

## Fecal microbiota transplantation for treating recurrent hepatic encephalopathy: Ready for clinical application?

Bajaj JS, Kassam Z, Fagan A, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. *Hepatology* 2017 Jun 6. doi: 10.1002/hep.29306. [Epub ahead of print].

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Bajaj et al. (1) presented a ground-breaking paper in *Hepatology*. They studied the safety and efficacy of fecal microbiota transplantation (FMT) for treating recurrent hepatic encephalopathy (HE).

Previous reports have indicated a profound dysbiosis in cirrhosis. Standard of care (SOC) involves the application of lactulose, rifaximin, and a protein-deficient diet in patients with HE. However, some patients are refractory to this treatment. The frequent administration of antibiotics further disrupts gut microbiota in cirrhotic patients. In HE patients, there is a reduced relative abundance of beneficial short-chain fatty acid-producing families of micro-organisms such as Lachnospiraceae and Ruminococcaceae and the potentially pathogenic family of micro-organisms Enterobacteriaceae is enriched (2-6). The authors published the first open-label randomized controlled trial RCT of single FMT versus SOC in 20 male patients with more than two episodes of overt HE. Patients received antibiotic pre-treatment for 5 days and then underwent FMT via enema. The most discriminating methodology in this study was the selection of a "rationally selected donor." This donor was selected by comparing recipient and donor microbiomes for obtaining an optimal match. This is a novel approach for using FMT in any medical disorder. Patients in the SOC group did not receive antibiotics, and all patients were on stable doses of lactulose and rifaximin throughout the study. The primary outcome was the occurrence of serious adverse events (SAEs), which were defined by the rate of mortality, rate of hospitalization, number of hospital admissions, and number infections. At 150 days post FMT, SAEs occurred significantly more frequently in the SOC group (80%) than in the FMT group (20%) ( $p < 0.05$ ). The secondary outcome was neurological and cognitive changes. Cognitive functions improved in the FMT group; there were no changes in the SOC group. The relative abundance of Lachnospiraceae and Rumi-

nococcaceae (primarily beneficial bacteria) increased in HE patients and significantly reduced after the administration of antibiotics. However, this situation improved after performing FMT in all but 2 patients in the FMT group. No changes in microbial diversity were seen in the SOC group.

This RCT systematically investigated the efficacy of FMT. The use of a "rationally selected donor" from a stool bank (microbiome profile is studied and well-known) is ground-breaking for gut microbiota modulation therapies.

There are some weak points that should be considered. The sample size of patients who underwent FMT was relatively small (although this is the largest trial on FMT in cirrhosis patients). The primary outcome was safety. Although short-term safety is well documented, long-term safety, such as the transmission of slow-acting pathogens, metabolic changes related to gut microbiota (obesity or insulin resistance), and colon cancer risk, needs to be studied.

Although there are some drawbacks in the sample size and length of follow-up, this study opened a new frontier for treating HE. Hopefully, emerging microbiome-based therapies will replace "FMT". This will result in the progression of scientific research and clinical applications.

Tarkan Karakan

Department of Gastroenterology, Gazi University School of Medicine, Ankara, Turkey

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**Address for Correspondence:** Tarkan Karakan

**E-mail:** tkarakan@gmail.com

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