Faecal microbiota transplantation: a review

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Abstract. Faecal microbiota transplantation (FMT) is the transfer of human faeces from a healthy donor to a recipient with a disease associated with gut dysbiosis. Here we review faecal microbiota transplantation as a treatment for *Clostridioides difficile* infection (CDI) and other conditions including decolonisation of multiresistant organisms. Donor selection and screening, adverse events, processing, administration and regulation of FMT are discussed.

Introduction

Faecal microbiota transplantation (FMT) is not a new concept, being first described in traditional Chinese medicine over 1000 years ago[1]. FMT delivered by faecal enema was successfully used in the treatment of pseudomembranous enterocolitis in 1958[2]. A timeline for FMT over the years is shown in Figure 1. FMT is now accepted to be the most effective treatment for recurrent or refractory *Clostridioides difficile* infection (CDI). Clinical trials have also been conducted using FMT in primary sclerosing cholangitis, non-alcoholic steatohepatitis, type II diabetes mellitus, irritable bowel syndrome, inflammatory bowel disease, hepatic encephalopathy, and eradication of multiresistant organisms[3].

Perturbations in the composition of intestinal microbiota occur after administration of antibiotics, other medications, dietary changes and travel. Antibiotic exposure decreases the alpha diversity with reduction in Firmicutes and Bacteroidetes phyla and proliferation of Proteobacteria including *Enterobacteriaceae*[4]. Following FMT there is reduction in Proteobacteria and expansion of Firmucutes, Ruminococcaceae, Lachnospiraceae, Clostridiaceae and Bacteroidetes[4]. Recipient microbiota engraftment has been demonstrated by day three after FMT[5]. This microbial community correlates with that of the donor's microbial community and has been observed to be stable for 4 months and up to one year[4–6]. Complete donor engraftment may not be necessary if functionally effective taxa are present and bacteria associate with secondary bile acid metabolism to provide resistance to recurrent infection[4].

C. difficile infection (CDI) and FMT

C. difficile is a Gram-positive anaerobic, spore forming and toxin-producing bacillus[1]. Spores are transmitted via the faecal–oral route and are an important cause of hospital-acquired infection. Between 15–70% of infants and 5% of adults are colonised, being more frequent in hospital and nursing home residents[1].

Antibiotic exposure, older age and hospitalisation are major risk factors for CDI[1]. Clinical spectrum spans diarrhoea, ileus and toxic megacolon, with severe CDI presenting with fever, haemodynamic instability and peritonitis. Recurrent CDI is classified as recurrence of CDI within 8 weeks of successful treatment and refractory CDI is defined as absent clinical improvement after 3–4 days of appropriate treatment[7].

FMT has been shown to be the most effective treatment for recurrent CDI and has repeatedly demonstrated superiority to comparators since the first randomised trial in 2013[8,9]. In a meta-analysis of seven randomised controlled trials and 30 case series, FMT was more effective than vancomycin (RR: 0.23) for recurrent and refractory CDI with clinical resolution rates of 92%[10].

The Australasian Society for Infectious Diseases published guidelines for management of CDI that includes FMT[7]. Australian therapeutic guidelines recommend FMT as preferred treatment for second and subsequent recurrences or ongoing refractory

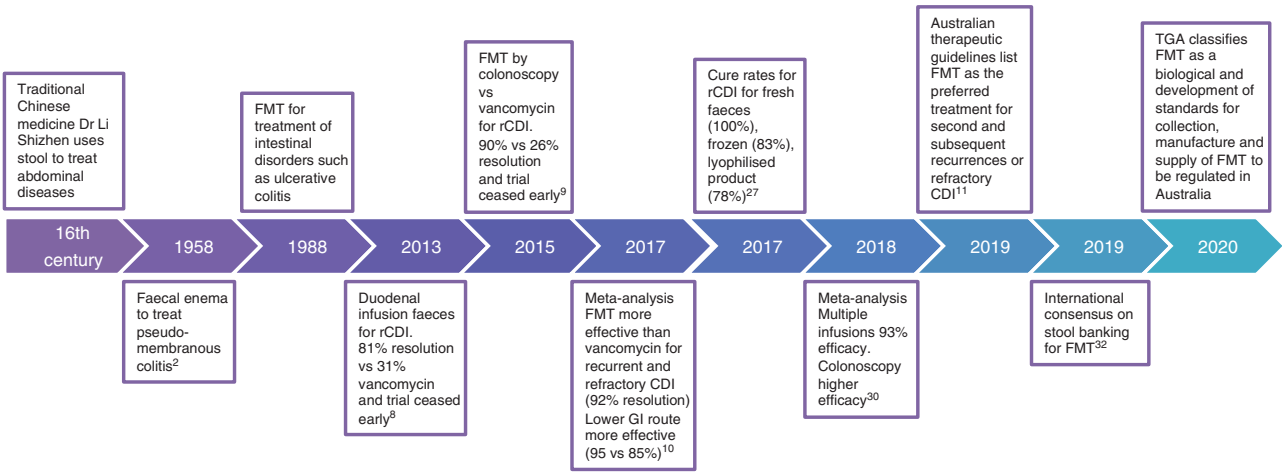

Figure 1. Timeline for faecal microbiota transplantation.

disease[11]. This is similar to American, European and British guidelines[12–14].

