Faecal Microbiota Transplantation as Primary Treatment for *Clostridioides difficile* Infection—Evidence for Change

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Abstract

In this mini-review, we summarise the significant body of evidence for the treatment of *Clostridioides difficile* infection (CDI) with Faecal Microbiota Transplantation (FMT) and propose the transition of FMT from 'last resort' treatment to the forefront of CDI management. To address the feasibility of this proposal, we examined the rates of efficacy in FMT treated patients with CDI and also reviewed the safety of FMT across available published studies. A considered view of safety, efficacy, product standardisation, quality control and Good Manufacturing Practices (GMP) allows for a prudent approach in positioning FMT as the primary or initial treatment for CDI.

Keywords: Faecal microbiota transplantation, *Clostridioides difficile* infection, Recurrent, Treatment, Safety, Efficacy, Donor screening, Colonoscopy, Nasogastric, Review

Introduction

*Clostridioides difficile* is an anaerobic spore-forming gram positive bacillus that infects the gut microbiota leading to gastrointestinal disease with varied severities ranging from self-limiting diarrhea to life-threatening pseudomembranous colitis, sepsis or death. In the last 20 years, there has been a marked increase in *Clostridioides difficile* infection (CDI) worldwide with almost 1% of all hospitalizations or 329,460 patients in the United States in 2017, which is due to CDI [1]. In part, this has been due to CDI also becoming more virulent, refractory, and relapsing after standard antibiotic therapy [2]. Current treatment guidelines specify antibiotics as frontline therapy (vancomycin, metronidazole, and fidaxomicin), however, such treatments may deplete bacterial classes and result in non-uniform intestinal microbiota dominated by Proteobacteria [3]. This preliminary antibiotic-induced dysbiosis may further promote resistance leading to relapsed or refractory CDI. Published data shows the relapse rate with vancomycin and metronidazole treatment to be as high as 37% and 50%, respectively [4]. On the other hand, there is now considerable evidence that (FMT) effectively cures CDI and may emerge as an effective initial treatment of CDI even in patients diagnosed with CDI for the first time [5]. There is now evidence to demonstrate a cure rate of up to 98% when more than one FMT infusion is performed [6,7]. Despite this growing new data, the FDA guidelines may be holding physicians back from curing more CDI patients. Current guidelines only approve a single FMT procedure and only in patients with two previous treatment failures with antibiotics [8,9].

Whilst FMT is becoming an increasingly common procedure, a minority of healthcare practitioners still hold reservations regarding its efficacy and safety. Primarily these perspectives have centred around safety, patient tolerability to colonoscopy and fear of infections from donor transplant material [10,11]. Indeed, while FMT has several contraindications [12] particularly for those with immunocompromised conditions, the risks of transmissible infection have been extremely low (as detailed later).
Since 2015 medical professionals have been debating positioning FMT as first-line therapy for CDI [13]. Given FMT involves the transplantation of a highly heterogeneous biological sample (stool) from a healthy donor to the sick patient, regulatory authorities are challenged with providing clear guidance for the regulation of the procedure. Currently, regulatory harmonization is lacking and guidelines continue to conservatively reserve FMT for unresponsive cases only [8]. More recently, FMT has also proved to be an effective treatment for a suite of other gastrointestinal and systemic diseases including Ulcerative Colitis (UC) and Irritable Bowel Syndrome (IBS) which has highlighted the need for further appraisal and guidelines on the standardisation of donor evaluations, production standards, and acceptable clinical indications. In 2019, published consensus statements from an international expert panel proposed a set of best practices in FMT [14], and in late 2020 the identification of possible COVID-19 transmission from FMT further highlighted the need for safety and certainty in donor screening [15].

The treatment of CDI is at a turning point. Given that: 1) FMT is very effective in curing CDI; 2) that using more than one FMT is more efficacious; 3) that antibiotics can compromise the microbiome and increase failure to cure (up to 60%), and 4) that FMT is a simple GI procedure best performed by trans-colonoscopic infusion or enema. Hence, we propose advancing FMT to a front line therapy to eradicate CDI. Furthermore, FMT has been demonstrated to repair the host’s microbiome from damage and replace missing flora simultaneously without delaying the recovery via using antibiotic pre-treatment. In this review, we also briefly update the recent data relating to FMT efficacy, safety and delivery methods in CDI management.

