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Study provides clues to improving fecal microbiota transplantation

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Results from a placebo-controlled trial provide a strategy for improving fecal microbiota transplantation (FMT) for patients with recurrent *Clostridium difficile* infection. The study, published online this week in *mBio*, an open-access journal of the American Society for Microbiology, identified microorganisms that are key for cure with fecal microbiota transplantation.

"This paper provides us data with which microbes to supplement into our preparations," said principal investigator of the study Michael Sadowsky, PhD, director of the BioTechnology Institute at the University of Minnesota, St. Paul, Minnesota.

Approximately 20% to 30% of patients who are treated with antibiotics for *C. difficile* get a recurrent infection. Typically, this is caused by a dysbiosis or microbial imbalance of the gut. Microbiota are integral to human physiology and health, and exposure to antibiotics can alter the composition and activity of microbiota, sparking many common health problems.

In the last decade, FMT has been increasingly used to treat patients who have recurrent *C. difficile* infection, with cure rates over 90%. The procedure involves collecting fecal matter from a healthy donor, purifying microbiota from the feces, mixing it with saline solution, and placing it in a patient, usually by colonoscopy. Eight years ago, the University of Minnesota established the Microbiota Therapeutics Program, through which patients can receive fecal microbiota

transplants.

In the new study, Dr. Sadowsky and colleagues conducted a clinical trial in 27 patients with recurrent *C. difficile* infection, using fecal microbiota from healthy patients (a heterologous transplant) and, as a placebo, the patient's own stool microbes (an autologous transplant). The cure rate with the transplantation from healthy donors was 90%, which is what the researchers expected, but surprisingly several patients who received the transplant with their own stool were also cured. Those who did not respond to the autologous transplant went on to receive a heterologous transplant.

Using Illumina-based next-generation sequencing to characterize bacterial communities, the researchers found that subjects cured by what was supposed to be the placebo transplantation had a greater abundance of *Clostridium Xia clade* and *Holdemania* prior to treatment, and the relative abundance of these microorganisms significantly increased after transplantation, compared to heterologous transplant and pre-transplant samples. Additional analyses showed that the microbiota of patients cured by the autologous transplant remained distinct from that of patients cured by the heterologous transplant.

The researchers also found that once the donor's fecal microbiota became established in the patient, it didn't stay static, but changed over time. Previous studies have shown that a couple weeks after a fecal microbiota transplant from a healthy donor, a patient's microbiota usually looks very similar to the donor's microbiota.

"As opposed to what we thought, complete engraftment of microbiota is not required to cure a patient," said Dr. Sadowsky. "The study provides insight into which microorganisms are the most important for curing *C. difficile* and may allow clinicians to better tailor therapy, by improving the donor material to facilitate a more rapid, effective, and lasting cure."

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