

# Faecal microbiota transplantation: indications, evidence and safety

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## SUMMARY

The human gut contains many species of microorganisms, many of which have a role in maintaining good health. The gut microbiota can be affected by diet, diseases and drugs, especially antibiotics.

Faecal microbiota transplantation involves transplanting faecal material from a healthy person to a patient, with the aim of treating disease. It is a recommended treatment option for patients with recurrent or refractory *Clostridioides difficile* as it has a cure rate over 90%.

There is evidence that faecal microbiota transplantation can induce remission in ulcerative colitis, however maintenance of remission data are lacking. For other diseases it currently should not be used outside a clinical trial.

Stool donors have to be healthy and are screened for a range of diseases. As faecal material is usually transplanted during colonoscopy, the recipient must have bowel preparation before the procedure.

Adverse effects are mainly gastrointestinal and usually resolve in the week following transplantation. There are limited data on long-term safety.

## Introduction

Faecal microbiota transplantation is the transfer of faecal material from a healthy individual to another person with the aim of treating a disease. It can be described as ‘the ultimate probiotic’ as it donates a much greater number and diversity of bacterial strains than any available probiotic.

The deliberate transfer of faecal material between individuals has a long history. It was first reported as a therapy in 4th century China. A human faecal suspension was given by mouth to treat patients with severe diarrhoea.<sup>1</sup> In North Africa camel faeces have been used as a treatment for dysentery.<sup>2</sup> Human faecal microbiota transplantation was first described in the western literature in 1958 for the treatment of four critically ill patients with pseudomembranous colitis.<sup>3</sup> The precise mechanisms by which faecal microbiota transplantation treats disease are not fully understood.

## Gut microbiome

The organisms living in the gut are termed the gut microbiota, while the gut microbiome consists of the genetic material of these organisms. The human gastrointestinal microbiota contains approximately  $3.9 \times 10^{13}$  organisms, a figure similar to the number of human cells in the body.<sup>4</sup> It consists of bacteria, fungi, protozoa, archaea and viruses (including phage viruses that infect bacteria). The gut microbiota is dominated by two main phyla of bacteria – Firmicutes and Bacteroidetes. These make up 90%, with eight other phyla making up the remaining 10%.<sup>5</sup>

Many of the microorganisms in the gut have co-evolved with humans and perform essential functions, such as the production of important metabolic products. For example, bacteria metabolise resistant starch in the colon to produce butyrate, a short chain fatty acid which is the primary and essential energy source of enteric colonocytes.<sup>6</sup> Some intestinal microbiota live in close association with the colonic epithelium and play a role in regulating local and distant immune function.<sup>7</sup> Others regulate intestinal barrier functions, or protect against pathogens such as vancomycin-resistant enterococci by competitive inhibition.<sup>8</sup>

## Dysbiosis

The gut microbiota is mostly acquired during the first 3–4 years of infancy, with mode of delivery, breastfeeding, diet and the local environment all playing a role.<sup>9,10</sup> Beyond this time the adult gut microbiome remains relatively stable. It can be altered by persistent dietary or lifestyle changes, disease, travel, drugs or surgery.<sup>11</sup>

The use of systemic antibiotics is the most well-studied risk factor for altering the gut microbiota. It results in a decreased diversity of species, loss of antimicrobial peptides produced by commensal bacteria, and loss of resistance to colonisation because the competitive inhibition of pathogens is reduced.<sup>12</sup>

Perturbation of the gut microbiota associated with disease is termed dysbiosis. This has been associated with multiple diseases including *Clostridioides difficile* infection, colonisation with drug-resistant

bacteria, inflammatory bowel disease, irritable bowel syndrome and metabolic syndrome.<sup>13</sup> These associations with dysbiosis have prompted research into possible aetiological roles that the microbiota may have and whether modification of the microbiota will have a therapeutic effect in these diseases.

