Evaluating donor microbiome before fecal microbiota transplantation: reply

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microbial consortia may both warrant higher levels of safety and improve the efficacy of FMT in other disorders beyond rCDI, and would expand the field of therapeutic microbiota modulation.

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References

1. Nooij S, et al. Gastroenterology 2021;161:P1218–P1228.e5.
2. Marcella C, et al. Aliment Pharmacol Ther 2021;53:33–42.
3. Ianiro G, et al. Ann Intern Med 2019;171:695–702.
4. Damman CJ, et al. PLoS One 2015;10:e0133925.
5. Kootte RS, et al. Cell Metab 2017;26:611–619.e6.
6. Drewes JL, et al. JCI Insight 2019;4:e130848.
7. Ianiro G, et al. Gut 2020;69:1555–1563.
8. Kuijper EJ, et al. Lancet Infect Dis 2019;19:1161–1162.
9. El-Salhy M, et al. Gut 2020;69:859–867.
10. Bibbò S, et al. J Clin Med 2020;9:1757.

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Reply. We thank Dr Gianluca Ianiro et al for the suggestion in their reaction to our article to evaluate the donor microbiome for fecal microbiota transplantation (FMT) by carefully assessing donor history and analyzing the microbiome to predict a favorable microbial signature. We agree that studying successful donor–patient pairs is crucial in understanding complex microbiome-related disease pathology and subsequent cure. However, there are several arguments against the existence of a favorable microbial signature for recurrent *Clostridioides difficile* infections (rCDI).[1] For other diseases, it is currently not yet reliable as a predictor on an individual donor level.

Fecal suspensions from carefully screened donors without specific targeted microbiome screening for the treatment of patients with rCDI always show high (>80%) success rates worldwide. Still, the working mechanism of FMT to prevent rCDI is not completely understood and immunological effects are probably involved, in addition to restoring the colonization resistance by reintroducing a healthy microbiome. FMT seems to enhance *C difficile*–specific cellular and antibody-mediated immunity, as it is associated with increased proportions of toxin B–specific T helper-17 cells, as well as IgG and IgA antibodies specific for toxin A and B.[2] Of note, the immunological effect that FMT can elicit may be of more relevance for other diseases, but is still difficult to predict. Interestingly, a study using FMT to promote response in patients with immunotherapy-refractory melanoma revealed that of the 2 donors rationally selected on the basis of a preferred microbiota profile, only 1 was associated with tumor suppression in the patients.[3] Nevertheless, donor selection is gaining ground, despite the lack of knowledge about a preferred microbial signature to define a super donor on the individual donor level. A large FMT center in China has performed more than 60,000 FMTs in more than 5000 patients for various gastrointestinal diseases (eg, rCDI, inflammatory bowel disease, and irritable bowel syndrome) and extraintestinal diseases (eg, autism spectrum disorder and Parkinson disease).[4] Our Chinese colleagues developed a very stringent donor screening program including 16S ribosomal RNA gene amplicon sequencing of stool samples to evaluate bacterial compositions. These data would provide a unique opportunity to evaluate the efficacy of FMT from various donors, (serious) adverse events, and long-term follow-up of patients.

Our Italian colleagues mention that engraftment of donor microbiota is low after a single fecal infusion and disappears gradually over time after FMT. However, Goloshchapov et al[5] found significant long-term changes in the gut microbiota of healthy people 1 year after FMT, accompanied by transient changes of systemic immune parameters. Similarly, Aggarwala et al[6] found stable engraftment of 71% of donor microbiota strains in recipients up to 5 years post FMT. Nonetheless, it remains unknown whether long-term bacterial engraftment is important for clinical success and of clinical significance. Notably, engraftment was not correlated with clinical success in studies of 5 different FMT-treated illnesses (ie, rCDI, ulcerative colitis, Crohn's disease, metabolic syndrome, and infection with extended-spectrum betalactamase-producing bacteria).[7] In addition, the statement that the identification of specific donor microbiome signatures before FMT can predict outcomes neglects the importance of the recipient microbiota. This was clearly demonstrated by Schmidt and colleagues[7] in a recent meta-analysis of 142 FMTs that found that recipient factors consistently outweighed donor factors in driving FMT outcomes.[7] Besides, it remains difficult to define a "healthy" microbiome without a thorough understanding of all of its constituents, including Archaea, viruses, and fungi and their function in the gut ecosystem.