Evidence of Efficacy

Over several decades FMT has been trialled in various formats for CDI with very promising results. In a 2017 systematic review and meta-analysis Quraishi et al. assessed the results of thirty-seven studies including seven randomised controlled trials (RCTs) and 30 case series. FMT was found to be more effective than vancomycin in resolving recurrent and refractory CDI, and clinical resolution across all studies was 92%. Furthermore, administering consecutive courses of FMT following the failure of the first FMT resulted in incrementally improved effects. The review also showed that successful outcomes after FMT were independent of preparation and route of delivery [16]. Moayyedi et al. also released a smaller systematic review of FMT for CDI associated diarrhoea in the same year analysing ten RCTs that evaluated 657 patients. Within this dataset, five RCTs were identified that compared FMT against placebo or vancomycin (total of 284 patients) with FMT demonstrating strong statistical superiority [17]. FMT was also used in a proof-of-concept trial to evaluate its use as a treatment for primary CDI with 78% success compared to 45% in a control metronidazole group, again highlighting FMT as an alternative to antibiotic therapy in primary CDI [18]. The use of FMT as first-line treatment is further supported by a pooled analysis of FMT treatment outcomes between patients receiving vancomycin before treatment versus no pre-treatment showing no difference in treatment outcomes [19].

The success of FMT by traditional colonoscopic infusion has also led to novel delivery systems to avoid the disadvantages of bowel prep, anaesthesia, and enteral access. Iqbal et al. performed a systematic review of FMT using donor samples in ingestible capsules. Covering a total of six studies, five case series and one randomized controlled trial, 341 patient data sets were analysed. Efficacy was observed in 285 patients in the first treatment, with no recurrence. An additional 28 patients received a second FMT with resolution and three received resolution on their third FMT. In sum, a resolution rate of 93%. Only one patient did not achieve long-term resolution of symptoms despite of receiving four treatments [20].

The majority of recorded studies have recruited patients diagnosed with recurrent symptoms of diarrhea and serially positive for C. difficile toxin on testing. In many cases, patients had been treated with several courses of Vancomycin with several failures to cure when tapering antibiotics. To investigate the effectiveness of FMT on their first episode of CDI diagnosis Roshan et al. completed a retrospective, single-centre study of 59 patients between 2012 and 2017 treated with FMT on their first episode of CDI [6]. In light of strong evidence that repeated FMT (more than one) leads to increased efficacy rates, all patients were first treated with colonoscopic infusion, followed by an enema the next day. 98% of the 58/59 patients were cleared of C. difficile as verified by culture and toxin testing over the next 4-8 weeks. There were also statistically significant symptomatic reductions in abdominal pain, diarrhoea, and blood in the stool [6].

The efficacy rates in treating CDI with FMT is summarized in (Table 1). Of note are the incremental increases in efficacy on second and third FMT infusions.

On comparing 25 of the studies in Table 1 that reported efficacy of single and multiple FMT’s, the mean efficacy of single FMT (80.17) versus >1 FMT (92.78) was a highly significant improvement, (p<0.00001) in achieving CDI cure. Please note some of these reports had overlapping data.
### Method of delivery

