Correspondence: Fecal Microbiota Transplant from a Rational Stool Donor Improves Hepatic Encephalopathy: A Randomized Clinical Trial

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To the Editor:

The study from Bajaj *et al* – evaluating the safety and efficacy of fecal microbiota transplant (FMT) as treatment for hepatic encephalopathy (HE)[1] – raises several questions.

A first issue concerns the omission of specific detail regarding the medical therapy being used to treat HE in participants at recruitment, and the implication that lactulose/ rifaximin was restarted after FMT in the treatment arm. If there was greater use of medical therapy for HE in the FMT arm compared to standard-of-care, this difference may be an alternative explanation for the apparent reduced HE burden in these patients. Furthermore, recommencement of rifaximin shortly after FMT would surely be inappropriate, as the broad-spectrum nature of this non-absorbable antibiotic[2,3] would intuitively minimise the chance of successful colonisation of recipients with bacterial communities present within the FMT.

Another issue regards appropriate donor selection. The authors describe using machine learning to select a donor with high stool relative abundance of *Lachnospiraceae* and *Ruminococcaceae,* given that these microbial families are found at reduced relative abundance in the stool of patients with HE[4]. However, the data presented demonstrate that relative abundance of these two families in FMT-treated patients appear no different than baseline levels by day 15 post-FMT (remaining throughout at levels much lower than that of the donor), and Shannon diversity index was also statistically unchanged from baseline at this timepoint. Given the timescale of these microbial changes, it seems unfeasible that the apparent improvement in PHES testing/ EncephalApp-Stroop and reduced HE events (all outcomes measured at day 15 post-FMT or later) was attributable to *Lachnospiraceae* and *Ruminococcaceae* members derived from the FMT. Recent data demonstrate that sterile stool filtrates may have similar efficacy in treating recurrent *Clostridium difficile* infection as conventional FMT[5], consistent with bacterially-derived proteins, gut metabolites, bacteriophages or other filtrate components being the mediators of FMT's efficacy in treating this condition, as opposed to intact microorganisms. By extrapolation, for future studies in this area, a more rational means of donor selection may be based around not purely matching the structure of the gut microbiota, but to select donors with the gut microbiota functionality missing in HE.

References:

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List of abbreviations:

FMT fecal microbiota transplantation

HE hepatic encephalopathy

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