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Swiss expert opinion: current approaches in faecal microbiota transplantation in daily practice

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Summary

INTRODUCTION: Faecal microbiota transplantation (FMT) is an established therapy for recurrent *C. difficile* infection, and recent studies have reported encouraging results of FMT in patients with ulcerative colitis. Few international consensus guidelines exist for this therapy, and thus FMT policies and practices differ among European countries. As of 2019, stool transplants are considered a non-standardised medicinal product in Switzerland, and a standardised production process requires authorisation by the Swiss Agency for Therapeutic Products. This authorisation leads to prolonged administrative procedures and increasing costs, which reduces treatment accessibility. In particular, patients with ulcerative colitis in Switzerland can only benefit from FMT off-label, even though it is a valid therapeutic option. Therefore, this study summarised the available data on FMT and established a framework for the standardised use of FMT.

METHODS: A panel of Swiss gastroenterologists with a special interest in inflammatory bowel disease was established to identify the current key issues of FMT. After a comprehensive review of the literature, statements were formulated about FMT indications, donor screening, stool transplant preparation and administration, and safety aspects. The panel then voted on the statements following the Delphi process; the statements were reformulated and revoted until a consensus was reached. The manuscript was then reviewed by an infectiologist (the head of Lausanne's FMT centre).

RESULTS: The established statements are summarised in the supplementary tables in the appendix to this paper. The working group hopes these will help standardise FMT practice in Switzerland and contribute to making faecal microbiota transplantation a safe and accessible treatment for patients with recurrent *C. difficile* infections and selected patients with ulcerative colitis, as well as other indications in the future.

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Introduction

Faecal microbiota transplantation (FMT) is a procedure in which faeces from a healthy donor are transferred to the gastrointestinal tract of a recipient patient. Over the past 10 years, studies have demonstrated that FMT is an effective treatment for recurrent *Clostridioides difficile* infection (rCDI), recently reclassified as *Clostridioides difficile* infection (CDI) [1–3]. In recent years, the role of the gut microbiota has been recognised in a variety of immune-mediated diseases and other disorders (e.g. metabolic disorders), raising the question of whether FMT has therapeutic potential [4–7]. Studies on the use of FMT in inflammatory bowel disease (IBD) have shown some benefits, mostly in patients with ulcerative colitis; studies on FMT in Crohn's disease have been less conclusive [8–10].

Currently, there is no international consensus on how FMT should be legislated, and standardised policies are lacking [11, 12]. Some countries handle FMT as a tissue sample, whereas others handle it as a medicinal product, demonstrating that different countries have very different regulation procedures [12, 13]. United European Gastroenterology (UEG) advocates that FMT should be uniformly recognised and regulated as a transplant product and not as a drug [14]. In July 2022, the EU Commission released a legislative proposal to include faecal microbiota in the European legislation on blood, tissues, and cells [15, 16]. The Council of Europe published the fifth version of the Guide to Quality and Safety of Tissues and Cells, which includes a chapter on intestinal microbiota. Screening recommendations are made but the most suitable framework remains a choice of the member states [17].

Recently, stool transplants were not regulated in Switzerland, leading to many procedural disparities. For example, the selection of donors varied depending on the centre; CHUV (Lausanne University Hospital) proceeded with a strict selection of traceable, healthy medical student donors, whereas in some private gastroenterology clinics, the patient had to recruit friends or relatives. As of 2019,

stool transplants are considered a non-standardised medicinal product, with a standardised production process requiring authorisation by Swissmedic (the Swiss Agency for Therapeutic Products) [18]. CHUV is accredited for the production of stool transplants. The obligation to obtain a marketing authorisation came into force in July 2020, and obtainment procedures are ongoing [12]. Since then, the administration of FMT outside of accredited centres is out of regulation. Each approval by Swissmedic is centre- and indication-dependent, and the administrative procedure must be repeated as indications evolve. This leads to reduced FMT accessibility. In 2021, CHUV estimated that, according to their local practices at that time, the cost of an FMT procedure was approximately CHF 15,000 (EUR 15,110) per transplant [12]. This estimate included donor selection (repeated clinical and biological assessment) as well as follow-up (until 5 years after donation) and the preparation of the sample. It did not include the administration to the recipient, which is typically endoscopic. With improved preselection of donors and increased consistency in the procedures, costs are expected to be halved. The final pricing and reimbursement will depend on the acceptance of the marketing authorisation.

FMT is a promising therapy, and the panel of gastroenterologist experts agreed that its accessibility should be improved without compromising its safety. United European Gastroenterology and other national interest groups have provided some guidance on the application of FMT in daily clinical practice, but Switzerland currently lacks such guidance. This paper provides an updated review of the current evidence concerning FMT efficacy, with a special focus on IBD, and establishes statements about the most relevant aspects of the FMT process, from donor screening to administration.

Materials and methods

The IBDnet is an official partner organisation of the Swiss Society of Gastroenterology. A panel of seven IBDnet delegates, gastroenterologists with expertise in IBD, from various Swiss academic and private gastroenterology centres was constituted to participate in this position statement. The purpose of this group was to establish statements about FMT following the Delphi method. Key issues regarding FMT were identified and distributed in 6 topics: indications for FMT, donor screening, preparation of donor faeces, transplant recipients, faecal delivery, and safety considerations. For each topic, literature searches were performed on PubMed in March 2022 to obtain the best available evidence. After the literature review, one member of the panel formulated draft statements.

The elaborated statements were distributed to each IBD expert for anonymous electronic voting in May 2022. For each statement, experts were asked to rate their level of agreement on a 4-item Likert scale: (1) strongly disagree, (2) disagree, (3) agree with reservation, and (4) strongly agree. All seven experts voted on each statement, and there were no missing or blank votes. The votes were collected by the facilitator, Nadine Zahnd, PhD, managing director of IBDnet, and then they were merged. A statement was accepted if its average rating was greater than or equal to 3. Panel experts gathered on 7 June 2022 to discuss the statements. If a mean score of 3 was not achieved, the statement was discussed to identify any ambiguities or contradictions with the available literature and then rephrased, after which a new voting round was performed. This process was repeated until a mean rating of greater than or equal to 3 was obtained. After redaction, the initial manuscript was sent to the head of CHUV's FMT Unit, Tatiana Galperine, MD, infectiologist, for interdisciplinary review.

Indications for FMT

Clostridioides difficile infections (CDI)

In 2021, the American College of Gastroenterology (ACG) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published guidelines on *Clostridioides difficile* infection treatment [19, 20]. The ESCMID recommended fidaxomicin as first-line therapy because it is associated with a reduced recurrence rate and has a narrower spectrum of activity compared with vancomycin and metronidazole [20–22]. However, this recommendation was controversial. The ACG considers both vancomycin and fidaxomicin to be valid first-line options [19]. The Swiss Society for Infectious Diseases (SSI) still recommends vancomycin (or even metronidazole) as the first-line treatment in patients without risk factors and with a low risk of relapse [23]. This is because they have satisfactory efficacy fidaxomicin *C. difficile* colitis in Switzerland and are less expensive and more accessible than fidaxomicin [23]. Fidaxomicin is recommended in patients at risk of *Clostridioides difficile* infection recurrence (i.e. patients older than 65 years meeting at least one of the following criteria: healthcare-associated *Clostridioides difficile* infection, recent hospitalisation, concomitant antibiotic use, and new proton pump-inhibitor prescription) [20]. In patients with *Clostridioides difficile* infection recurrence, antibiotic treatment can be further optimised by switching their medication to fidaxomicin if they have not yet received it, or combining fidaxomicin with bezlotoxumab, a monoclonal antibody against *C. difficile* toxin B [20, 23]. The AGC, ESCMID and the SSI agree that for further recurrences, FMT should be discussed [19, 20, 23].

The efficacy of FMT for recurrent *C. difficile* colitis has been demonstrated in multiple randomised studies, and the most recent European and American guidelines recommend FMT after the second recurrence of *Clostridioides difficile* infection [20, 24–27]. The efficacy of FMT in *Clostridioides difficile* infection is estimated to lie between 85% and 90%, and it has better cure rates than vancomycin and fidaxomicin regimens [28–30]. Despite the initial impression that FMT is associated with high costs, its efficacy in preventing further Clostridioides difficile infection makes it a cost-effective procedure [31]. This strong evidence led to statement 1.1 (see supplementary table S1 in the PDF version of this article).

A retrospective clinical review indicated that FMT could be an effective first-line treatment for initial *Clostridioides difficile* infection in a small population (54 patients) [32]. This was confirmed in a recent randomised placebo-controlled study in which FMT was compared with placebo after a 10-day vancomycin treatment for the first and second episodes of *Clostridioides difficile* infection [33]. Because FMT is more complex and costly than 10-day antibiotic treatment alone, we do not currently recommend FMT

as a first-line treatment for *Clostridioides difficile* infection (statement 1.2).

A recent meta-analysis showed that FMT could be used not only for recurrent *Clostridioides difficile* infection but also for antibiotic-refractory *Clostridioides difficile* infection (statement 1.3) [34]. In such cases, the diagnosis must first be challenged, and other causes of diarrhoea apart from *C. difficile* colonisation must be ruled out. Another meta-analysis has also found that FMT was effective and safe in patients with severe *C. difficile* infections [35]. After consideration of this article, we rephrased statement 1.4 and revoted on it.

According to a meta-analysis published in 2021, FMT for *Clostridioides difficile* infection in patients with underlying IBD is highly effective, with a pooled cure rate of 78% [36].

Contrary to initial fears that FMT could induce flares, FMT can be used to treat *Clostridioides difficile* infection in patients with IBD; in these patients, FMT has a potential secondary benefit of improving their underlying disease, as clinical IBD-scores (partial Mayo score or Harvey-Bradshaw index) were improved in patients with ulcerative colitis and those with Crohn's disease (supplementary table S1, statement 1.5) [37, 38].