Adverse events

In general, FMT is considered a safe procedure with rare adverse events. Some of the common adverse effects include fever, abdominal pain, bloating and alteration to bowel habits[15,16]. Procedural complications include bowel perforation and mucosal tears[15,16]. Infectious complications including transmission of norovirus, Gram-negative bacteraemia and transmission of multiresistant organisms have been reported[15]. Deaths have been due to polymicrobial bacteremia in the setting of toxic megacolon, aspiration pneumonia as a complication of anaesthesia during colonoscopic FMT and regurgitation of faeculant material during endoscopic FMT[15–18]. Donor stool screening for multiresistant organisms is now mandatory following two cases of donor derived *Escherichia coli* Extended Spectrum Beta-Lactamase bacteraemia, resulting in the death of one patient[19]. The United States Food and Drug Administration (FDA) have recently issued a safety alert regarding FMT after cases of enteropathogenic *E. coli* (EPEC) and Shigatoxin-producing *E. coli* (STEC) infection in recipients possibly linked to a stool bank (www.fda.gov).

Food allergy with anaphylaxis is a contraindication to FMT[12]. FMT should be offered with caution in patients with decompensated chronic liver disease or immunosuppression and special consideration to donor screening (for CMV, EBV and *Strongyloides*) should be given for immunosuppressed recipients[12]. Elderly and debilitated patients have been treated with FMT for CDI with success, however they may have a lower primary cure rate and higher recurrence rate compared to a younger cohort[18,20]. Adverse events in the elderly population have included aspiration; therefore the colonoscopy route has been suggested as the preferred route of administration[18].

Limited data exists on long-term adverse effects. Jalanka *et al*.[21] found no difference in incidence of severe diseases or weight gain after 3.8 years of FMT and improved bowel habits and mental health were reported.

Donors

Traditionally, donors known to the patient were selected, however this could result in ethical and confidentiality issues if identifying a disease in the donor or a transmission event to recipient[22]. Alternatively, FMT is best sourced from a centralised stool bank from healthy unrelated donors[12]. Donors should be between 18 and 60 years of age and BMI between 18 and 30 kg/m^3 [12,23]. Donors are screened with a questionnaire followed by blood and stool testing with recommendations in Table 1. Woodworth *et al*.[3] recommend screening for carbapenem resistant *Enterobacteriaceae,* vancomycin resistant Enterococci and those with frequent contact with health care should be excluded. The risk of transmission of non-communicable diseases remains unknown; therefore, donors with cardiovascular disease, stroke, diabetes mellitus, obesity, metabolic syndrome and malnutrition are excluded[3].

Processing and preparation: impact on efficiency

Stool should be processed within 6 hours of defaecation. FMT material prepared in aerobic conditions has been effective for the treatment of recurrent *C. difficile* associated diarrhea[8]. However, ambient air exposure impacts on viable bacterial composition particularly for oxygen sensitive species[24]. Processing stool in an anaerobic chamber allows preservation of commensal species[24]. Freezing reduces the overall viability but the microbiota composition is not significantly different to fresh specimens[24], with viable

Table 1. Example of donor questionnaire and donor blood and stool testing.

Infectious diseases and risk factors	HIV, hepatitis B, hepatitis C, syphilis, HTLVI and II Current infection Risk factors for blood-borne viruses: illicit drugs, high-risk sexual behaviour, needle stick tattoo, piercing, acupuncture, blood transfusion <6 months Organ transplantation Recent hospitalisation or care facility High-risk travel <6 months Enteric pathogen <2 months Gastroenteritis <2 months Live attenuated virus vaccination <6 months Previous or latent tuberculosis
Medical history	Chronic gastrointestinal disease Systemic autoimmune disease Malignancy Recent gastrointestinal symptoms Neurological or psychiatric disorders or risk of prion disease Obesity, metabolic syndrome or diabetes Family history of colon cancer or other gastrointestinal conditions Atopy Chronic pain syndrome
Medication history	Antimicrobial drugs, immunosuppressants, chemotherapy <3 months Proton pump inhibitors >3 months Growth hormone, insulin from cows or clotting factor concentrates Experimental medicine or vaccine <6 months
Blood testing	Hepatitis A IgM HBsAg and HBcAb Hepatitis C antibody Hepatitis E IgM HIV-1 and HIV-2 antibodies HTLV-1 and HTLV-2 antibodies *Treponema pallidum* antibodies *Strongyloides stercoralis* IgG EBV serology (immunosuppressed) CMV serology (immunosuppressed) *Entamoeba histolytica* serology Full blood count and differential Creatinine and electrolytes Liver enzymes C-reactive protein
Stool testing	*Clostridioides difficile* PCR *Salmonella*, *Shigella*, *Campylobacter*, Shiga toxin-producing *E. coli*, *Yersinia*, *Vibrio cholerae* PCR +/- culture. Vancomycin-resistant *Enterococci* Methicillin-resistant *Staphylococcus aureus* ESBL *Enterobacteriaceae* Carbapenem-resistant and carbapenemase-producing *Enterobacteriaceae* Norovirus, rotavirus, adenovirus PCR Ova, cysts, parasite analysis *Giardia lamblia*, *Cryptosporidium*, *Isospora*, *Microsporidia* Protozoa and helminths *Helicobacter pylori* faecal antigen (upper route)