| Year – Author | Method of delivery | Sample No. | Efficacy After Single FMT (%) | Efficacy after additional FMTs (%) |
|---------------|--------------------|------------|------------------------------|----------------------------------|
| 2020–Roshan et al. [6] | Colonoscopy and enema | 59 | — | 98 |
| 2020–Perler et al. [21] | Colonoscopy, capsule | 207 | 85.5 | 95.1 |
| 2003–Aas et al. [22] | Nasogastric | 18 | 83.3 | — |
| 2016–Agrawal et al. [23] | Esophagogastroduodenoscopy, push enteroscopy, colonoscopy, flexible sigmoidoscopy, and retention enema | 146 | 82.9 | 95.9 |
| 2014–Allegretti et al. [24] | Colonoscopy | 13 | 84.6 | 92.3 |
| 2012–Brandt et al. [25] | Colonoscopy | 77 | 91 | 98 |
| 2014–Emanuelsson et al. [26] | Rectal catheter | 31 | 74 | — |
| 2015–Ganc et al. [27] | Oral push enteroscopy | 12 | 90 | — |
| 2010–Garborg et al. [28] | Duodenal, colonoscopy | 29 | 73 | 83 |
| 2012–Hamilton et al. [29] | Colonoscopy | 43 | 86 | 95 |
| 2016–Kelly et al. [30] | Colonoscopy | 46 | 90.9 | 93.5 |
| 2017–Kao et al. [31] | Colonoscopy, capsule | 116 | 96.2 | — |
| 2012–Kassam et al. [32] | Enema | 27 | 81 | 93 |
| 2012–Kelly et al. [33] | Colonoscopy | 26 | 92 | — |
| 2014–Khan et al. [34] | Colonoscopy | 20 | 90 | 100 |
| 2014–Lee et al. [35] | Retention enema | 94 | 47.9 | 86 |
| 2016–Lee et al. [36] | Enema | 219 | 84 | 93 |
| 2009–Macconnachie et al. [37] | Nasogastric | 15 | 73 | 80 |
| 2011–Mattila et al. [38] | Colonoscopy | 36 | 89 | 94 |
| 2013–Patel et al. [39] | Colonoscopy | 31 | 90 | 100 |
| 2013–Pathak et al. [40] | Colonoscopy | 12 | 92 | 100 |
| 2014–Ray et al. [41] | Colonoscopy | 20 | 100 | — |
| 2010–Rohlke et al. [42] | Colonoscopy | 19 | 94 | 100 |
| 2013–Rubin et al. [43] | Nasogastric | 74 | 79 | 90.7 |
| 2015–Tauxe et al. [44] | Colonoscopy and upper GI | 31 | 75 | 87 |
| 2014–Vigvári et al. [45] | Nasoduodenal | 15 | 100 | — |
| 2010–Yoon et al. [46] | Colonoscopy | 12 | 100 | — |
| 2014–Zainah et al. [47] | Nasogastric | 14 | 79 | — |
| 2016–Allegretti et al. [24] | Capsules | 19 | 73.5 | 94 |
| 2015–Cammarota et al. [7] | Colonoscopy | 20 | 65 | 90 |
| 2015–Kao et al. [48] | Colonoscopy, Capsule | 29 | — | 96 |
| 2016–Lee et al. [36] | Enema | 232 | 56 | 91 |
| 2013–Van Nood et al. [49] | Duodenal infusion | 16 | 81 | 94 |
| 2014–Youngster et al. [50] | Capsule | 20 | 70 | 90 |
| 2017–Hota et al. [51] | Enema | 16 | 43.8 | — |
Evidence of Safety

FMT is generally considered safe with a very low risk of infection transmission. The majority of the short-term safety concerns are attributable to the mode of administration rather than FMT itself. Several studies have been conducted recently to assess the efficacy and safety of FMT for the treatment of CDI. Saha et al. conducted a prospective survey-based study to assess the short-term adverse events (n=609) and long-term safety (n=447) of FMT for treating recurrent CDI (rCDI) [56]. The majority of the short-term adverse events were limited to diarrhoea (>60%) and constipation (19%-33%) and the long term risk of adverse events and infectious complication were low [20]. Although several new diagnoses were observed in their study, none were related to FMT. Similarly, in the largest and longest study on efficacy and safety of FMT treatment of rCDI, Perler et al. reported long term cure with no adverse events related to FMT or downstream disease associated with dysbiosis [21].

Although safety concerns of post-FMT infection transmission was announced by the FDA, regarding 2 cases of drug resistant *Escherichia coli* infections transmitted by donor stool, a growing number of studies have emphasized the rarity of infection transmission through FMT, even in high risk patient groups [8]. A review by Wang et al. reported remarkably rare infectious complications (2.5% of more than 1000 patients treated) post-FMT [57]. Low risks of FMT related infectious transmission was also observed in high-risk immunocompromised patients [55,58]. More recently, the FMT National registry, designed to assess FMT methods and both safety and effectiveness outcomes, also reported high effectiveness of FMT for CDI with a good safety profile [59].