Inflammatory bowel disease

FMT may be a therapeutic option to induce remission in ulcerative colitis (supplementary table S2). Over the past years, several randomised controlled trials (RCTs) have shown increased remission rates in patients with ulcerative colitis who received FMT compared to those who received placebo [39–45]. However, all these studies included a limited number of patients (between 15 and 42 in the FMT arms) and had different methodologies. The route of administration (nasoduodenal tube, enema, colonoscopy, or oral lyophilised tablets) as well as the frequency of administration varied. The remission rates varied between 24% and 57% in the FMT groups compared with between 5% to 36% in the placebo groups. Overall, the mean benefit difference was 22% between FMT and placebo. A nonsignificant difference was only observed in the study in which the FMT was administrated via nasoduodenal tube [42]. FMT seems to be a promising therapy to induce remission in patients with active ulcerative colitis, but this treatment must be studied further before it is encouraged more strongly (statement 1.7). These remission rates must be put into perspective. On the one hand, the response rates of FMT therapy in patients with ulcerative colitis are not quite as impressive as those in patients with *Clostridioides difficile* infection. This could be explained by the difference in underlying pathogenesis; *Clostridioides difficile* infection is a typical example of gut microbiota dysbiosis, whereas in ulcerative colitis, the gut microbiota is only part of a complex multifactorial etiological model [46]. On the other hand, the FMT remission rate is similar to the remission rate seen with biological therapies (approximately 30%), making it a relevant therapeutic option to consider [47].

A randomised pilot study conducted on patients with ulcerative colitis in remission in which FMT was administered via repeated colonoscopy also showed increased maintained remission rates compared with placebo [48].

In severe ulcerative colitis, the expert panel agreed that FMT should not be used as rescue therapy before colectomy until further evidence is available (statement 1.8) because of the potential complications among this subgroup of patients.

Although FMT in patients with Crohn's disease could result in an expansion of the microbial bacterial diversity, the clinical response is not obvious, and robust data are lacking [8, 49]. Most studies have been performed on small clinical cohorts without control groups [50, 51]. A cohort study including 174 patients showed clinical improvement after FMT [52]. One RCT compared upper gastrointestinal and lower gastrointestinal administration routes of FMT and showed similar response rates of over 60%, but it did not include a placebo group [53]. To assess the efficacy of FMT for maintaining remission, another RCT compared colonoscopy FMT with sham transplantation, but only included nine patients with Crohn's disease, making drawing conclusions difficult [54]. Therefore, until further data are available, FMT is not recommended in patients with Crohn's disease (statement 1.9).

Other indications

Gut microbiota has been suggested to play a role in many diseases, but the available evidence does not currently support the use of FMT in these clinical scenarios [55–59] (supplementary table S3, statement 1.10). At the moment, if FMT is considered in these indications, it should only be performed within a clinical study protocol.

A 2022 study showed symptomatic improvement in irritable bowel syndrome (IBS) up to 3 years after FMT in 65% to 72% of patients (depending on the faeces volume delivered) compared with 27% of patients in the placebo group [60]. This response rate was higher than that reported in previous studies. The authors hypothesised that the administration route, which was duodenal and not colonic, may have played a significant role in the response difference [61]. Further studies are needed to support FMT for this indication.

A recent placebo-controlled study on 55 patients with small intestinal bacterial overgrowth (SIBO) showed clinical improvement after FMT (lyophilised capsules once weekly for 4 weeks) and no clinical improvement with placebo [62]. However, larger studies are needed to make clear recommendations.

Donor screening

Donor selection is crucial to reducing adverse events related to the administered faecal material by minimising the risk of transferring infectious diseases as well as adverse gut microbiota traits.

The European Commission established a directive for the selection of allogenic living donors of human tissue transplants in 2006 (updated in 2012), which requires a thorough donor assessment to exclude persons with active/past malignant disease; those with recent (not further specified) vaccination with a live attenuated vaccine; and those with a risk of transmission of diseases caused by prions, systemic infection (bacterial, viral, fungal, or parasitic), or blood-born diseases, such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and

syphilis (as well as human T-lymphotropic virus type 1 [HTLV-1] in populations in high-prevalence areas) [63]. The last European consensus conference on FMT in 2017 and the French Group of FMT made detailed recommendations for donor screening [27, 64]. Our expert panel considered these recommendations, as well as the international consensus conference statements on stool banking and the latest foreign national consensus (Korea), to make the following statements: 2.1.5, 2.1.7, 2.1.9, 2.1.10. 2.1.13, 2.2.2 to 2.2.10, 2.3.1, and 2.3.2 (supplementary tables S4–S6) [26, 65].

As highlighted by a recent United States Food and Drug Administration (FDA) alert, Shiga toxigenic *Escherichia coli* (STEC) and enteropathogenic *Escherichia coli* (EPEC) should also be tested [66]. As these are included in the PCR multiplex test, they are not explicitly mentioned in the table but should be tested for. In a Dutch study, the transmission of *Blastocystis hominis* by FMT was documented and did not result in complications, symptoms, or adverse FMT outcomes in the recipient [67]. Nevertheless, the international consensus statements recommend testing for *Blastocystis hominis*, so we included it in this expert statement. However, if the non-pathogenicity of this strain is confirmed, this statement could be adapted. In addition, the pathogenicity of *Entamoeba histolytica* and *Dientamoeba fragilis* and their FMT transmission risk are subject to debate [68, 69]. In the United States, stool donors are no longer screened for *Blastocystis hominis* or *Dientamoeba fragilis* [70], and CHUV has adopted the same practice [12].

Our panel added an extra donor prerequisite for immunocompromised recipients − donors should not carry out cytomegalovirus (CMV), Epstein-Barr virus (EBV), or toxoplasmosis (statement 2.2.1) − following consensus reports for additional safety in this at-risk subpopulation [13, 26]. However, in the absence of reported cases of FMT-associated transmission of CMV, EBV, and toxoplasmosis, the benefit of this practice is unclear [70].

There have been reports of FMT complicated by extended-spectrum beta-lactamase *E. Coli* (ESBL) bacteraemia, with one case leading to death, in which ESBL was subsequently identified in the donor's stool by genome sequencing [71]. The implicated donor did not have any risk factors of multidrug-resistant organism carriage and was thus not tested for them. Other data show that a substantial proportion of healthy donors (17%) carried multidrug-resistant organisms [72]. This reminds us that healthy, fit individuals can harbour organisms that might be fatal to others; therefore, testing for these is crucial [73]. To prevent the transmission of multidrug-resistant organisms and possible subsequent complications, our panel recommends systematic screening for the most common multidrug-resistant strains (statement 2.2.11).

The SARS-CoV-2 pandemic required FMT services to adapt to optimise safety for donors, recipients, and healthcare professionals [74]. It has been demonstrated that patients infected with SARS-CoV-2 shed virus in their stool well beyond the average clearance time for upper respiratory tract shedding, independent of the presence of symptoms [75]. The pathogenic consequences of this shedding remain unclear. Currently, donors with recent SARS-CoV-2 infection should be excluded (statement 2.2.14).

Because of the role the microbiota could play in the development of autoimmune diseases, including inflammatory bowel disease, allergies, and psychiatric diseases, the expert panel recommends that people suffering from these diseases should not become stool donors (statements 2.1.3, 2.1.4, 2.1.6, 2.1.12, and 2.3.3) [6, 76–78]. Because microbiota composition seems to differ in underweight people with anorexia and obese individuals, the panel recommends that donors should have a normal body mass index (BMI) (statement 2.1.2) [5, 79]. Antibiotic treatment influences the microbiota composition and increases the risk of *Clostridioides difficile* infection up to 3 months after treatment; therefore, individuals with recent antibiotic use should also be excluded as donors (statement 2.1.11) [80, 81].

A recent study demonstrated that bariatric surgery (sleeve gastrectomy and Roux-en-Y bypass) influences microbiota composition [82]. Thus, our panel recommends excluding donors who have had major surgeries, especially those leading to blind loop syndromes, because of the risk of altered microbiota (statement 2.1.8) [82].

Older adults have an increased risk of comorbidities and may have modified microbiota [83]. Therefore, following international consensus, our panel suggests that donors should be between 18 and 70 years old (statement 2.1.1) [26, 64]. Given the age-dependent risk of colorectal cancer, stricter policies excluding donors over 50 years old should also be discussed [84].

These statements consider proven risks (transmission of pathogenic bacteria) as well as potential risks that are more debatable (colorectal cancer, dysbiotic traits, etc.). In addition, the frequency (single vs repeated) of FMT administration, should be considered in the risk balance. The enforcement of the different statements can thus vary. Restrictive donor screening criteria ultimately lead to a small pool of eligible donors − 10% of possible donors, according to Dutch and Swiss estimates − as well as increased costs [12, 85]. In the Dutch study, a large proportion of screen failures were due to the asymptomatic carriage of bacteria with controversial pathogenicity (*Dientamoeba fragilis* and *Blastocystis spp.*) [85]. This raises difficult questions about screening strategies, safety, and the costs we are willing to accept to achieve said safety.

Preparation of donor faeces

Despite the lack of comparative studies, the response rate of FMT in *Clostridioides difficile* infection was better in studies in which donor faeces were processed within 6 hours of defecation compared with those in which an interval of up to 48 hours was allowed. Therefore, we recommend that fresh stool should be used within 6 hours of defecation, and the storage and preparation of stool should be as brief as possible (statements 3.1 and 3.2) (supplementary table S7).

