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TITLE: MICROBIOME AND METABOLIC MARKERS OF CLOSTRIDIUM DIFFICILE RECURRANCE

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ABSTRACT BODY:

Abstract Body: Background: Recurrent Clostridium difficile infection (CDI) is thought to arise, in part, from loss of intestinal commensal bacteria that inhibit C. difficile proliferation and toxin production through the action of their microbial bile salt hydrolases (BSH), including 7-alpha-dehydroxylase (7aD), to produce secondary bile acids. We conducted a longitudinal clinical study, and used a novel machine learning approach to identify microbiota as well as BSH, including 7aD, activities that predict CDI recurrence.

Methods: We conducted a prospective study of first episode uncomplicated CDI. Patients collected stool at CDI diagnosis and weekly to bi-weekly for 6 weeks following treatment. Recurrence was defined as diarrhea with a positive stool test for CDI. Stool 16S rRNA gene next generation sequencing and bile acid metabolomic analyses were performed on all samples. Liquid chromatography (LCMS) was performed on lyophilised stool. To quantify BSH activity, fecal water was incubated with taurodeoxycholic acid and precipitate formation measured on spectrophotometry. A novel Bayesian machine learning approach (MITRE) that incorporates microbiota time series data with phylogenetic structure to learn interpretable predictive rules, was used to discover microbial predictors of recurrence.

Results: 29 first episode CDI patients were enrolled: mean age 59.2±16.8 years and 68% female. Ten patients recurred (34.5%) during the 6-week follow up period. Average time to recurrence was 1.9 weeks. The top MITRE rule predicted greatly decreased odds of CDI recurrence (>1000 fold) for subjects with a microbiota with relative abundance above 0.4% for bacterial clade 13220, consisting of Clostridium scindens and Clostridium hylemonae (species with known 7aD activity) in the preceding week (Figure 1). Additionally, patients that did not recur (NR-CDI), had significantly more taurocholic acid (TCA), a conjugated primary bile acid in the stool, at week 0 compared to week 6 (p=0.005). Conversely, amongst patients who did recur (R-CDI), there was no decline in TCA (and a trend towards an increase) each week closer to the recurrence (p=0.76) (Figure 2a/b). BSH activity also recovered over time in NR-CDI (week 0 vs week 6, p=0.028, one-tailed Mann-Whitney), but did not recover in R-CDI (Figure 2c/d).

Conclusion: The primary bile acid, TCA, a potent trigger to CDI germination, decreases over time in NR-CDI, but not in R-CDI. Conversely, BSH activity, the key microbial enzymes that degrade TCA, recovers over time in NR-CDI but not in R-CDI. C. scindens and C. hylemonae, two established producers of 7aD, were strong predictors of recurrence. Collectively, our findings support use of microbiota and associated bile acid signatures as predictors for C. difficile recurrence.