Although the majority of FMT related adverse events and potential risk of infection transmission are mitigated by stringent selection and screening process of prospective donors, there are still a few reports of distinct adverse reactions.

Brumbaugh et al. performed an analysis in a medium-sized cohort of children where FMT was delivered by nasogastric feeding tube. A total of 47 procedures were performed in 42 children. Vomiting, which was self-limiting, was observed within 24 hours of the FMT occurring in 6 of 47 (13%) procedures [60]. Lai et al. conducted a larger study reviewing 407 articles that referenced FMT and their overall Adverse Events (AEs) [61]. In total 135 studies reported AEs for 4493 patients, with 36 studies experiencing no AEs. The commonest AEs in this group were related to the gastrointestinal system including diarrhoea (13.0%), abdominal distension/flatulence (11.6%), nausea/vomiting (6.1%), abdominal pain (5.5%) and constipation (2.1%). Other common AEs included fever (2.7%), respiratory difficulty (2.4%), headache (1.5%) and fatigue (1.4%). In IBD patients 1.3% experienced IBD flares or IBD-like symptoms. Despite several reviews reporting efficacy outcomes being independent of FMT type (i.e. oral vs colonoscopic), AEs and safety outcomes do appear to be somewhat related. The same review study found AE rates were generally higher in upper GI FMT compared to lower infusions, with exception to IBD cases where IBD flares and fevers were higher but not statistically significant (7.9% vs 1.7%) compared with those who had CDI only.

Soo et al. in 2020 similarly reviewed the short-term safety record of FMT finding very few adverse effects directly attributed to the procedure with most adverse events being self-limiting gastrointestinal symptoms including abdominal cramps, diarrhoea and constipation, which resolved within one week. Of note, the review reported two deaths from aspiration pneumonia related to sedation given at the time of faecal microbiota transplantation and one death from transmission of a multidrug resistant *Escherichia coli* [62,63]. Nasogastric and nasoduodenal delivery also tended to have higher rates of minor adverse effects relative to other methods despite the seemingly less-invasive procedure [64].
A comprehensive safety study into FMT was conducted by Cicilia Marcella et al. published in 2021. With a stricter set of inclusion criteria, 129 studies were included covering 4241 patients (5688 FMTs). AEs occurred in 19% of FMT procedures compared with <1% reported by Lai et al [61]. The most frequently reported AEs were diarrhea (10%) and abdominal discomfort/pain/cramping (7%). FMT-related serious adverse events (SAEs), including infections and deaths occurred in 1.4% of patients who underwent FMT (0.99% microbiota-related SAEs). Four of five FMT-related deaths were reported in patients receiving FMT via the upper gastrointestinal route. Of special note was that all reported FMT-related SAEs were in patients with mucosal barrier injury. The report however concluded that most FMT-related AEs were mild or moderate and self-limiting. Thus although FMT appears to be highly safe, AEs were related to the method of implantation, thus highlighting the need for improvements to reduce both delivery-related AEs and, microbiota-related AEs [65].

There is a growing increase in the number of FMT indications such as inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn’s disease which deserves mention. IBD /UC patients share some overlap with CDI with reported incidences ranging from 1.8%-4.6% [66]. There is some evidence that suggests FMT could worsen symptoms of underlying IBD. Qazi et al. reviewed twenty-nine studies including 514 IBD patients treated with FMT. The data showed a pooled rate of IBD worsening of 14.9%, with higher rates of IBD worsening using lower GI FMT (16.5%) compared with upper GI delivery (5.6%) [67]. Sood et al. analysed the data of 129 patients with active UC who received extensive multisession FMT via colonoscopy. Minor short-term adverse events included abdominal discomfort, flatulence, abdominal distension, borborygmi, and low-grade fever (30.8%, 15.9%, 9.8%, 7.9%, and 7.6%, respectively). Long-term adverse events included new-onset urticaria (4.3%), arthritis/arthralgia (6.5%), depression (2.2%), partial sensorineural hearing loss (2.2%), and allergic bronchitis (2.2%). Thirteen (12.9%) patients dropped out because of adverse events however it is unclear if these were linked to a single session FMT or the extended length and course of the trial [68]. Due to the prevalence of immunosuppressant medication in the above conditions, FMT studies in the immunosuppressed patient have also been investigated extensively. Shogbesan et al. reviewed forty-four studies covering 303 immunocompromised patients finding equivalent efficacy as high as 93% when multiple treatments were included. Serious AEs included 2 reported deaths, 2 colectomies, 5 treatment-related infections, and 10 subsequent hospitalizations. However, Shogbesan concluded these AE rates in immunocompromised patients were similar to those of immunocompetent patients [55].

