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Letter: faecal microbiota transplantation for irritable bowel syndrome

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Letter: faecal microbiota transplantation for irritable bowel syndrome

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JPS, BHM, MNQ, TI wrote the manuscript; TI provided critical revisions

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None to declare

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We read with interest the recent paper by Lahtinen *et al* [1] evaluating faecal microbiota transplantation (FMT) in irritable bowel syndrome (IBS); 49 IBS patients were randomised to receive either autologous stool or allogenic FMT *via* colonoscopy. The primary endpoint was a 50-point reduction in the IBS severity score at week 12. There were no significant differences between autologous stool or allogenic FMT.

This study included patients with diarrhoea-predominant IBS (IBS-D), mixed IBS and un-subtyped IBS. Currently, mechanisms underpinning the demonstrated efficacy of FMT for treating *Clostridioides difficile* infection and inflammatory bowel disease are not understood [2,3]. This is despite the clear definition of phenotype in these studies. The pathogenesis of IBS is probably multifactorial [4]. From a mechanistic and efficacy perspective, we believe that it is imperative for IBS-FMT interventional studies to rigorously phenotype IBS subtypes to achieve sufficient power. Outcomes, including microbiome composition and functional changes, should be explored separately.

The importance of phenotyping IBS patients may explain some of the mixed results in the current literature from using FMT for IBS symptoms. Data from FMT trials are also difficult to interpret due to the widely varying methodologies employed. A meta-analysis including all sub-types of IBS concluded that the relative risk of IBS symptoms not improving after FMT was 0.98 (95% CI 0.58-1.66). Furthermore, placebo capsules were superior to capsules containing donor stool in two pooled trials (RR = 1.96; 95% CI 1.19-3.20) [5]. When looking at specific randomised controlled trials, one for IBS-D found that placebo was no better than FMT at inducing symptom relief [6]. Hence, FMT for functional symptoms became a less attractive research proposition. However, this was later challenged with a strongly positive study for FMT in IBS that used a single "super donor". In that study, a 50 point reduction in the IBS severity score was achieved in 23.6%, 76.9% ($p<0.0001$) and 89.1% ($p<0.0001$) of the patients who received placebo, 30 g FMT and 60 g FMT, respectively [7], suggesting a dose-dependent

response. Furthermore, the "super donor" phenomenon suggests that there are specific constituents within the FMT that are important. Trying to characterise these may be vital to refine and improve FMT efficacy.

We therefore suggest that future FMT-IBS studies have microbiome composition and functional analysis before and after FMT. We commend the authors for reporting both richness and composition changes pre- and post-FMT and would further encourage publication of specific compositional changes in the microbiome that may help our understanding of how FMT works. We further detail some considerations for future FMT-IBS studies in Table 1.

Despite another negative IBS-FMT study, FMT may have some benefit for highly selected patients with IBS. Future studies should try and understand the mechanisms that underpin this.

Table 1: Recommendations for consideration in future FMT studies in IBS

Patient characteristics	Selecting patients based on well-defined specific IBS subgroups based on Rome IV criteria along with presence of gut microbial dysbiosis at inclusion. Detailed information on potential confounders such as diet should be collected for covariate analyses.
Donor characteristics	Developing a framework of rational donor selection by understanding mechanisms that dictate donor-recipient compatibility in IBS. There may be a role for exploring strategies around optimising donors possibly through specific dietary modifications prior to the donation process.
FMT characteristics	Heterogeneity in FMT preparation methods, mode of FMT administration and number of treatments/infusions delivered have traditionally made it challenging to establish optimum disease specific FMT protocols.
Study design	As there are currently no valid biochemical manifestations of IBS, clinical outcomes in IBS patients are generally limited to self-reported symptoms. In addition, blinding is often challenging due to difficulties in replicating the smell and appearance of FMT in the placebo. Trial investigators should therefore ensure the blinding process is made as robust as possible in order to minimize bias and maximize the validity of the results.
Study endpoints	Including objective mechanistic endpoints that explore correlation of clinical outcomes with shifts in gut microbial

	dysbiosis, donor microbiota similarity indices, strain engraftment and metabolomic profiles.

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