

Response to Reviewers

The line numbers we refer to below are taken from the “clean” version of the manuscript we have submitted (manuscript.docx).

Reviewer #1 (Comments for the Author):

Overall, I appreciate the work that the authors did to address my concerns with the manuscript and I look forward to seeing it published.

The one point on which I still disagree with the authors interpretations is the extent to which the existing literature supports their theory that full FMT lacks adequate diversity to occupy all available niches and that is what necessitates treatment with multiple FMTs and/or enriched communities. In the two studies that they cited for increased efficacy of multiple FMTs (ref 28 and 29), microbiome disruption/diversity was not examined and other potential co-variables (disease severity, immunocompromised state (28)), were identified as correlated with failure of first FMT. In the the third study the authors cited (ref 30), there were no significant clinical or microbial community differences between patients treated with FMT vs FMT + Lactobacillus. In contrast, the data which I cited in my original critique (Seekatz et al 2014 mBio 5:300893-14) failed to find correlation between FMT engraftment and clinical FMT failure, suggesting that factors in addition to ability to occupy niche space factor into FMT success/failure. If the authors are aware of more recent literature that can be cited that shows a correlation between FMT failure and inability to fill niche space, that should be included. Otherwise, the authors should consider revising this sentence. As the authors indicated they were unclear about what type of revision was being requested, a suggestion revision is provided below.

Original text:

In this scenario, a full FMT may be insufficient to provide adequate diversity and abundance to outcompete and occupy all the exposed niches. Multiple FMTs (28, 29) or transplant of an enriched fecal community (30) may be necessary to recover the microbiota enough to outcompete *C. difficile* for the nutrient niches and replace the missing protective functions.

Proposed revision:

In this scenario, community restoration will require transplantation with microbes that provide adequate diversity and abundance to outcompete and occupy all the exposed niches. If this diversity is not provided through a single FMT, multiple FMTs (28, 29) or transplant of an enriched fecal community (30) may be necessary to recover the microbiota enough to outcompete *C. difficile* for the nutrient niches and replace the missing protective functions.

This revision retains the primary emphasis of the authors' original statement while reducing the implication that a single FMT is insufficient to provide adequate diversity which is more difficult to support from the existing literature.

We appreciate the reviewers clarification of the their feedback on this statement in the manuscript and understand their criticism with the language used. We have incorporated the reviewer's recommended language. (Lines 300-305)