In summary, FMT appears to be safe, as the majority of studies demonstrate that FMT doesn’t appear to raise adverse events above the rates seen in the underlying condition. However, in the case of colonoscopy based FMT it is difficult to ascertain whether adverse events (i.e. diarrhea, irregular bowel movements) are related to the FMT procedure or from underlying disease. In the rare reports of death following FMT, the elderly demographic and common presence of multiple co-morbidities makes it difficult to assess whether FMT has any interrelationship. Nevertheless, the nature of the procedure and the risks for donor-recipient infection, or immunological flare from IBD or other co-morbidity remains. Thus, vigilant implementation of standardised quality screening of both patient and recipient remains highly relevant.

| Year – Author | Adverse Event Description | Cases Reviewed | Minor Adverse Event No. | Serious Adverse Event No. |
|---------------|---------------------------|---------------|-------------------------|--------------------------|
| 2018–Iqbal et al. [20] | Serious AE: high grade fever, Ulcerative Colitis | 341 | – | 3 |
| 2021–Saha et al. [56] | Mild & Moderate AE: diarrhea (60%), constipation (60%), cramping (50%), IBS (16.9%) Unrelated Serious AE: unrelated deaths (3.8%) | 609 | 365 | 23 |
| 2016–Wang et al. [57] | Mild & Moderate AE: all (28.5%) Serious AE: all (9.2%), death (3.5%), infection (2.5%), relapse of IBD (0.6%), CDI (0.9%) | 1089 | 310 | 100 |
| 2021–Kelly et al. [59] | Mild & Moderate AE: diarrhea (2%), abdominal pain (2%) Serious AE: hospitalizations (1%), IBS (1%), IBD (1%) | 222 | 9 | 7 |
| Year       | Study                          | Mild & Moderate AE                                                                 | Total (AE) |
|------------|-------------------------------|-----------------------------------------------------------------------------------|------------|
| 2014       | Youngster et al. [50]          | Abdominal cramping and bloating                                                   | 30         |
|            |                               |                                     | 6          |
|            |                               |                                     | 0          |
| 2016       | Youngster et al. [54]          | Fever, diarrhea, vomiting, nausea/bloating, abdominal pain, fatigue, headache     | 180        |
|            |                               | Other complaints (270 occurrences)                                                | 112        |
|            |                               | Unrelated Serious AE: hospitalisation, death (40)                                 | 49         |
| 2018       | Brumbaugh et al. [60]          | Vomiting                                                                           | 42         |
|            |                               |                                     | 6          |
|            |                               |                                     | 0          |
| 2019       | Lai et al. [61]                | Diarrhoea (13.0%), abdominal distension/flatulence, nausea/vomiting, abdominal     | 4609       |
|            |                               | pain (5.5%), and constipation (2.1%), fever (2.7%), respiratory difficulty,        | –          |
|            |                               | headache (1.5%) and fatigue (1.4%). 1.3% patients also experienced IBD flares or  | 21         |
|            |                               | IBD-like symptoms                                                                  |            |
| 2002       | Cicilia Marcella et al. [65]   | Abdominal discomfort/pain/cramping (7%)                                           | 5688       |
|            |                               | Infections, death, other (1.4%).                                                   | 875        |
|            |                               | Serious AE: aspiration or aspiration pneumonia, sedation complications, bowel       | 59         |
|            |                               | perforation, sepsis, hospitalisation, death                                        |            |
| 2018       | Shogbesan et al. [55]          | Abdominal pain, irritable bowel syndrome, nausea, fever, diverticulitis.           | 303        |
|            |                               | Serious AE: colectomies, bacteremia, hospitalisation, inflammatory bowel disease,  | 28         |
|            |                               | pneumonia, aspiration pneumonia, death.                                            | 33         |
| 2013       | Van Nood et al. [49]           | Diarrhoea (94%), cramping (31%), belching (19%), constipation (19%).               | 16         |
|            |                               |                                     | 15         |
|            |                               |                                     | 0          |
| 2016       | Lee et al. [69]                | Transient diarrhea (70%), abdominal cramps (10%), nausea (<5%), constipation (20%)| 232        |
|            |                               | and excess flatulence (25%)                                                        | 162        |
|            |                               | Serious AE: urinary tract infections (<5%), respiratory tract infection             | 11         |
| 2015       | Cammarota et al. [7]           | Diarrhoea (94%), bloating and abdominal cramping (60%)                             | 20         |
|            |                               |                                     | 19         |
|            |                               |                                     | 0          |
| 2014       | Dutta et al. [70]              | Low-grade fever (18%), bloating (11%).                                            | 27         |
|            |                               |                                     | 8          |
|            |                               |                                     | 0          |
| 2017       | Jiang et al. [52]              | Nausea, mild diarrhoea and transient abdominal discomfort (86%), fever (2%),      | 72         |
|            |                               | fatigue (8%), headache (6%), weight gain (3%)                                     | 62         |
|            |                               |                                     | 0          |
Protocols and Methods