bacteria remaining after 6 months of frozen storage in 10% glycerol[22,25] and no difference in FMT efficacy observed when used for CDI[10].

There are a number of preparations for FMT including fresh, frozen and encapsulated faecal suspensions. Encapsulated freeze-dried preparations had 88% clinical success (49 patients) with no recurrence over two months[26]. In a randomised study of 72 patients with recurrent CDI, cure rates were highest for fresh faeces (100%), lowest for lyophilized product (78%; $P = 0.022$ vs fresh) and intermediate for frozen product (83%; $P = 0.233$ vs fresh)[27]. CDI recurrence was prevented in 84% receiving oral lyophilized microbiota capsules compared to 88% with FMT by enema ($P = 0.74$)[28]. In a non-inferiority randomised trial there was no difference after single treatment with capsule or colonoscopy delivery (both 96.2% without recurrent CDI at 12 weeks)[29].

Administration procedure: impact on efficiency

Bowel lavage is administered prior to FMT particularly for the lower gastrointestinal route. There should be minimum 24 hours free from antibiotics before FMT and at least 72 hours after FMT[12]. FMT can be delivered to upper (nasogastric, nasoduodenal or nasojejunal tube or upper endoscopy) or lower gastrointestinal tract (colonoscopic administration to caecum or terminal ileum or enema if not possible). Ianiro *et al*.[30] conducted a systematic review and meta-analysis of fifteen studies on different protocols of FMT for CDI. Multiple infusions increased efficacy compared to single infusion (93% vs 76%)[30]. Duodenal delivery had lower efficacy ($P = 0.039$) and colonoscopy had higher efficacy rates ($P = 0.006$). Lower faecal amount (≤50g) and enema had lower efficacy rates after single infusion[30]. Another meta-analysis also demonstrated administration by lower gastrointestinal route was more effective (95%) compared to upper gastrointestinal delivery (85%) with no difference between fresh or frozen FMT[10]. Consecutive courses after failure of first FMT showed incremental effect[10].

FMT services, stool banking and regulation

Historically, FMT has been performed with varying levels of sophistication across Australia, ranging from the *ad hoc* and infrequent preparation of fresh FMT material for recurrent CDI to specialised centres operating stool banks, such as the Biomebank (Adelaide, SA) and the Centre for Digestive Diseases (Sydney, NSW). In September 2019, the Australian Minister for Health determined that supply of faecal microbiota transplant products be regulated by the Therapeutic Goods Administration (TGA). The new regulatory model classifies most FMT products as class 1 or 2 biologicals depending on the extent of manipulation and whether manufactured in a hospital and used onsite. A Draft Standards for Faecal Microbiota Transplant Products is available with finalised FMT regulatory requirements expected in early 2020 (www.tga.gov.au). The American Gastroenterological Association (AGA) has proposed an FMT National Registry to collect outcomes to assess short- and long-term safety and effectiveness and current practices[31]. An international consensus on stool banking for FMT in clinical practice is available[32]. There are now Australian consensus statements for the regulation, production and use of FMT in clinical practice[23].

FMT for decolonisation of multiresistant organisms and treatment of other conditions

Small sample studies have shown that FMT was effective in reducing the number of antibiotic resistance genes in patients' resistome[33]. Huttner *et al*.[34] hypothesised that decolonisation could be achieved with oral antibiotics (colistin and neomycin) followed by recolonisation to restore intestinal microbiota. The results were only slightly in favour of the intervention group (OR 1.7). Nine uncontrolled studies with heterogeneity have evaluated the use of FMT for multidrug resistant Gram-negative bacteria decolonisation. However, the European guidelines suggest there is insufficient evidence for or against FMT in this context[35]. Similarly, UK guidelines do not recommend FMT as treatment for inflammatory bowel disease or other gastrointestinal or non-gastrointestinal disease[12]. Australian guidelines suggest FMT has been shown to be successful in induction therapy for mild to moderate ulcerative colitis however more studies are required before it can be implemented into standard care[23]. This is a developing research field and future treatment of conditions with FMT will be seen in the future.

Conflicts of interest

The authors declare no conflicts of interest.

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