Initial recommendations encouraged the transplantation of a minimum weight of 50 g of stool because higher relapse rates of *Clostridioides difficile* infection (up to 4 times higher) were observed with lower amounts [11, 13, 86, 87]. Newer data indicate that 30 g or even 25 g could suffice [88, 89]. Following the European consensus, statement 3.3 was made [27]. However, stool weight is an imper-

fect measure of microbiota quantity [90]. This could partially explain the divergent study results. The stool amount also depends on the modality of administration [87]. The above-mentioned stool weights are applicable for colonoscopy only. These studies were performed on patients with *Clostridioides difficile* infection; therefore, our statement is only applicable in this clinical context. The optimal FMT stool weight for recipients with UC has still not been defined.

Following previously published consensus reports and considering the absence of new relevant data, the expert panel made statements 3.4 to 3.6 [11, 13, 26].

Frozen and fresh faecal suspensions are equally effective for the treatment of *Clostridioides difficile* infection [89, 91, 92]. However, frozen samples have some advantages over fresh samples: safety (allows for donor retesting and sample quarantine for possible incubating viral infections) and availability (the sample does not need to be used within 6 hours) [93].

Frozen samples can be stored at −20 °C for up to 30 days, but long-term storage should be performed at −80 °C [11, 13, 26]. Two RCTs have shown similar efficacy for the treatment of *Clostridioides difficile* infection between lyophilised products and fresh or frozen faecal products [94, 95].

According to these data, statement 3.7 was made.

Both anaerobically and aerobically prepared stool samples are effective for the treatment of *Clostridioides difficile* infection. However, it is possible that in other disorders, such as IBS and IBD, in which the anaerobic bacteria content of the microbiota is reduced, the preparation method is relevant for therapeutic success [27].

Transplant recipient

Bowel preparation is essential before any colonoscopy, including colonoscopy for FMT. It is unknown whether bowel lavage increases the clinical efficacy of *Clostridioides difficile* infection treatment. However, bowel lavage could help eliminate *C. difficile* toxins, spores, vegetative cells, and residual antibiotics, and it could facilitate the engraftment of the transplanted microorganisms [96]. This benefit would be expected to be seen independently from the means of administration. A recent trial showed improved response outcomes for *Clostridioides difficile* infection following oral capsule FMT administration with prior bowel preparation compared with the outcomes of prior studies with capsule administration without bowel preparation [97]. In a recent meta-analysis, poor bowel preparation was associated with a significantly increased risk of failure after FMT [98]. Therefore following current consensus guidelines, we recommend performing bowel preparation regardless of the FMT application method (statement 4.1, table 8) [13, 27, 65]. Prior intestinal cleansing could also have benefits for patients with ulcerative colitis, but robust data are lacking [99].

Because antibiotics may adversely affect the FMT material, most studies have implemented a washout period between antibiotic regimen completion and FMT administration. The duration of the washout varied greatly between study protocols and was never specifically compared. On the other hand, the first-line treatment for a *Clostridioides difficile* infection includes antibiotic treatment, and it is unclear whether pretreatment with antibiotics increases the effectiveness of FMT.

Antibiotic treatment for *Clostridioides difficile* infection should be administered before FMT because outcomes are worse with FMT alone, particularly for severe *Clostridioides difficile* infection [100].

Interestingly, one study showed that antibiotic pretreatment could also be beneficial when FMT was administered in patients with ulcerative colitis without *Clostridioides difficile* infection [101].

Consensus guidelines recommend stopping antibiotic treatment between 24 and 48 hours before FMT [13, 27]. Our panel of experts recommends stopping antibiotic use 48 hours prior to FMT. A longer washout period of 4 days may be reasonable for vancomycin because inhibitory concentrations can remain in stool for 4 to 5 days after suspending therapy [102]. Therefore, statement 4.2 was rephrased for more flexibility depending on the antibiotic treatment.

Faecal delivery

Means of faecal delivery

FMT can be administered via upper gastrointestinal routes (through gastroscope, nasojejunal tube, or oral capsule) or lower gastrointestinal routes (through colonoscopy, sigmoidoscopy, or retention enema). Supplementary table S9 summarises the expert statements on this topic.

Lower gastrointestinal route

FMT administration via colonoscopy is a clearly established method in *Clostridioides difficile* infection [1, 103]. According to the Europe-wide survey that took place in FMT centres in 2020, most centres preferred colonoscopy as the FMT delivery method [104]. Following all recent consensuses, our expert panel stated that when delivered through colonoscopy, the stool should preferably be administered in the right colon to increase the retention time (statement 5.1) [27, 65, 105]. However, in cases of severe colitis, the faecal suspension could be administered in the left colon for safety reasons.

Last year, a published meta-analysis concluded that *Clostridioides difficile* infection cure rates with colonoscopy-administered FMT were superior to those of FMT administered via nasogastric tube or enema, whereas the cure rates with capsule FMT were comparable to those of colonoscopy-administered FMT [106].

Independent of the route of administration, the cure rate of *Clostridioides difficile* infection after FMT is higher with repeated FMT than with a single administration. This is particularly true for enema-administered FMT, for which the response rises from 56% to 92% [87]. Enemas can be a good alternative to colonoscopy because of their ease of administration and reduced invasiveness, but they need to be repeated to achieve similar high cure rates of *Clostridioides difficile* infection to those for colonoscopy [107, 108]. To increase the retention time, previous consensus and our expert panel recommend that the patient should retain the stool for at least 30 minutes after the infusion while maintaining a supine position (statement 5.3) [27, 65]. Failed retention contributes to response failure, and

we encourage a careful selection of eligible patients with a good understanding of the instructions and preserved continence.

Upper gastrointestinal route

Multiple RCTs and meta-analyses support the use of oral capsule FMT as an effective treatment for *Clostridioides difficile* infection, reporting similar cure rates compared to FMT via colonoscopy [97, 106, 109].

This justifies statement 5.4.

FMT administration via nasogastric tube (NGT) is more controversial.

Its efficiency in *Clostridioides difficile* infection has been demonstrated, and it could be more appealing because it is less invasive than colonoscopy, especially in patients with an inflamed bowel [2, 110, 111].

However, a review article and a recent meta-analysis showed that NGT FMT had inferior efficacy compared with colonoscopy [106, 112]. Furthermore, it was associated with more complications (regurgitations, vomiting, and broncho-aspiration) [113]. Additionally, from the patient's perspective, it seems to be the most unappealing application route [114]. Considering this information, our expert panel favours other ways of administration when possible.

If FMT is administered with NGT, preventive measures should be implemented to minimise risks, such as maintaining a 45° upright position during the 4 hours following the delivery (statement 5.2) [27, 113].

A question that remains unanswered regarding upper gastrointestinal administration FMT is what impact gastric acidity has and how it influences the engraftment of transplanted microorganisms [105, 115]

The above data refer to FMT in *Clostridioides difficile* infection. In patients with ulcerative colitis, the same modalities of administration − repeated enemas with and without initial colonoscopy and oral capsules − have been studied and have shown efficacy [39–41, 43, 44]. With nasoduodenal tube administration, more disease improvement was observed in the FMT group compared with the placebo group, but this difference was not statistically significant, possibly because the study population was too small [42]. In the absence of head-to-head trials, we cannot easily compare the efficacy of each modality of administration.

In conclusion, the route of FMT application, regardless of its indication, should be guided by the complication risk of each patient and local expertise.

Repeated FMT

In severe *Clostridioides difficile* infection, repetition of faecal infusion has shown better results for inducing clinical remission compared with a single administration [27, 116, 117].

In ulcerative colitis, repeated FMTs have been reported to increase the success rate, but the optimal frequency remains to be determined [27].

Several stool donors

In ulcerative colitis, it is not known whether individual-donor protocols and pooled multi-donor protocols have different impacts on the effectiveness of the FMT, as these strategies have not been compared head-to-head. However, a super donor phenomenon has been suggested in two studies, in which an increased response was observed in patients who received stool from a particular donor [40,43]. This supports the hypothesis that FMT efficacy could be improved by carefully selecting donors, but the exact selection criteria are unknown [118].

In chronic pouchitis, multiple studies have been performed to assess the response to FMT. Interestingly, only one multi-donor FMT study showed a statistically significant remission rate [119]. By contrast, studies that used a single donor's stool have not shown results in favour of FMT [120]. Other parameters also differed between the studies (delivery method and administration frequency), making it difficult to draw firm conclusions.

Multi-donor FMTs have the disadvantage of complexifying pharmacovigilance in cases of adverse events, raising safety concerns.

Safety considerations

Overall, FMT is a safe procedure, and our expert panel made the statements summarised in supplementary table S12 [121].

It is important to distinguish the risks attributable to the delivery method, such as perforation or aspiration risk, from those attributable to FMT itself.

Most FMT adverse events are mild and self-limiting, and they disappear within a few days. They consist of fever, abdominal discomfort (cramps, bloating, and flatulence), and changes in stool consistency (diarrhoea and constipation) [122–124].

According to a systematic review of the FMT studies published over the past 20 years, the most frequently reported gastrointestinal FMT-related adverse events include diarrhoea (in 10% of cases), abdominal discomfort, pain, or cramping (in 7% of cases), nausea or vomiting (in 3% of cases), and flatulence (in 3% of cases) [124]. Severe adverse events were reported in 1.4% of patients who underwent FMT. Interestingly, all the FMT-related severe adverse events occurred in the subgroup of patients with mucosal barrier injuries. Over the past 20 years, five FMT-related deaths (out of a total of 5688 FMT administrations) were declared. Four were a consequence of aspiration (one during colonoscopy sedation and three after inhalation of the gastroscopy-administered faecal suspension). The remaining FMT-related death was due to resistant *E. coli* bacteraemia. Recent systematic reviews have shown that FMT treatment via the upper gastrointestinal route was associated with a higher incidence of adverse events and severe adverse events [122, 124]. This can be partially explained by the known increased aspiration risk, but unspecific adverse events, such as abdominal discomfort, were described more frequently [122, 125].