Implementing fundamental safety precautions will limit the spread of pathogenic organisms to the recipient, thus selective and regular screening of donors has been the focus of most institutions performing FMT on a regular basis. Donor screening requirements include general health, absence of gastrointestinal (GI) disease and no antibiotic therapy in the last 90 days. Other exclusions include autoimmune disease, chronic pain syndromes, neurologic disease, certain neuropsychiatric syndromes, metabolic syndrome, obesity, moderate or severe malnutrition, malignancy, ongoing oncologic therapy and being immunocompromised, as well negative serological and stool test results (Table 3).

As screening can be both time and resource intensive, to limit the delays in recruiting fresh donors, access to universal donors via a biobank allows physicians in the US to obtain stool from biobanks without needing to submit Investigational New Drug applications and more recently to be compliant with COVID safety precautions [74]. There are several notable stool biobanks globally. Terveer et al. compiled a brief list of faeces banks that have been well established and describes the methodologies used at the Netherlands Donor Feces Bank including detailed screening procedures, example questionnaires and personal interviews of the donors concerning risk factors for transmissible diseases [75]. Such risk factors for transmissible disease include body mass index (BMI) > 25 kg/m2; as obesity may also be associated with a specific microbiota composition and other gastrointestinal disorder (e.g., irritable bowel syndrome (IBS), Crohn’s disease, or ulcerative colitis) which are increasingly showing a link to the host’s microbiome. These exclusion criteria, taken altogether, limit the risks of biota-based infection risks to the recipient which has been the main attention of safety concerns. Biobanking also provides the ability to track, measure and validate success rates from specific donor batches which provides added safety precautions, eliminating the risk factors associated from new donors in fresh transplant procedures.

Table 2: A safety summary of the literature tabulating reported adverse events including both original studies and systematic analyses.

| 2016 Baxter et al. [71] | Mild & Moderate AE: abdominal distension/bloating/cramping (2.3%), flatulence (2%), diarrhoea (1.9%), irregular bowel movement (1.2%), IBS Symptoms (1.09%), constipation (1%), other (4%). | 1190 | 162 | 3 |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|---|
|                        | Serious AE: bacteremia, perforations, death (3)                                                                                                                                                                                                                 |      |      |   |

1Publications and authors are listed in detail in the references section.

2Adverse events were categorised into mild & moderate and serious. Symptoms such as cramping or diarrhea may include overlap in the single participant. Percentage figures were provided in the description where available from original authors. In some studies, minor events were omitted and denoted with (-).