Long-term adverse events definitively related to FMT have not been reported and seem rare,[8] but long-term follow-up with microbiome analyses, immunological parameters, and clinical data are needed to recognize persistent engraftment and late adverse events. This is of particular importance for younger patient populations with non-CDI, FMT-treated disorders. A recently completed

survey in Europe demonstrated that in 31 FMT centers from 17 countries, 42% of all FMTs were administered for experimental indications other than rCDI.[9] This illustrates the urgent need for an international registry to collect information from both donors and FMT-treated patients with follow-up of at least 10 years, and storage of stool samples from patients and donors by FMT centers. Such a registry is active in the United States (ie, American Gastroenterological Association) and is currently initiated in Europe by the European Working Group. We think this is an essential next step in both rationalized donor selection and establishing the safety of FMT in the long term and enables action on previously unforeseen potential adverse events.

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References

1. Budree S, et al. Gastroenterology 2017;152:S349.
2. Cook L, et al. Gastroenterology 2021;160:2155–2158.e4.
3. Baruch EN, et al. Science 2021;371(6529):602–609.
4. Zhang S, et al. Gastroenterology 2022;162:966–968.
5. Goloshchapov OV, et al. BMC Microbiol 2019;19:312.
6. Aggarwala V, et al. Nat Microbiol 2021;6:1309–1318.
7. Schmidt SB, et al. bioRxiv 2021.09.30.462010
8. Ooijevaar RE, et al. Microorganisms 2021;9:548.
9. Baunwall SMD, et al. Lancet Reg Health Eur 2021;9:100181.

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Serum Phosphate Levels and Alcohol-Induced Pancreatitis

Dear Editors:

Why doesn't everyone who drinks alcohol heavily develop pancreatitis? In fact, epidemiologic studies suggest that only 2%–5% of heavy drinkers develop pancreatitis.[1] Studies have suggested that co-factors such as smoking add to the risk of pancreatitis in patients who drink heavily.[2] There are also potential genetic co-factors that increase the susceptibility to pancreatitis with heavy alcohol drinking,[3] as well as lipopolysaccharide from leaky gut with heavy alcohol drinking.[4] However, there remains a large gap in our understanding of the combination of risks with heavy alcohol drinking that lead to pancreatitis. Also critically important is the fact that a patient with an attack of acute alcoholic pancreatitis has a high likelihood of recurrent attacks of acute pancreatitis, often resulting in progression to chronic pancreatitis with additional risks of diabetes, exocrine pancreatic insufficiency, and pancreatic adenocarcinoma.[1] This continuum of pancreatic diseases is very uncommon in patients who have an attack of acute pancreatitis due to gallstones post cholecystectomy.

The article by Farooq et al[5] and a highly expert pancreas research team at Duke University presents an interesting animal study showing the potential role of serum phosphate levels in promoting acute alcoholic pancreatitis. The work presents an important potential factor that could be involved in triggering pancreatitis in heavy drinkers. The Duke team reasoned that because the exocrine acinar cell of the pancreas, the likely site for initiation of pancreatitis, has a significant energy demand to carry out synthesis and secretion of a large payload of digestive enzymes, the energy generating mitochondria could represent a locus of organellar injury initiating pancreatitis, and that phosphate is necessary for adenosine triphosphate (ATP) production by mitochondria. The authors point out that a previous report indicated that 29% of patients admitted to the hospital for alcohol-related disorders had hypophosphatemia, and that hypophosphatemia occurs during acute pancreatitis.

Previous studies have shown that alcohol feeding sensitizes mitochondria in acinar cells to depolarization and decreased ATP production involving "opening" of the mitochondrial permeability transition pore.[6] As pointed out by Farooq et al,[5] ethanol feeding alone does not cause mitochondrial failure. However, the alcohol sensitizes mitochondria to depolarization more readily, resulting in decreased ATP production with calcium signaling in the acinar cell. Of note, calcium signaling in the acinar cell is necessary for the secretion of digestive enzymes from the acinar cell.[7] However, excessive calcium in the cytoplasm of the acinar cell or sensitization of the mitochondria of the acinar cell leads to mitochondrial permeability transition pore "opening," followed by mitochondrial de-energization and pancreatitis in animal models. These effects can be prevented by blocking of the "opening" of the mitochondrial permeability transition pore by both genetic and pharmacologic means.[6]

To determine whether hypophosphatemia promotes pancreatitis in ethanol-fed animals, the Duke team caused hypophosphatemia in a rodent model, then gave the animals intragastric doses of ethanol to mimic binge drinking in humans. Compared with animals with normal phosphate levels, animals with hypophosphatemia developed severe pancreatitis. Furthermore, phosphate repletion prevented the pancreatitis response. The team further investigated the mechanisms underlying the combined effects of ethanol and low phosphate in pancreatic acinar cell studies. The key finding was that the combination of low phosphate availability and presence of ethanol led to mitochondrial dysfunction, decreased ATP production, and cellular pancreatitis pathobiology features, such as increased intracellular trypsin activation. Again, these cellular disorders were reversed by adding phosphate back to the cells. Looking further into the effects of the dual treatments on cellular function, these investigators found that pancreatic