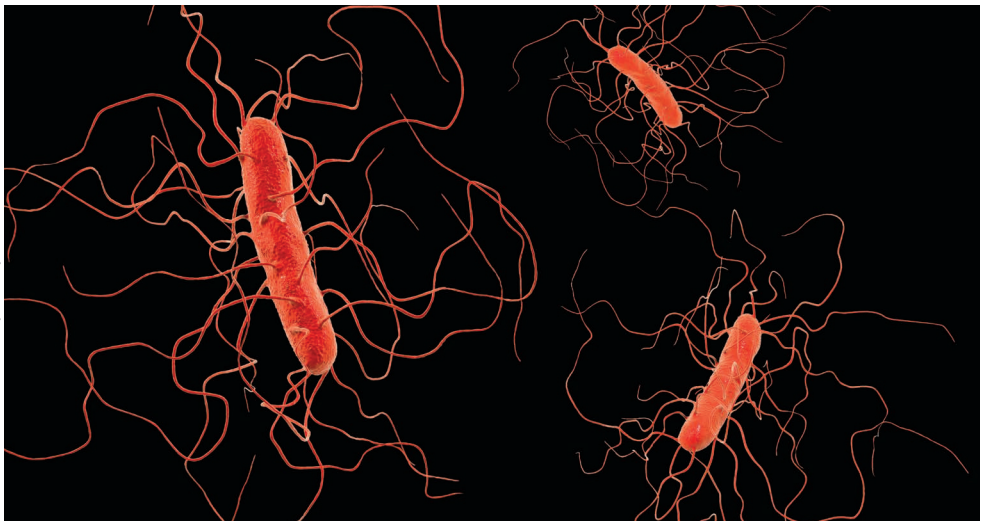
MILESTONE 2

Faecal microbiota transplantation for *Clostridioides difficile* infection



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In 1958, Eiseman et al. reported the successful treatment of pseudomembranous enterocolitis using a faecal enema. Since then, faecal microbiota transplantation (FMT) has become widely accepted as a successful rescue treatment for recurrent *Clostridioides difficile* infection. FMT is also being investigated for other indications.

Eiseman and colleagues presented the cases of four patients with pseudomembranous enterocolitis. They used enemas with faeces from healthy donors after other therapy options failed. The patients had a rapid recovery from their symptoms.

C. difficile infection can cause debilitating diarrhoeal symptoms when the bacterial spores germinate into vegetative cells that produce enterotoxins, resulting in colonic inflammation and the formation of 'pseudomembranes' consisting of inflammatory cells, dead cells and debris. Over the past couple of decades, *C. difficile* infection has increased in incidence, morbidity and mortality, and has become known as a 'superbug'. Despite antibiotics being the standard treatment for *C. difficile* infection, they also often are the cause of infection owing to their suppressive effects on native gut microbiota and subsequent overgrowth of *C. difficile*. Eiseman and colleagues also noted this link to prior broad-spectrum antibiotic treatment in their patients and speculated that disruption of the 'healthy gut flora' underlies infection.

The intention of performing FMT is restoration of the normal function of the gut microbiota. In Eiseman and colleagues' report, culture of stool samples obtained during infection showed the presence of *Staphylococcus aureus*, which, at the time, was considered to be a possible cause of pseudomembranous enterocolitis. *S. aureus* disappeared from the stool sample cultures after administration of a faecal enema in association with clinical improvement. The authors suggested that normal colonic non-pathogens displaced the colitis-causing pathogen, which, decades later, was demonstrated to be *C. difficile*.

Since Eiseman and co-workers' publication, others have reported success using faecal enemas, *Lactobacillus rhamnosus* GG (a probiotic) and bacteriotherapy (using a mixture of facultatively aerobic and anaerobic bacteria) to treat relapsing *C. difficile* enterocolitis.

FMT is now an effective treatment option for recurrent *C. difficile* infection and is believed to normalize the microbial diversity and community structure in the colon. Currently, a research consortium is recruiting patients to a clinical trial examining whether FMT is safe, and can prevent recurrent *C. difficile*-associated disease. FMT could inhibit *C. difficile* by multiple mechanisms, such as suppression by antimicrobial peptides, inhibition of spore germination and vegetative growth, competition for nutrients, and activation of colonization resistance (MILESTONE 13).

To reduce costs and increase patient and clinician convenience, oral delivery of faecal microbiota has been tested. In 2017, a randomized clinical trial showed that FMT delivery by oral capsule was non-inferior to delivery via colonoscopy, suggesting oral capsules could be an effective treatment approach for recurrent *C. difficile* infection.

FMT has also been investigated for non-*C. difficile* indications, such as ulcerative and drug-induced colitis, and has shown some promise. FMT from lean donors has also been shown to increase insulin sensitivity in men with metabolic syndrome.

Thus, since the pioneering report from Eiseman and colleagues, FMT has become an effective therapy for recurrent *C. difficile* infection and shows promise for treating other diseases.

Louise Stone, *Nature Reviews Urology*

> “FMT is now an effective treatment option for recurrent *C. difficile* infection and is believed to normalize the microbial diversity and community structure in the colon”

ORIGINAL ARTICLE Eiseman B. et al. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery* **44**, 854–859 (1958).

FURTHER READING Khoruts A. & Sadowsky M. J. Understanding the mechanisms of faecal microbiota transplantation. *Nat. Rev. Gastro. Hep.* **13**, 508–516 (2016) | Pamer, E. G. Fecal microbiota transplantation: effectiveness, complexities, and lingering concerns. *Mucosal Immunol.* **7**, 210–2014 (2014) | Schwan A. et al. Relapsing *Clostridium difficile* enterocolitis cured by rectal infusion of homologous faeces. *Lancet* **322**, 845 (1983) | Gorbach S. L., Chang T. W. & Goldin B. Successful treatment of relapsing *Clostridium difficile* colitis with *Lactobacillus* GG. *Lancet* **330**, 1519 (1987) | Tvede M, Rask-Madsen J. Bacteriotherapy for *Clostridium difficile* diarrhoea. *Lancet* **1**, 1156–1160 (1989) | US National Library of Medicine. *Microbial Restoration for Individuals With One or More Recurrences of Clostridium Difficile Associated Disease (CDAD)* https://ClinicalTrials.gov/show/NCT03548051 (2018) | Kao, D. et al. Effect of oral capsule- vs. colonoscopy-delivered fecal microbiota transplantation on recurrent *Clostridium difficile* infection: a randomized clinical trial. *JAMA* **318**, 1985–1993 (2017) | Vrieze, A. et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* **143**, 913–916 (2012).