## Indications

At present, faecal microbiota transplantation is predominantly used for the treatment of *C. difficile*. First-line treatment for mild *C. difficile* is oral metronidazole and, for more severe infection or recurrent episodes, vancomycin is recommended.<sup>14</sup> Patients who have had two or more recurrences of *C. difficile* despite recommended antibiotic therapy have a low chance of responding to further antibiotic therapy. Transplantation offers a better chance of cure and its efficacy is supported by evidence from multiple randomised controlled trials.<sup>13,14</sup> A single faecal transplant cures 80–90% of *C. difficile* cases, compared to cure rates of 26–30% with vancomycin, and repeated transplantation increases cure rates to more than 95%.<sup>15</sup> Evidence also supports the use of transplantation following severe *C. difficile* infection which has resulted in shock or supportive care, as well as in cases of disease refractory to antibiotic therapy.<sup>14,16–18</sup> Faecal microbiota transplantation reduces cost and at the same time improves quality of life compared with vancomycin, saving over A\$4,000 per patient treated.<sup>19</sup> It is thus a recommended therapy for recurrent, refractory or severe *C. difficile* in national and international guidelines.<sup>14,16</sup>

There is evidence that faecal microbiota transplantation induces remission of active ulcerative colitis.<sup>17,18,20</sup> However, more data are required before it can be recommended as maintenance therapy in ulcerative colitis.<sup>21</sup>

## Donor screening protocol

Preferred stool donors are healthy people without pre-existing disease or risk factors for disease. These individuals are recruited by stool banks and undergo a thorough screening process that includes a questionnaire to exclude those with disease, exposure to transmissible diseases, or behavioural risk factors for transmissible diseases. Disease exclusions include, but are not limited to, blood- or stool-borne infections, gastrointestinal disorders, malignancy, atopy, metabolic syndrome and autoimmune diseases. People who have recently taken antibiotics or have travelled to areas with a high risk of traveller's diarrhoea are excluded. BMI is then calculated and those who are obese or underweight are excluded.

Donors who pass the screening questionnaire and BMI measure then undergo extensive blood and stool tests for transmissible diseases. This includes checking for blood- and stool-borne infections and multidrug resistant organisms in the stool.

## Preparation and delivery

Currently there is no universal protocol for preparing a patient for faecal microbiota transplantation. Stool is usually mixed with saline or water with between 12.5% and 25% stool in the suspension by weight. The transplant can be fresh or thawed frozen stool as these are equally effective.<sup>22</sup> When freezing stools 10% glycerol is often added to preserve bacterial viability.<sup>23</sup>

Patients preparing to receive a faecal microbiota transplantation for *C. difficile* are required to take vancomycin for 5–10 days and then stop 24–36 hours before the procedure. For colonoscopic delivery, patients undergo bowel preparation approximately 12 hours before the procedure. On the day it is common for the patient to be given loperamide to assist with retaining the transplanted material.<sup>24</sup>

The methods of delivery are via the upper gastrointestinal route (nasoduodenal, oral capsules), or lower gastrointestinal route (colonoscopic delivery into the ascending colon, or retention enemas). However, colonoscopic delivery is the most common method. It has the most evidence in the literature, with high rates of cure across studies.<sup>25</sup> Nasogastric and nasoduodenal delivery tend to have higher rates of minor adverse effects relative to other methods.<sup>15</sup>

## Safety

Faecal microbiota transplantation for recurrent *C. difficile* has a good short-term safety record. There are very few adverse effects directly attributed to the procedure. Most reported adverse events have been self-limiting gastrointestinal symptoms including abdominal cramps, diarrhoea and constipation, which resolved within one week.<sup>25</sup> There have been at least two deaths from aspiration pneumonia related to sedation given at the time of faecal microbiota transplantation. There has been at least one death from transmission of a multidrug resistant *Escherichia coli* organism, however the donor in this case had not been tested for this organism.<sup>26</sup> These deaths are relatively small in number compared to the large number of transplantations performed (at least 50,000 in the USA since 2013).<sup>27</sup>

The long-term safety of faecal microbiota transplantation is not yet well established. Most of the studies have only been reported in the last decade and there have been no registries until recently.

## Emerging indications

A large number of diseases have been associated with gut dysbiosis and the success of faecal microbiota transplantation in treating recurrent *C. difficile* has encouraged research into transplantation as a potential therapy for these diseases. There have been trials in irritable bowel syndrome,<sup>28–30</sup> hepatic encephalopathy,<sup>31</sup> Crohn's disease,<sup>32</sup> primary sclerosing cholangitis<sup>33</sup> and autism.<sup>34</sup> However, the evidence for the efficacy and safety of faecal microbiota transplantation for these

conditions is currently limited and further studies are warranted before it can be recommended as therapy outside of clinical trials. While trials have the possibility of broadening the indications for transplantation, they could also guide the development of microbial therapeutics that may replace or complement faecal microbiota transplantation in the future.

## Conclusion

Faecal microbiota transplantation is an effective treatment option for recurrent infection with

*C. difficile*. Its use in other indications at present should be part of a clinical trial. ◀

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