Transfer of altered behaviour and irritable bowel syndrome with diarrhea (IBS-D) through fecal microbiota transplant in mouse model indicates need for stricter donor screening criteria

Laura J. Craven1,2, Michael Silverman1,2,3, Jeremy P. Burton1,2,4

1Department of Microbiology and Immunology, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada; 2Lawson Health Research Institute, London, ON, Canada; 3Department of Infectious Disease, St. Joseph’s Health Care, London, ON, Canada; 4Division of Urology, Department of Surgery, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

Correspondence to: Dr. Jeremy P. Burton. 268 Grosvenor St., London, ON N6A 4V2, Canada. Email: jeremy.burton@lawsonresearch.com.

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Experimental studies performing fecal microbiota transplants (FMTs) from human to animals and between animals is providing enlightening information with regards to phenotypical characteristics that can potentially be influenced by the microbiome. A recent study by De Palma (1) has shown that fecal material from humans with irritable bowel syndrome (IBS) with diarrhea (IBS-D) invoked physical changes in the intestinal environment and in behavior. This is an interesting outcome, given the questions that have been raised about the relevance of certain models’ in light of the differences between the rodent gut physiology, the microbiome and the human condition (2,3).

IBS is characterized by discomfort of the abdomen associated with altered bowel functions, where structural and biochemical abnormalities are absent (4). IBS is prevalent in 11.2% of the global population with more women being affected than men (5). Patients with IBS have significantly higher rates of anxiety and depression than healthy people (6) and they have been shown to have a reduced quality of life (7). IBS can be broken down further into different subtypes including: IBS-D (the focus in this De Palma study), constipation-predominant IBS (IBS-C), mixed-IBS (IBS-M) and unsubtyped IBS (IBS-U).

Since IBS is a condition of the gastrointestinal tract, it has been postulated that the disease is caused by alterations in the composition of the gut microbiome. Multiple studies have been conducted trying to determine if patients with IBS have a microbiota that differs from people without the disease. The most conserved finding has been a decrease in diversity of the gut microbiota (8-12). Attempts to identify specific differences in the relative abundances of the gut microbiota of IBS patients have found various results for each study. There is also the possibility that changes in the gut microbiota in IBS patients may be a result of the syndrome, rather than a cause of it, as a variety of other factors may predispose someone to develop IBS, such as genetics, food sensitivities, and food poisoning. Due to the evidence that the microbiota plays a role in the development of IBS, De Palma et al. hypothesized that germ-free mice given a FMT from an IBS-D patient would have altered behaviour, gastrointestinal transit, gut barrier function, and immune activation.

In the De Palma study, stool was collected from five healthy controls (HCs) (two men and three women, mean age: 42 years) and eight IBS-D patients (three men and five women, mean age: 40 years). Patients with IBS were diagnosed using the Rome-III criteria and Bristol stool form scale (≥6), with more than three bowel movements per day and symptoms for at least 2 years. Of the IBS-D patients, four were characterized as having anxiety by the Hospital Anxiety and Depression Scale (HADS) (HADS score, 11–14) and four IBS-D patients did not have anxiety (HADS
had a composition of microbiota that was similar, but it could not be concluded with certainty if mice colonized by IBS-D or HC patients had differing microbial compositions in their guts. The authors suggest that due to the higher relative abundances of DNA sequences of certain organisms being present in the IBS-D patients with and without anxiety and HC, there may be indicator species for IBS-D and anxiety. They found that humans with IBS-D had a higher relative abundance of the genus Blautia and humans with anxiety had higher relative abundances of the genera Blautia, Coprococcus, Streptococcus, and the species Clostridium butyricum and Eggerthella lenta. Mice colonized by IBS-D patients had higher relative abundances of the genera Oscillospira, Bacteroides, and the species Clostridium citronia and mice with anxiety had higher relative abundances of the genus Oscillospira and the species Bacteroides fragilis, Akkermansia muciniphila, Sbewanella algae, and Blautia producta.

The De Palma study provides promising data with regards to advancing our understanding of the microbial contribution to the pathophysiology of IBS-D and its psychiatric comorbidities. Past research from these authors demonstrated antibiotics administered to mice altered their behaviour (13) and this was the basis for their hypothesis that an altered microbiota could contribute to the psychiatric conditions commonly observed in IBS patients. Overall, they found that the phenotypes of altered behaviour, decreased gastrointestinal transit time and immune activation could be conferred to mice through an FMT from IBS-D patients.