The risk of infectious complications after FMT due to pathogen transfer was addressed earlier in this article, and it can be minimised by vigorous screening [65]. As was the case when the SARS-CoV-2 pandemic began, it is important to continue adapting procedures with the arrival of new pathogens [74]. Recently, the FDA issued a safety alert regarding the use of FMT during the current monkey-

pox outbreak, emphasising the need to stay updated and flexible [126].

Long-term adverse events are more difficult to determine. Long-term donor/recipient traceability and centralised databases are valuable in addressing the long-term safety concerns of FMT [104]. Many concerns still exist regarding the risk of transmission of non-infectious diseases, such as metabolic diseases (e.g. obesity), immune-mediated diseases, and procarcinogenic bacteria [127, 128]. A long-term safety study with a mean follow-up of over 1 year reported the development of new disorders after FMT (neuropathy, Sjögren's disease, idiopathic thrombopenic purpura, and rheumatoid arthritis) but was not able to determine whether this was associated with FMT [129]. A recent cohort study included 1000 patients with more than 1 year follow-up after FMT; the results did not show an increased risk of immune-mediated disease (rheumatoid arthritis, psoriasis, or IBD), irritable bowel syndrome, diabetes, hypertension, or stroke in patients treated with FMT compared with patients treated with antibiotics [130]. However, a slightly elevated risk of myocardial infarctions was observed in the FMT group. Furthermore, confounding bias was likely because the patients with *Clostridioides difficile* infection treated with FMT tended to have a higher Charlson comorbidity score and thus might have had a different baseline cardiovascular profile than their counterparts in the control group.

Several studies have suggested worsening IBD activity following FMT, motivating meta-analyses [38, 131]; according to high-quality studies and RCTs, the risk of IBD activity worsening is 4.6%. This is considered a marginal risk and may also reflect the natural course of IBD.

Most long-term safety data concern FMT for *Clostridioides difficile* infection because it is a longer established indication.

The safety profile of FMT for ulcerative colitis seems to be similar to that for *Clostridioides difficile* infection, as the same adverse events have been reported [43, 48]. Additionally, rectal abscesses were observed after infusion of both faeces and placebo enemas [40]. This could be associated with the administration method or IBD itself.

Limitations

The current article summarises the position of experts in gastroenterology, which is based on current guidelines, literature review, and clinical expertise. This article is not a systematic review, and grey literature may have been omitted.

Conclusion

Currently, robust evidence supports the use of FMT for *Clostridioides difficile* infection. FMT can also be effective in ulcerative colitis and should be considered in selected patients who are refractory to standard therapies. FMT can only be offered off-label to these patients at the moment. This paper highlights the need for updated regulations to make FMT more accessible to patients who could benefit from it, preventing the use of do-it-yourself FMTs and exposure to significant risks. We hope that the expert statements detailed in this article will serve as a framework for the standardised use of FMT in Switzerland.

FMT is generally well-tolerated and safe. Extensive donor screening is necessary to limit infectious and non-infectious disease transmission. The traceability of donors, an important factor to improve safety, can be offered by specialised FMT centres.

FMT administration via the lower gastrointestinal tract seems to be the optimal administration method, with fewer adverse events, but the selected route should ultimately be based on local expertise, patient characteristics, and indication. With the expected increase in FMT indications, transitioning to treatment modalities other than colonoscopy, such as oral capsules, could be necessary to improve logistics. It is important to keep in mind that most FMT studies have focused on *Clostridioides difficile* infection, and their findings and recommendations should not be generalised to emerging indications. This refers, for example, to the stool amount and the route and frequency of administration as well as pre-FMT preparation (bowel preparation and antibiotic treatment).

Many questions remain unanswered, particularly regarding the determination and selection of donors with the most adequate microbiota profile as well as the prediction of responses in the recipients.

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References

1. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol. 2013 Apr;108(4):500–8. http://dx.doi.org/10.1038/ajg.2013.59.
2. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013 Jan;368(5):407–15. http://dx.doi.org/10.1056/NEJMoa1205037.
3. Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclassification of Clostridium difficile as Clostridioides difficile (Hall and O'Toole 1935) Prévot 1938. Anaerobe. 2016 Aug;40:95–9. http://dx.doi.org/10.1016/j.anaerobe.2016.06.008.
4. D Goldenberg S, Merrick B; D. Goldenberg S. The role of faecal microbiota transplantation: looking beyond *Clostridioides difficile* infection. Ther Adv Infect Dis. 2021 Jan;8:2049936120981526. http://dx.doi.org/10.1177/2049936120981526.
5. Tilg H, Kaser A. Gut microbiome, obesity, and metabolic dysfunction. J Clin Invest. 2011 Jun;121(6):2126–32. http://dx.doi.org/10.1172/JCI58109.
6. De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. Clin Exp Immunol. 2019 Jan;195(1):74–85. http://dx.doi.org/10.1111/cei.13158.
7. Najafi S, Majidpoor J, Mortezaee K. The impact of microbiota on PD-1/PD-L1 inhibitor therapy outcomes: A focus on solid tumors. Life Sci. 2022 Dec;310:121138. http://dx.doi.org/10.1016/j.lfs.2022.121138.
8. Fehily SR, Basnayake C, Wright EK, Kamm MA. Fecal microbiota transplantation therapy in Crohn's disease: systematic review. J Gastroenterol Hepatol. 2021 Oct;36(10):2672–86. http://dx.doi.org/10.1111/jgh.15598.
9. Tan P, Li X, Shen J, Feng Q. Fecal Microbiota Transplantation for the Treatment of Inflammatory Bowel Disease: an Update. Front Pharmacol. 2020 Sep;11:574533. http://dx.doi.org/10.3389/fphar.2020.574533.
10. Borody TJ, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. Curr Gastroenterol Rep. 2013 Aug;15(8):337. http://dx.doi.org/10.1007/s11894-013-0337-1.
11. Terveer EM, van Beurden YH, Goorhuis A, Seegers JF, Bauer MP, van Nood E, et al. How to: establish and run a stool bank. Clin Microbiol In-