Table 3: A typical serological and stool screening list for donors [72,73].

| Human Immunodeficiency Virus (HIV) | Hepatitis C (HBC IgM) | Epstein-Barr virus (EBV) | Clostridium difficile (EIA) |
|-----------------------------------|-----------------------|--------------------------|----------------------------|
| Treponema pallidum                | Syphilis              | Hepatitis B (HBsAg)      | Clostridium difficile toxin PCR |
| Cytomegalovirus (CMV)             | Liver enzyme (Aminotransferases) | H.pylori (EIA) | Shigatoxin-producing Escherichia coli (STEC) |
| Hepatitis A (HAV IgM)             | Human T-Lymphotrophic virus (HTLV 1 & 2) | Viral tests (Adenovirus, Norovirus, Rotavirus) | Extended-spectrum beta-lactamase (ESBL)–producing Escherichia coli |
| Epstein-Barr virus (EBV)          | Hepatitis B (HBV IgM) | Enteric pathogen culture (Salmonella, Shigella, Campylobacter) | Parasitic tests, (Ovum, Isospora, Cryptosporidium, Giardia) |

Table 3: A typical serological and stool screening list for donors [72,73].
Next, the physician has several options in the choice of transplantation into the GI tract. FMT has been shown to be robust and viably delivered to the lower gut through specialised tools such as colonoscopy, ileocolonoscopy, enema, distal ileum stoma and colostomy. Historically, the most validated procedure has been through retention enema or infusions into the colon aided by colonoscopy [76]. Where patients are deemed unsuitable for a colonic based infusion, methods for upper and mid-gut delivery (stomach, duodenum) have also been well developed; for example, FMT via gastroscope and the nasogastric tube [77]. This method involves insertion of a tube via the nasal cavity, or orally to reach the intestinal tract and the use of smaller more concentrated infusions of 30mL to 60mL with or without x-ray guidance and or the use of a gastroscope [77]. More recently, a few groups have concentrated donor stool into orally ingested capsules which has avoided the need for anesthesia and enteral access altogether, with some reports of equivalent efficacy rates comparable to colonoscopic procedures [31,54,78]. Though this approach appears promising, laboratory facilities to centrifuge and concentrate faecal samples are required, and the ingestion of 30-40 capsules can be challenging in some patients. Nevertheless, further randomised clinical trials are needed to validate this recent approach.

**Conclusions**

FMT is a proven effective treatment for rCDI. In this review, we highlighted the effectiveness and safety of FMT in CDI and thus demonstrated its readiness as the initial treatment for CDI. While this review only briefly covers issues of efficacy, safety and delivery, we believe that in general cases of CDI there is strong evidence to remove antibiotic treatment which is known to delay cure, promote antimicrobial resistance, dysbiosis and induce CDI recurrence when treatment is tapered. This study was limited by the availability of primary treatment data whereby patients are treated with FMT without antibiotic treatment. Ultimately, larger datasets of primary treatment outcome studies will be the greatest asset in assessing FMT for widespread application. Although the majority of FMT is well tolerated with only minor adverse events and rare infection transmission, there have been some notable adverse events. To advance FMT to the first line of CDI treatment safely, uniform and stringent regulatory guidelines need to be implemented regarding the source, production and processing of the transplantable FMT products. Recently, GMP manufacturing guidelines for FMT products have been established in some countries which have led to improved availability, safety, standardisation, and quality control of FMT products. Indeed, implementing widespread quality control of GMP–FMT products could raise the effectiveness and safety standards for FMT in line with other biological therapies. Whilst there remain questions on the underlying mechanisms of action and cure, or how FMT re-establishes microbial diversity, we propose that FMT should now become the first-line treatment for CDI.

**Conflicts of Interest**

SD, JN, SH, VD- none.

TJB is the Medical Director of Centre for Digestive Diseases offering FMT, and has filed patents in this field.

**Author Contributions Statement**

T.B. and S.D. conceived of the presented idea. S.D., J.N, S.H developed the review structure. V.D. encouraged and supervised J.N. to investigate and further research the findings presented in this work.

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