A few limitations of the data presentation are worth noting. Large amounts of variability were observed within mouse groups for intestinal transit, step-down and light preference test scores. Therefore, presenting the individual data points would have allowed enhanced visualization of the data distribution, as some mice were potentially responders to the treatment and others were not. In the supplement, data for the step-down and light preference tests of germ-free mice were included to show that mice colonized with the microbiome from patients with IBS-D with anxiety had altered behaviour. Gastrointestinal transit scores and immune activation in the germ-free mice were not included within the paper or the supplement and baseline values for these mice could not be determined. It would be interesting to know whether the mice colonized by IBS-D patients truly have increased gastrointestinal transit scores and immune activation or did the mice colonized by HCs have reduced values compared to a germ-free mouse making the IBS-D colonized mice appear elevated?
Mice receiving an FMT from the same donor had microbiota compositions that clustered together 3 weeks after FMT. Mice colonized by IBS-D patients (with and without anxiety) and HCs did not cluster separately during 16S rRNA gene sequencing analysis, indicating in this analysis that there is not a discrete microbiota pattern associated with IBS-D colonized mice. This finding could be due to the small sample size of this study: with only eight IBS-D donors. This study did not find that the microbiota of HCs and IBS-D patients clustered separately during analysis, but an attempt was made to identify organisms that may be linked to IBS-D. Again, given the numbers in both arms of the study (five HCs vs. eight IBS-D patients), it cannot be said with certainty if these organisms are associated with the disease state, but the physiological changes observed in the mice indicate that human fecal contents can confer IBS-D-like symptoms and behavioral changes. The authors plan to use larger sample sizes of human participants in the future, which have the potential to realize exciting results.

This study raises questions of other interesting animal studies that could be performed. It would be interesting to undertake repeated FMT passaging from the anxiety-afflicted mice into other germ-free mice to determine the minimal microbial contribution to the induced psychological state, which may give clues to specific microbial contributors. It could be worthwhile to determine if the physiological changes observed in the IBS-D colonized mice could be reversed with antibiotics or a second FMT from a HC. Double-blinded randomized control trials treating IBS-D are in progress and results from these studies will be more definitive in determining if IBS-D can be treated with FMT. The authors acknowledged that human host factors could have been the source of the physiological changes observed in the germ-free mice, and in future experiments this problem could be solved by cultivating the microbiota from a human stool in a chemostat system and gavaging the mice with this material.

What could the results of this study mean for the clinical use of FMT? For its use in treating recurrent Clostridium difficile, the screening process for donors varies between clinics, and acceptance rates can range from 10% to 37% (14,15). Screening for IBS-D and any gastrointestinal disease is common practice for all FMT clinics, however, there are discrepancies in screening protocols when it comes to psychiatric history. Stool banks that distribute a large number of samples to many different clinics are of a particular concern because they don’t necessarily screen for psychiatric conditions. Use of validated scoring systems to quantify anxiety will have to be utilized. However, it is unclear if even mild degrees of subclinical variation in psychiatric morbidity may be transferred and so identification of the optimal screening systems will require a comprehensive review and ongoing monitoring of patient cohorts for psychiatric morbidity post-transplant. In particular, it is unknown whether some FMT donors may carry a fecal microbiome capable of inducing psychiatric or functional gastrointestinal morbidity in a susceptible host, but due to host factors in the donor the phenotype is not expressed and so would not be identified by symptomatic screening. The ability to develop microbiome directed screening rather than donor phenotype screening will require further study.

It is uncertain whether the gut and psychological changes seen in this animal model are relevant to the human FMT model. Human FMTs do not occur in a baseline germ-free environment and although the recipient microbiome approaches that of the donor post-transplant, many differences persist (16) and thus whether the phenotypes described here would be transferred between humans is unclear. Furthermore, it is unknown if the stage of development of the FMT recipient impacts susceptibility to the microbial changes. The impact of gut microbiome changes on symptoms when performed in childhood vs. adulthood would require investigation.

This study showed that significant psychological and gut functional changes could be transferred to mice from diseased humans via FMT. While it may be possible that animal models are more susceptible to phenotype alterations induced by microbes in an FMT, or that humans are not typically given an FMT in a germ-free state or at a pivotal developmental stage of their lives, it may still be wise at this relatively early stage of FMT clinical use to assure that the exclusion criteria for donors for FMT include IBS and history of mental illness.

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Footnote
Conflicts of Interest: The authors have no conflicts of interest to declare.
References