fect. 2017 Dec;23(12):924–30. http://dx.doi.org/10.1016/j.cmi.2017.05.015.
12. Transplantation de microbiote fécal : de l'évidence aux réalités du terrain. Rev Med Suisse n.d. https://www.revmed.ch/revue-medicale-suisse/2021/revue-medicale-suisse-734/transplantation-de-microbiote-fecal-de-l-evidence-aux-realites-du-terrain (accessed July 22, 2022).
13. Keller JJ, Ooijevaar RE, Hvas CL, Terveer EM, Lieberknecht SC, Högenauer C, et al. A standardised model for stool banking for faecal microbiota transplantation: a consensus report from a multidisciplinary UEG working group. United European Gastroenterol J. 2021 Mar;9(2):229–47. http://dx.doi.org/10.1177/2050640620967898.
14. Keller JJ, Vehreschild MJ, Hvas CL, Jørgensen SM, Kupciskas J, Link A, et al.; UEG working group of the Standards and Guidelines initiative Stool banking for FMT. Stool for fecal microbiota transplantation should be classified as a transplant product and not as a drug. United European Gastroenterol J. 2019 Dec;7(10):1408–10. http://dx.doi.org/10.1177/2050640619887579.
15. Evaluation of the EU legislation on blood, tissues and cells n.d. https://health.ec.europa.eu/blood-tissues-cells-and-organs/overview/evaluation-eu-legislation-blood-tissues-and-cells_en (accessed November 6, 2022).
16. Revision of the EU legislation on blood, tissues and cells n.d. https://health.ec.europa.eu/blood-tissues-cells-and-organs/overview/revision-eu-legislation-blood-tissues-and-cells_en (accessed November 6, 2022).
17. European Directorate for the Quality of Medicines & HealthCare. Guide to the quality and safety of tissues and cells for human application. vol. 5th ed. EDQM Council of Europe; 2022.
18. Swissmedic 2019 © Copyright. Advanced Therapy Medicinal Products, transplants and procedures n.d. https://www.swissmedic.ch/swissmedic/en/home/services/documents/transplantatprodukte.html (accessed July 22, 2022).
19. Kelly CR, Fischer M, Allegretti JR, LaPlante K, Stewart DB, Limketkai BN, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. Am J Gastroenterol. 2021 Jun;116(6):1124–47. http://dx.doi.org/10.14309/ajg.0000000000001278.
20. van Prehn J, Reigadas E, Vogelzang EH, Bouza E, Hristea A, Guery B, et al.; Guideline Committee of the European Study Group on Clostridioides difficile. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults. Clin Microbiol Infect. 2021 Dec;27 Suppl 2:S1–21. http://dx.doi.org/10.1016/j.cmi.2021.09.038.
21. Allegretti JR, Marcus J, Storm M, Sitko J, Kennedy K, Gerber GK, et al. Clinical Predictors of Recurrence After Primary Clostridioides difficile Infection: A Prospective Cohort Study. Dig Dis Sci. 2020 Jun;65(6):1761–6. http://dx.doi.org/10.1007/s10620-019-05900-3.
22. Johnson S, Louie TJ, Gerding DN, Cornely OA, Chasan-Taber S, Fitts D, et al.; Polymer Alternative for CDI Treatment (PACT) investigators. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. Clin Infect Dis. 2014 Aug;59(3):345–54. http://dx.doi.org/10.1093/cid/ciu313.
23. Infection à Clostridioides difficile : approches thérapeutiques diverses. Rev Med Suisse n.d. https://www.revmed.ch/revue-medicale-suisse/2022/revue-medicale-suisse-799/infection-a-clostridioides-difficile-approches-therapeutiques-diverses (accessed October 17, 2022).
24. Johnson S, Lavergne V, Skinner AM, Gonzales-Luna AJ, Garey KW, Kelly CP, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021 Sep;73(5):e1029–44. http://dx.doi.org/10.1093/cid/ciab549.
25. Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection: A Randomized Trial. Ann Intern Med. 2016 Nov;165(9):609–16. http://dx.doi.org/10.7326/M16-0271.
26. Cammarota G, Ianiro G, Kelly CR, Mullish BH, Allegretti JR, Kassam Z, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. Gut. 2019 Dec;68(12):2111–21. http://dx.doi.org/10.1136/gutjnl-2019-319548.
27. Cammarota G, Ianiro G, Tilg H, Rajilić-Stojanović M, Kump P, Satokari R, et al.; European FMT Working Group. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017 Apr;66(4):569–80. http://dx.doi.org/10.1136/gutjnl-2016-313017.
28. Hvas CL, Dahl Jørgensen SM, Jørgensen SP, Storgaard M, Lemming L, Hansen MM, et al. Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent Clostridium difficile Infection. Gastroenterology. 2019 Apr;156(5):1324–1332.e3. http://dx.doi.org/10.1053/j.gastro.2018.12.019.
29. Kelly CR, Yen EF, Grinspan AM, Kahn SA, Atreja A, Lewis JD, et al. Fecal Microbiota Transplantation Is Highly Effective in Real-World Practice: Initial Results From the FMT National Registry. Gastroenterology. 2021 Jan;160(1):183–192.e3. http://dx.doi.org/10.1053/j.gastro.2020.09.038.
30. Cammarota G, Masucci L, Ianiro G, Bibbò S, Dinoi G, Costamagna G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther. 2015 May;41(9):835–43. http://dx.doi.org/10.1111/apt.13144.
31. Shaffer SR, Witt J, Targownik LE, Kao D, Lee C, Smieliauskas F, et al. Cost-effectiveness analysis of a fecal microbiota transplant center for treating recurrent C.difficile infection. J Infect. 2020 Nov;81(5):758–65. http://dx.doi.org/10.1016/j.jinf.2020.09.025.
32. Roshan N, Clancy AK, Borody TJ. Faecal Microbiota Transplantation is Effective for the Initial Treatment of Clostridium difficile Infection: A Retrospective Clinical Review. Infect Dis Ther. 2020 Dec;9(4):935–42. http://dx.doi.org/10.1007/s40121-020-00339-w.
33. Baunwall SM, Andreasen SE, Hansen MM, Kelsen J, Høyer KL, Rågård N, et al. Faecal microbiota transplantation for first or second Clostridioides difficile infection (EarlyFMT): a randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol Hepatol. 2022 Dec;7(12):1083–91. http://dx.doi.org/10.1016/S2468-1253(22)00276-X.
34. Quraishi MN, Widlak M, Bhala N, Moore D, Price M, Sharma N, et al. Systematic review with meta-analysis: the efficacy of faecal micro-biota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. Aliment Pharmacol Ther. 2017 Sep;46(5):479–93. http://dx.doi.org/10.1111/apt.14201.
35. Song YN, Yang DY, Veldhuyzen van Zanten S, Wong K, McArthur E, Song CZ, et al. Fecal Microbiota Transplantation for Severe or Fulminant *Clostridioides difficile* Infection: Systematic Review and Meta-analysis. J Can Assoc Gastroenterol. 2021 Jul;5(1):e1–11. http://dx.doi.org/10.1093/jcag/gwab023.
36. Tariq R, Syed T, Yadav D, Prokop LJ, Singh S, Loftus EV, et al. Outcomes of Fecal Microbiota Transplantation for C. difficile Infection in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. J Clin Gastroenterol. 2021; http://dx.doi.org/10.1097/MCG.0000000000001633.
37. Allegretti JR, Kelly CR, Grinspan A, Mullish BH, Hurtado J, Carrel-las M, et al. Inflammatory Bowel Disease Outcomes Following Fecal Microbiota Transplantation for Recurrent C. difficile Infection. Inflamm Bowel Dis. 2021 Aug;27(9):1371–8. http://dx.doi.org/10.1093/ibd/izaa283.
38. Qazi T, Amaratunga T, Barnes EL, Fischer M, Kassam Z, Allegretti JR. The risk of inflammatory bowel disease flares after fecal microbiota transplantation: systematic review and meta-analysis. Gut Microbes. 2017 Nov;8(6):574–88. http://dx.doi.org/10.1080/19490976.2017.1353848.
39. Březina J, Bajer L, Wohl P, Ďuricová D, Hrabák P, Novotný A, et al. Fecal Microbial Transplantation versus Mesalamine Enema for Treatment of Active Left-Sided Ulcerative Colitis-Results of a Randomized Controlled Trial. J Clin Med. 2021 Jun;10(13):2753. http://dx.doi.org/10.3390/jcm10132753.
40. Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, et al. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology. 2015 Jul;149(1):102–109.e6. http://dx.doi.org/10.1053/j.gastro.2015.04.001.
41. Haifer C, Paramsothy S, Kaakoush NO, Saikal A, Ghaly S, Yang T, et al. Lyophilised oral faecal microbiota transplantation for ulcerative colitis (LOTUS): a randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol Hepatol. 2022 Feb;7(2):141–51. http://dx.doi.org/10.1016/S2468-1253(21)00400-3.
42. Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology. 2015 Jul;149(1):110–118.e4. http://dx.doi.org/10.1053/j.gastro.2015.03.045.
43. Paramsothy S, Kamm MA, Kaakoush NO, Walsh AJ, van den Bo-gaerde J, Samuel D, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet. 2017 Mar;389(10075):1218–28. http://dx.doi.org/10.1016/S0140-6736(17)30182-4.

