ertapenem (30 mg/kg, IV, SID) for 4 days. Serum antibiotic levels were measured and fecal DNA whole-genome shotgun sequence analyses were performed.

Results. In dogs and pigs, systemic antibiotic levels were not significantly different ±SYN-007 or SYN-006. Fecal DNA metagenomics analyses demonstrated that oral amoxicillin and IV ertapenem resulted in significant changes to the gut microbiome. SYN-007 and SYN-006 attenuated microbiome damage and reduced emergence of antibiotic resistance.

Conclusion. Ribaxamase, SYN-007, and SYN-006 have the potential to protect the commensal gut microbiota from antibiotic-mediated collateral damage and to mitigate emergence and spread of antibiotic resistance, thereby broadening the utility of this prophylactic approach to include all classes of β-lactam antibiotics, delivered both systemically and orally. Antibiotic inactivation represents a new paradigm for preservation of the gut microbiome and reduction of antibiotic resistance.



Oral beta-lactamases do not affect systemic antibiotic levels and protect the gut microbiome from antibiotic-mediated damage. Serum was tested for amoxicillin or ertapenem using LC/MS/MS analysis. Area under the curve was not significantly different between oral amoxicillin alone vs. oral amoxicillin + SYN-007 (p=0.703) or for IV ertapenem alone vs. IV ertapenem + SYN-006 (p=0.742), indicating that the beta-lactamases did not affect serum antibiotic levels (left panels). Fecal DNA collected before and after antibiotic administration was subjected to metagenomics sequencing analyses. Shannon alpha diversity ratios (pretreatment/post-treatment) were significantly different for oral amoxicillin alone vs. oral amoxicillin + SYN-007 (p=0.0083) and for IV ertapenem alone vs. IV ertapenem + SYN-006 (p=0.00007). Both SYN-007 and SYN-006 cohorts displayed a ratio close to 1 indicating minimal change in diversity of the gut microbiome pre and post antibiotic exposure (right panels). These data demonstrate that oral beta-lactamases protect the gut microbiome from antibiotic collateral damage without affecting antibiotic blood levels.

Disclosures. **S. Connelly**, Synthetic Biologics, Inc.: Employee and Shareholder, Salary. **C. Furlan-Freguia**, Synthetic Biologics, Inc.: Employee and Shareholder, Salary. **B. Fanelli**, CosmosID, Inc.: Employee, Salary. **N. A. Hasan**, CosmosID, Inc.: Employee, Salary. **R. R. Colwell**, CosmosID, Inc.: Employee and Shareholder, Salary. **M. Kaleko**, Synthetic Biologics, Inc.: Employee and Shareholder, Salary.

621. Treatment of Recurrent *Clostridium difficile* Infection with SER-109 Increases the Concentration of Secondary Bile Acids in a Dose-Dependent Manner

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Background. *C. difficile* recurs when dormant spores germinate in the dysbiotic gut, facilitated by an increase of 1° vs. 2° bile acids. SER-109, an ecology of bacterial spores purified from stool of healthy donors, is an investigational first-in-class microbiome therapeutic intended to facilitate microbiome restoration and reduce risk of recurrent *C. difficile* (rCDI). Rapid engraftment of spore-forming species is associated with (i) higher doses of SER-109 in our dose-ranging Phase 1b study (Ph1b) and (ii) reduced rCDI in our Phase 2 trial (Ph2). We explored whether higher doses of SER-109 were associated with an increase in 2° bile acids.

Methods. Whole metagenomic shotgun (WMS) data were generated from stool, and species were identified using a proprietary build of MetaPhlAn. Evaluation of spore-forming species richness and bile acid concentrations identified effects of SER-109 treatment. A triple stage bioreactor model of the human gut and rCDI was used to evaluate the impact of microbial therapeutics.

Results. Ph1b subjects who received a higher dose (>1.5×10^8 SporQ) had significantly higher spore-forming species richness than subjects who received a low dose (<1.5×10^8 SporQ) at Week 1 post-treatment ($P = 0.017$, Figure 1). Spore-forming species richness in patients receiving a low dose in Ph1b was comparable to that observed in non-recurrent patients in Ph2, who received the same mean dose (Figure 1). Ph1b subjects in the high dose group had a significantly higher concentration of 2° bile acids as compared with Ph1b low dose subjects and non-recurrent Ph2 subjects ($P = 0.036$, $P < 0.001$, respectively, Figure 2). A higher dose (3×10^8 SporQ × 3 days) suppressed recurrence in a gut model of rCDI; a single dose did not.

Conclusion. Higher doses of SER-109 are significantly associated with (i) higher spore-forming species richness, (ii) concentrations of secondary bile acids, and (iii) prevention of recurrence in an gut model of CDI. These results suggest that SER-109 in the Phase 2 trial was biologically active and catalyzed a functional change in the microbiome of a subset of subjects; a dose increase may optimize efficacy across a broad population. Seres has initiated a Phase 3 study of SER-109 to reduce rCDI, which includes an increase in dose titer and frequency.