44. Costello SP, Hughes PA, Waters O, Bryant RV, Vincent AD, Blatchford P, et al. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial. JAMA. 2019 Jan;321(2):156–64. http://dx.doi.org/10.1001/jama.2018.20046.
45. Costello S, Waters O, Bryant R, Katsikeros R, Makanyanga J, Schoeman M, et al. OP036 Short duration, low intensity pooled faecal microbiota transplantation induces remission in patients with mild-moderately active ulcerative colitis: a randomised controlled trial. J Crohn's Colitis. 2017;11 suppl_1:S23. http://dx.doi.org/10.1093/ecco-jcc/jjx002.035.
46. Lavelle A, Sokol H. Understanding and predicting the efficacy of FMT. Nat Med. 2022 Sep;28(9):1759–60. http://dx.doi.org/10.1038/s41591-022-01991-0.
47. Herrlinger KR, Stange EF. Twenty-five years of biologicals in IBD: what´s all the hype about? J Intern Med. 2021 Oct;290(4):806–25. http://dx.doi.org/10.1111/joim.13345.
48. Sood A, Mahajan R, Singh A, Midha V, Mehta V, Narang V, et al. Role of Faecal Microbiota Transplantation for Maintenance of Remission in Patients With Ulcerative Colitis: A Pilot Study. J Crohn's Colitis. 2019 Sep;13(10):1311–7. http://dx.doi.org/10.1093/ecco-jcc/jjz060.
49. Vaughn BP, Vatanen T, Allegretti JR, Bai A, Xavier RJ, Korzenik J, et al. Increased Intestinal Microbial Diversity Following Fecal Microbiota Transplant for Active Crohn's Disease. Inflamm Bowel Dis. 2016 Sep;22(9):2182–90. http://dx.doi.org/10.1097/MIB.0000000000000893.
50. Suskind DL, Brittnacher MJ, Wahbeh G, Shaffer ML, Hayden HS, Qin X, et al. Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn's disease. Inflamm Bowel Dis. 2015 Mar;21(3):556–63. http://dx.doi.org/10.1097/MIB.0000000000000307.
51. Gutin L, Piceno Y, Fadrosh D, Lynch K, Zydek M, Kassam Z, et al. Fecal microbiota transplant for Crohn disease: A study evaluating safety, efficacy, and microbiome profile. United European Gastroenterol J. 2019 Jul;7(6):807–14. http://dx.doi.org/10.1177/2050640619845986.
52. Xiang L, Ding X, Li Q, Wu X, Dai M, Long C, et al. Efficacy of faecal microbiota transplantation in Crohn's disease: a new target treatment? Microb Biotechnol. 2020 May;13(3):760–9. http://dx.doi.org/10.1111/1751-7915.13536.
53. Yang Z, Bu C, Yuan W, Shen Z, Quan Y, Wu S, et al. Fecal Microbiota Transplant via Endoscopic Delivering Through Small Intestine and Colon: No Difference for Crohn's Disease. Dig Dis Sci. 2020 Jan;65(1):150–7. http://dx.doi.org/10.1007/s10620-019-05751-y.
54. Sokol H, Landman C, Seksik P, Berard L, Montil M, Nion-Larmurier I, et al.; Saint-Antoine IBD Network. Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. Microbiome. 2020 Feb;8(1):12. http://dx.doi.org/10.1186/s40168-020-0792-5.
55. Johnsen PH, Hilpüsch F, Valle PC, Goll R. The effect of fecal microbiota transplantation on IBS related quality of life and fatigue in moderate to severe non-constipated irritable bowel: secondary endpoints of a double blind, randomized, placebo-controlled trial. EBioMedicine. 2020 Jan;51:102562. http://dx.doi.org/10.1016/j.ebiom.2019.11.023.
56. Ooijevaar RE, Terveer EM, Verspaget HW, Kuijper EJ, Keller JJ. Clinical Application and Potential of Fecal Microbiota Transplantation. Annu Rev Med. 2019 Jan;70(1):335–51. http://dx.doi.org/10.1146/annurev-med-111717-122956.
57. Yu EW, Gao L, Stastka P, Cheney MC, Mahabamunuge J, Torres Soto M, et al. Fecal microbiota transplantation for the improvement of metabolism in obesity: the FMT-TRIM double-blind placebo-controlled pilot trial. PLoS Med. 2020 Mar;17(3):e1003051. http://dx.doi.org/10.1371/journal.pmed.1003051.
58. Vendrik KE, Ooijevaar RE, de Jong PR, Laman JD, van Oosten BW, van Hilten JJ, et al. Fecal Microbiota Transplantation in Neurological Disorders. Front Cell Infect Microbiol. 2020 Mar;10:98. http://dx.doi.org/10.3389/fcimb.2020.00098.
59. El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A, Hausken T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. Gut. 2020 May;69(5):859–67. http://dx.doi.org/10.1136/gutjnl-2019-319630.
60. El-Salhy M, Winkel R, Casen C, Hausken T, Gilja OH, Hatlebakk JG. Efficacy of Fecal Microbiota Transplantation for Patients With Irritable Bowel Syndrome at 3 Years After Transplantation. Gastroenterology. 2022 Oct;163(4):982–994.e14. http://dx.doi.org/10.1053/j.gastro.2022.06.020.
61. FMT in IBS. "We've Been Targeting Wrong Part of the Intestine." Medscape n.d. https://www.medscape.com/viewarticle/982505 (accessed October 22, 2022).
62. Xu F, Li N, Wang C, Xing H, Chen D, Wei Y. Clinical efficacy of fecal microbiota transplantation for patients with small intestinal bacterial overgrowth: a randomized, placebo-controlled clinic study. BMC Gastroenterol. 2021 Feb;21(1):54. http://dx.doi.org/10.1186/s12876-021-01630-x.
63. Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells (Text with EEA relevance). vol. 038. 2006.
64. Sokol H, Galperine T, Kapel N, Bourlioux P, Seksik P, Barbut F, et al.; French Group of Faecal microbiota Transplantation (FGFT). Faecal microbiota transplantation in recurrent Clostridium difficile infection: Recommendations from the French Group of Faecal microbiota Transplantation. Dig Liver Dis. 2016 Mar;48(3):242–7. http://dx.doi.org/10.1016/j.dld.2015.08.017.
65. Gweon TG, Lee YJ, Kim KO, Yim SK, Soh JS, Kim SY, et al.; Gut Microbiota and Therapy Research Group Under the Korean Society of Neurogastroenterology and Motility. Clinical Practice Guidelines for Fecal Microbiota Transplantation in Korea. J Neurogastroenterol Motil. 2022 Jan;28(1):28–42. http://dx.doi.org/10.5056/jnm21221.
66. Commissioner O of the. Fecal Microbiota for Transplantation: Safety Alert - Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms. FDA; 2020.
67. Terveer EM, van Gool T, Ooijevaar RE, Sanders IM, Boeije-Koppenol E, Keller JJ, et al.; Netherlands Donor Feces Bank (NDFB) Study Group. Human Transmission of Blastocystis by Fecal Microbiota Transplantation Without Development of Gastrointestinal Symptoms in Recipients. Clin Infect Dis. 2020 Dec;71(10):2630–6. http://dx.doi.org/10.1093/cid/ciz1122.
68. Aykur M, Calıskan Kurt C, Dirim Erdogan D, Biray Avcı C, Vardar R, Aydemir S, et al. Investigation of Dientamoeba fragilis Prevalence and Evaluation of Sociodemographic and Clinical Features in Patients with Gastrointestinal Symptoms. Acta Parasitol. 2019 Mar;64(1):162–70. http://dx.doi.org/10.2478/s11686-018-00017-5.
69. Chou A, Austin RL. Entamoeba Histolytica. StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
70. Mehta N, Wang T, Friedman-Moraco RJ, Carpentieri C, Mehta AK, Rouphael N, et al. Fecal Microbiota Transplantation Donor Screening Updates and Research Gaps for Solid Organ Transplant Recipients. J Clin Microbiol. 2022 Feb;60(2):e0016121. http://dx.doi.org/10.1128/JCM.00161-21.
71. DeFilipp Z, Bloom PP, Torres Soto M, Mansour MK, Sater MR, Huntley MH, et al. Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant. N Engl J Med. 2019 Nov;381(21):2043–50. http://dx.doi.org/10.1056/NEJMoa1910437.
72. Vendrik KE, Terveer EM, Kuijper EJ, Nooij S, Boeije-Koppenol E, Sanders IM, et al.; Netherlands Donor Faeces Bank Study Group. Periodic screening of donor faeces with a quarantine period to prevent transmission of multidrug-resistant organisms during faecal microbiota transplantation: a retrospective cohort study. Lancet Infect Dis. 2021 May;21(5):711–21. http://dx.doi.org/10.1016/S1473-3099(20)30473-4.
73. Hohmann EL. Faecal microbiota transplantation: more screening for old and new pathogens. Lancet Infect Dis. 2021 May;21(5):587–9. http://dx.doi.org/10.1016/S1473-3099(20)30850-1.
74. Ianiro G, Mullish BH, Kelly CR, Kassam Z, Kuijper EJ, Ng SC, et al. Reorganisation of faecal microbiota transplant services during the COVID-19 pandemic. Gut. 2020 Sep;69(9):1555–63. http://dx.doi.org/10.1136/gutjnl-2020-321829.
75. Manzoor SE, Zaman S, Whalley C, Inglis D, Bosworth A, Kidd M, et al. Multi-modality detection of SARS-CoV-2 in faecal donor samples for transplantation and in asymptomatic emergency surgical admissions. F1000 Res. 2021 May;10:373. http://dx.doi.org/10.12688/f1000research.52178.1.
76. Bastiaanssen TF, Cowan CS, Claesson MJ, Dinan TG, Cryan JF. Making Sense of … the Microbiome in Psychiatry. Int J Neuropsychopharmacol. 2019 Jan;22(1):37–52. http://dx.doi.org/10.1093/ijnp/pyy067.
77. Glassner KL, Abraham BP, Quigley EM. The microbiome and inflammatory bowel disease. J Allergy Clin Immunol. 2020 Jan;145(1):16–27. http://dx.doi.org/10.1016/j.jaci.2019.11.003.
78. Inoue Y, Shimojo N. Microbiome/microbiota and allergies. Semin Immunopathol. 2015 Jan;37(1):57–64. http://dx.doi.org/10.1007/s00281-014-0453-5.
79. Ruusunen A, Rocks T, Jacka F, Loughman A. The gut microbiome in anorexia nervosa: relevance for nutritional rehabilitation. Psychopharmacology (Berl). 2019 May;236(5):1545–58. http://dx.doi.org/10.1007/s00213-018-5159-2.

80. Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for Clostridium difficile infection after exposure to antibiotics. J Antimicrob Chemother. 2012 Mar;67(3):742–8. http://dx.doi.org/10.1093/jac/dkr508.
81. Becattini S, Taur Y, Pamer EG. Antibiotic-Induced Changes in the Intestinal Microbiota and Disease. Trends Mol Med. 2016 Jun;22(6):458–78. http://dx.doi.org/10.1016/j.molmed.2016.04.003.
82. Stefura T, Zapała B, Gosiewski T, Skomarovska O, Pędziwiatr M, Major P. Changes in the Composition of Oral and Intestinal Microbiota After Sleeve Gastrectomy and Roux-En-Y Gastric Bypass and Their Impact on Outcomes of Bariatric Surgery. Obes Surg. 2022 May;32(5):1439–50. http://dx.doi.org/10.1007/s11695-022-05954-9.
83. Mangiola F, Nicoletti A, Gasbarrini A, Ponziani FR. Gut microbiota and aging. Eur Rev Med Pharmacol Sci. 2018 Nov;22(21):7404–13. http://dx.doi.org/10.26355/eurrev_201811_16280.
84. Steele SR, Park GE, Johnson EK, Martin MJ, Stojadinovic A, Maykel JA, et al. The impact of age on colorectal cancer incidence, treatment, and outcomes in an equal-access health care system. Dis Colon Rectum. 2014 Mar;57(3):303–10. http://dx.doi.org/10.1097/DCR.0b013e3182a586e7.
85. Bénard MV, de Bruijn CM, Fenneman AC, Wortelboer K, Zeevenhoven J, Rethans B, et al. Challenges and costs of donor screening for fecal microbiota transplantations. PLoS One. 2022 Oct;17(10):e0276323. http://dx.doi.org/10.1371/journal.pone.0276323.
86. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis. 2011 Nov;53(10):994–1002. http://dx.doi.org/10.1093/cid/cir632.
87. Ianiro G, Maida M, Burisch J, Simonelli C, Hold G, Ventimiglia M, et al. Efficacy of different faecal microbiota transplantation protocols for *Clostridium difficile* infection: A systematic review and meta-analysis. United European Gastroenterol J. 2018 Oct;6(8):1232–44. http://dx.doi.org/10.1177/2050640618780762.
88. Osman M, Budree S, Kelly CR, Panchal P, Allegretti JR, Kassam Z, et al.; OpenBiome Collaborators. Effectiveness and Safety of Fecal Microbiota Transplantation for Clostridioides Difficile Infection: Results From a 5344-Patient Cohort Study. Gastroenterology. 2022 Jul;163(1):319–22. http://dx.doi.org/10.1053/j.gastro.2022.03.051.
89. Satokari R, Mattila E, Kainulainen V, Arkkila PE. Simple faecal preparation and efficacy of frozen inoculum in faecal microbiota transplantation for recurrent Clostridium difficile infection—an observational cohort study. Aliment Pharmacol Ther. 2015 Jan;41(1):46–53. http://dx.doi.org/10.1111/apt.13009.
90. Nicco C, Paule A, Konturek P, Edeas M. From Donor to Patient: Collection, Preparation and Cryopreservation of Fecal Samples for Fecal Microbiota Transplantation. Diseases. 2020 Apr;8(2):E9. http://dx.doi.org/10.3390/diseases8020009.
91. Tang G, Yin W, Liu W. Is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation in patients with recurrent or refractory Clostridium difficile infection: A meta-analysis? Diagn Microbiol Infect Dis. 2017 Aug;88(4):322–9. http://dx.doi.org/10.1016/j.diagmicrobio.2017.05.007.
92. Lee CH, Steiner T, Petrof EO, Smieja M, Roscoe D, Nematallah A, et al. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA. 2016 Jan;315(2):142–9. http://dx.doi.org/10.1001/jama.2015.18098.
93. Fadda HM. The Route to Palatable Fecal Microbiota Transplantation. AAPS PharmSciTech. 2020 Apr;21(3):114. http://dx.doi.org/10.1208/s12249-020-1637-z.
94. Jiang ZD, Ajami NJ, Petrosino JF, Jun G, Hanis CL, Shah M, et al. Randomised clinical trial: faecal microbiota transplantation for recurrent Clostridum difficile infection - fresh, or frozen, or lyophilised microbiota from a small pool of healthy donors delivered by colonoscopy. Aliment Pharmacol Ther. 2017 Apr;45(7):899–908. http://dx.doi.org/10.1111/apt.13969.
95. Jiang ZD, Jenq RR, Ajami NJ, Petrosino JF, Alexander AA, Ke S, et al. Safety and preliminary efficacy of orally administered lyophilized fecal microbiota product compared with frozen product given by enema for recurrent Clostridium difficile infection: A randomized clinical trial. PLoS One. 2018 Nov;13(11):e0205064. http://dx.doi.org/10.1371/journal.pone.0205064.
96. Jalanka J, Salonen A, Salojärvi J, Ritari J, Immonen O, Marciani L, et al. Effects of bowel cleansing on the intestinal microbiota. Gut. 2015 Oct;64(10):1562–8. http://dx.doi.org/10.1136/gutjnl-2014-307240.
97. Kao D, Roach B, Silva M, Beck P, Rioux K, Kaplan GG, et al. Effect of Oral Capsule- vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA. 2017 Nov;318(20):1985–93. http://dx.doi.org/10.1001/jama.2017.17077.
98. Tariq R, Hayat M, Pardi D, Khanna S. Predictors of failure after fecal microbiota transplantation for recurrent Clostridioides difficile infection: a systematic review and meta-analysis. Eur J Clin Microbiol Infect Dis. 2021 Jul;40(7):1383–92. http://dx.doi.org/10.1007/s10096-021-04163-z.
99. Chen QY, Tian HL, Yang B, Lin ZL, Zhao D, Ye C, et al. [Effect of intestinal preparation on the efficacy and safety of fecal microbiota transplantation treatment]. Zhonghua Wei Chang Wai Ke Za Zhi. 2020 Jul;23 Z1:48–55. http://dx.doi.org/10.3760/cma.j.cn.441530-20200418-00225.
100. Fischer M, Sipe B, Cheng YW, Phelps E, Rogers N, Sagi S, et al. Fecal microbiota transplant in severe and severe-complicated Clostridium difficile: A promising treatment approach. Gut Microbes. 2017 May;8(3):289–302. http://dx.doi.org/10.1080/19490976.2016.1273998.
101. Smith BJ, Piceno Y, Zydek M, Zhang B, Syriani LA, Terdiman JP, et al. Strain-resolved analysis in a randomized trial of antibiotic pretreatment and maintenance dose delivery mode with fecal microbiota transplant for ulcerative colitis. Sci Rep. 2022 Apr;12(1):5517. http://dx.doi.org/10.1038/s41598-022-09307-5.
102. Abujamel T, Cadnum JL, Jury LA, Sunkesula VC, Kundrapu S, Jump RL, et al. Defining the vulnerable period for re-establishment of Clostridium difficile colonization after treatment of C. difficile infection with oral vancomycin or metronidazole. PLoS One. 2013 Oct;8(10):e76269. http://dx.doi.org/10.1371/journal.pone.0076269.
103. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. J Clin Gastroenterol. 2014 Sep;48(8):693–702. http://dx.doi.org/10.1097/MCG.0000000000000046.
104. Baunwall SM, Terveer EM, Dahlerup JF, Erikstrup C, Arkkila P, Vehreschild MJ, et al. The use of Faecal Microbiota Transplantation (FMT) in Europe: A Europe-wide survey. Lancet Reg Health Eur. 2021 Jul;9:100181. http://dx.doi.org/10.1016/j.lanepe.2021.100181.
105. Mullish BH, Quraishi MN, Segal JP, McCune VL, Baxter M, Marsden GL, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. J Hosp Infect. 2018 Sep;100 Suppl 1:S1–31. http://dx.doi.org/10.1016/j.jhin.2018.07.037.
106. Ramai D, Zakhia K, Fields PJ, Ofosu A, Patel G, Shahnazarian V, et al. Fecal Microbiota Transplantation (FMT) with Colonoscopy Is Superior to Enema and Nasogastric Tube While Comparable to Capsule for the Treatment of Recurrent Clostridioides difficile Infection: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2021 Feb;66(2):369–80. http://dx.doi.org/10.1007/s10620-020-06185-7.
107. Lee CH, Belanger JE, Kassam Z, Smieja M, Higgins D, Broukhanski G, et al. The outcome and long-term follow-up of 94 patients with recurrent and refractory Clostridium difficile infection using single to multiple fecal microbiota transplantation via retention enema. Eur J Clin Microbiol Infect Dis. 2014 Aug;33(8):1425–8. http://dx.doi.org/10.1007/s10096-014-2088-9.
108. Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent Clostridium difficile Infection: An Open-Label, Randomized Controlled Trial - PubMed n.d. https://pubmed.ncbi.nlm.nih.gov/28011612/ (accessed August 19, 2022).
109. Du C, Luo Y, Walsh S, Grinspan A. Oral Fecal Microbiota Transplant Capsules Are Safe and Effective for Recurrent Clostridioides difficile Infection: A Systematic Review and Meta-Analysis. J Clin Gastroenterol. 2021 Apr;55(4):300–8. http://dx.doi.org/10.1097/MCG.0000000000001495.
110. Terveer EM, van Beurden YH, van Dorp S, Keller JJ, Kuijper EJ. Is the Lower Gastrointestinal Route Really Preferred Over the Upper Gastrointestinal Route for Fecal Microbiota Transfer? J Clin Gastroenterol. 2016;50(10):895. http://dx.doi.org/10.1097/MCG.0000000000000595.
111. Youngster I, Sauk J, Pindar C, Wilson RG, Kaplan JL, Smith MB, et al. Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. Clin Infect Dis. 2014 Jun;58(11):1515–22. http://dx.doi.org/10.1093/cid/ciu135.
112. Furuya-Kanamori L, Doi SA, Paterson DL, Helms SK, Yakob L, McKenzie SJ, et al. Upper Versus Lower Gastrointestinal Delivery for Transplantation of Fecal Microbiota in Recurrent or Refractory Clostrid-

ium difficile Infection: A Collaborative Analysis of Individual Patient Data From 14 Studies. J Clin Gastroenterol. 2017 Feb;51(2):145–50. http://dx.doi.org/10.1097/MCG.0000000000000511.

113. van Beurden YH, de Groot PF, van Nood E, Nieuwdorp M, Keller JJ, Goorhuis A. Complications, effectiveness, and long term follow-up of fecal microbiota transfer by nasoduodenal tube for treatment of recurrent *Clostridium difficile* infection. United European Gastroenterol J. 2017 Oct;5(6):868–79. http://dx.doi.org/10.1177/2050640616678099.
114. Zipursky JS, Sidorsky TI, Freedman CA, Sidorsky MN, Kirkland KB. Patient attitudes toward the use of fecal microbiota transplantation in the treatment of recurrent Clostridium difficile infection. Clin Infect Dis. 2012 Dec;55(12):1652–8. http://dx.doi.org/10.1093/cid/cis809.
115. Hong AS, Yu WY, Hong JM, Cross CL, Azab M, Ohning G, et al. Proton pump inhibitor in upper gastrointestinal fecal microbiota transplant: A systematic review and analysis. J Gastroenterol Hepatol. 2020 Jun;35(6):932–40. http://dx.doi.org/10.1111/jgh.14958.
116. Weingarden AR, Hamilton MJ, Sadowsky MJ, Khoruts A. Resolution of severe Clostridium difficile infection following sequential fecal microbiota transplantation. J Clin Gastroenterol. 2013 Sep;47(8):735–7. http://dx.doi.org/10.1097/MCG.0b013e31829004ae.
117. Ianiro G, Masucci L, Quaranta G, Simonelli C, Lopetuso LR, Sanguinetti M, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory Clostridium difficile infection-single versus multiple infusions. Aliment Pharmacol Ther. 2018 Jul;48(2):152–9. http://dx.doi.org/10.1111/apt.14816.
118. Danne C, Rolhion N, Sokol H. Recipient factors in faecal microbiota transplantation: one stool does not fit all. Nat Rev Gastroenterol Hepatol. 2021 Jul;18(7):503–13. http://dx.doi.org/10.1038/s41575-021-00441-5.
119. Stallmach A, Lange K, Buening J, Sina C, Vital M, Pieper DH. Fecal Microbiota Transfer in Patients With Chronic Antibiotic-Refractory Pouchitis. Am J Gastroenterol. 2016 Mar;111(3):441–3. http://dx.doi.org/10.1038/ajg.2015.436.
120. Selvig D, Piceno Y, Terdiman J, Zydek M, Umetsu SE, Balitzer D, et al. Fecal Microbiota Transplantation in Pouchitis: Clinical, Endoscopic, Histologic, and Microbiota Results from a Pilot Study. Dig Dis Sci. 2020 Apr;65(4):1099–106. http://dx.doi.org/10.1007/s10620-019-05715-2.
121. Park SY, Seo GS. Fecal Microbiota Transplantation: Is It Safe? Clin Endosc. 2021 Mar;54(2):157–60. http://dx.doi.org/10.5946/ce.2021.072.
122. Wang S, Xu M, Wang W, Cao X, Piao M, Khan S, et al. Systematic Review: Adverse Events of Fecal Microbiota Transplantation. PLoS One. 2016 Aug;11(8):e0161174. http://dx.doi.org/10.1371/journal.pone.0161174.
123. Baxter M, Colville A. Adverse events in faecal microbiota transplant: a review of the literature. J Hosp Infect. 2016 Feb;92(2):117–27. http://dx.doi.org/10.1016/j.jhin.2015.10.024.
124. Marcella C, Cui B, Kelly CR, Ianiro G, Cammarota G, Zhang F. Systematic review: the global incidence of faecal microbiota transplantation-related adverse events from 2000 to 2020. Aliment Pharmacol Ther. 2021 Jan;53(1):33–42. http://dx.doi.org/10.1111/apt.16148.
125. Baxter M, Ahmad T, Colville A, Sheridan R. Fatal Aspiration Pneumonia as a Complication of Fecal Microbiota Transplant. Clin Infect Dis. 2015 Jul;61(1):136–7. http://dx.doi.org/10.1093/cid/civ247.
126. Research C for BE and. Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Additional Safety Protections Pertaining to Monkeypox Virus. FDA; 2022.
127. Drewes JL, Corona A, Sanchez U, Fan Y, Hourigan SK, Weidner M, et al. Transmission and clearance of potential procarcinogenic bacteria during fecal microbiota transplantation for recurrent *Clostridioides difficile*. JCI Insight. 2019 Oct;4(19):e130848. http://dx.doi.org/10.1172/jci.insight.130848.
128. Alang N, Kelly CR. Weight gain after fecal microbiota transplantation. Open Forum Infect Dis. 2015 Feb;2(1):ofv004. http://dx.doi.org/10.1093/ofid/ofv004.
129. Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. Am J Gastroenterol. 2012 Jul;107(7):1079–87. http://dx.doi.org/10.1038/ajg.2012.60.
130. Dawwas GK, Brensinger CM, Vajravelu RK, Wu Q, Kelly CR, Laine L, et al. Long-term Outcomes Following Multiply Recurrent Clostridioides difficile Infection and Fecal Microbiota Transplantation. Clin Gastroenterol Hepatol. 2022 Apr;20(4):806–816.e6. http://dx.doi.org/10.1016/j.cgh.2020.12.004.
131. De Leon LM, Watson JB, Kelly CR. Transient flare of ulcerative colitis after fecal microbiota transplantation for recurrent Clostridium difficile infection. Clin Gastroenterol Hepatol. 2013 Aug;11(8):1036–8. http://dx.doi.org/10.1016/j.cgh.2013.04.045.

Appendix: supplementary tables

Table S1 - Expert statements concerning FMT in CDI

Statements	**Mean rating**	**Voting rounds**
1.1 FMT should be used in recurrent *C. difficile* enterocolitis (after antibiotics)	4.0	2
1.2 FMT should not be used in a first episode of *C. difficile* enterocolitis	3.9	1
1.3 FMT should be used in *C. difficile* enterocolitis refractory to antibiotics	4.0	2
1.4 FMT is an effective treatment option in fulminant *C. difficile* enterocolitis.	3,7	2
1.5 FMT may be considered in *C. difficile* enterocolitis in IBD patients	3.4	1
1.6 In either indication (*C. difficile* or IBD), FMT should not be offered as a primary therapeutic procedure	3.4	1

Table S2 - Expert statements concerning FMT in IBD

Statement	**Mean rating**	**Voting rounds**
1.7 FMT may be a therapeutic option in active UC.	3	1
1.8 In active severe UC, FMT should not be used as a rescue therapy before colectomy.	3.6	2
1.9 FMT is not recommendable, outside of a study protocol, for Crohn's Disease.	3.7	1

Table S3 - Expert statements concerning FMT for other indications

Statement:	**Mean rating**	**Voting rounds**
1.10 Currently there is not enough evidence to use FMT in these indications:		2
- Autism	4.0	
- Depression	4.0	
- Multiple sclerosis	4.0	
- Irritable bowel syndrome (IBS)	4.0	
- Idiopathic thrombocytopenic purpura	4.0	
- Obesity	4.0	
- Chronic fatigue	4.0	

Table S4 - Expert statements concerning donor screening - anamnestic assessment

Statement	**Mean rating**	**Voting rounds**
2.1 Stool donors have to undergo a mandatory evaluation to assess following points:		
- Age >18 and <70 {2.1.1}	4.0	1
- BMI >17 kg/m^2 and <30 kg/m^2 {2.1.2}	3.7	2
- No autoimmune diseases {2.1.3}	4.0	1
- No allergies nor atopy {2.1.4}	3.7	1
- No malignant diseases {2.1.5}	4.0	1
- No psychiatric diseases {2.1.6}	4.0	1
- No risk behavior (drugs, unprotected sexual relations, recent tattoo/piercing) {2.1.7}	4.0	1
- No major intestinal surgery {2.1.8}	3.6	2
- No parasitic infections {2.1.9}	3.9	1
- No intestinal infection within 3 months {2.1.10}	3.9	1
- No antibiotics within 3 months {2.1.11}	3.9	1
- No current immune suppressive treatment {2.1.12}	3.9	1
- No live vaccines within 6 months {2.1.13}	4.0	2
- No SARS-CoV-2 infection within 6 months {2.1.14}	4.0	1

Table S5 - Expert statements concerning donor screening - serological evaluation

Statements	**Mean rating**	**Voting rounds**
2.2 The following laboratory tests should be performed in stool donors and come back normal:		
− CMV, EBV and Toxoplasmosis serology (only if recipient is immunocompromised) {2.2.1}	4,0	2
− Hepatitis A virus {2.2.2}	3.9	1
− Hepatitis B virus {2.2.3}	3.9	1
− Hepatits C virus {2.2.4}	3.9	1
− Hepatitis E virus {2.2.5}	3.6	1
− HIV 1 and HIV−2 {2.2.6}	3.9	1
− Complete blood cell count with differential {2.2.7}	3.7	1
− CRP {2.2.8}	3.7	1
− Syphilis−Screening (LUES) {2.2.9}	3.7	1
− Tuberculosis−Screening (QuantiFERON−TB Gold®) {2.2.10}	3.7	1
− Multidrug−resistant bacteria (MRSA, CRE, VRE, ESBL) {2.2.11}	3.6	1

Table S6 − Expert statements concerning donor screening − feces evaluation

Statements	**Mean rating**	**Voting rounds**
2.3 The following laboratory tests should be performed in stool donors:		
− Negative fecal multiplex PCR testing (Salmonella sp, Campylobacter sp, Shigella sp, Yersinia enterocolitica, Aeromonas sp, Giardia sp, Entamoeba histolytica, Dientamoeba sp, Blastocystis sp and Cryptosporidium sp.) {2.3.1}	4	1
− Negative parasite screening {2.3.2}	4	1
− Calprotectin < 50µg/ml {2.3.3}	3.9	1

Table S7 − Expert statements concerning donor feces preparation

Statement	**Mean rating**	**Voting Round**
3.1 Fresh stool should be used within 6 hours after defecation	3.4	1
3.2 The storage and preparation should be as brief as possible	3.9	1
3.3 Depending on administration method and clinical context a minimum amount of 30 g of fresh feces should be used	3.3	1
3.4 Fecal material should be suspended in saline using a blender, manual effort or a bag mixer and sieved in order to avoid the clogging of infusion syringes and tubes	4	1
3.5 A dedicated space, disinfected using measures that are effective against sporulating bacteria, should be used	3.7	1
3.6 Protective gloves and facial masks should be used during preparation	4	1
3.7 Fresh, frozen and lyophilized stool can be used in CDI	4.0	1

Table S8 − Expert statements concerning recipient preparation

Statements	**Mean rating**	**Voting rounds**
Patients receiving a stool transplant should be prepared as following:		
− Bowel lavage {4.1}	3.7	1
− Antibiotic treatment should be stopped at least 2 days prior to FMT {4.2}	4.0	2

Table S9 − Expert statements concerning faecal delivery techniques

Statements	**Mean rating**	**Voting Round**
The following procedures are techniques of choice for faecal delivery:		
− Colonoscopy: Delivery of donor stool through working channel of colonoscope preferably into the right colon {5.1}	3.9	1
− Upper GI tract − gastroscope or nasogatric tube: Patients must be kept in 45° upright position for 4 hours after infusion to prevent aspiration {5.2}	3.4	1
− Enema: Patients should be instructed to hold the infusion material for at least 30 min {5.3}	3.4	1
− Lyophilized fecal microbiota transplantation is efficient when orally administered {5.4}	3.4	1

Table S10 − Expert statements concerning repeated FMT

Statement	**Mean rating**	**Voting Round**
6.1 C. diff: In severe CDI repeated FMT is recommended within 2 weeks to induce clinical remission	3.4	1
6.2 UC: repetitive FMT is better than a single FMT in patients with UC	3.3	1

Table S11 – Expert statements concerning multi−donors

Statement	**Mean rating**	**Voting rounds**
7 Currently, it is unknown if a combination of several donor stools has a beneficial effect in UC.	3,4	2

Table S12 − Expert statements concerning FMT and safety

Statements	**Mean rating**	**Voting rounds**
8.1 FMT is mostly well−tolerated and complications are rare	3.6	1
8.2 Mild adverse events occur more often in upper GI routes of FMT compared to lower GI routes	3.7	1
8.3 Serious adverse events seem to be higher in patients receiving FMT via upper GI tract	3.7	1
8.4 Patients need to be informed for the following complications:		
− Infections	3.7	1
− Possible transfer of non−infectious diseases	3.9	2
− IBD flare	3.2	1