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# The first international Rome consensus conference on gut microbiota and faecal microbiota transplantation in inflammatory bowel disease

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## ABSTRACT

**Background** Several randomised clinical trials (RCTs) performing faecal microbiota transplantation (FMT) for the management of inflammatory bowel disease (IBD), particularly for ulcerative colitis, have recently been published, but with major variations in study design. These include differences in administered dose, route and frequency of delivery, type of placebo and evaluated endpoints. Although the overall outcomes appear to be promising, they are highly dependent on both donor and recipient factors.

**Objective** To develop consensus-based statements and recommendations for the evaluation, management and potential treatment of IBD using FMT in order to move towards standardised practices.

**Design** An international panel of experts convened several times to generate evidence-based guidelines by performing a deep evaluation of currently available and/or published data. Twenty-five experts in IBD, immunology and microbiology collaborated in different working groups to provide statements on the following key issues related to FMT in IBD: (A) pathogenesis and rationale, (B) donor selection and biobanking, (C) FMT practices and (D) consideration of future studies and perspectives. Statements were evaluated and voted on by all members using an electronic Delphi process, culminating in a plenary consensus conference and generation of proposed guidelines.

**Results and conclusions** Our group has provided specific statements and recommendations, based on best available evidence, with the end goal of providing guidance and general criteria required to promote FMT as a recognised strategy for the treatment of IBD.

## INTRODUCTION

Faecal microbiota transplantation (FMT) is defined as the infusion of faeces from healthy donors into the gastrointestinal tract of recipients to treat disease-associated gut dysbiosis. It is an established and highly effective treatment option for recurrent *Clostridioides difficile* infection, as reported by several randomised controlled trials (RCTs)<sup>1–5</sup>

and meta-analyses,<sup>6–8</sup> which has culminated in the establishment of international guidelines to standardise its use as a viable therapeutic modality for *C. difficile* infection.<sup>9 10</sup>

Following its success for the treatment of *C. difficile* infection, FMT has also been investigated in patients with inflammatory bowel disease (IBD), first in non-randomised studies,<sup>11–13</sup> and subsequently, in RCTs,<sup>14–16</sup> both showing promising results, although with significant differences in FMT protocols and procedures. In fact, the adoption of FMT for the treatment of IBD is compromised by several limitations, including recruitment of donors, preparation of faecal material, determining the optimal route of administration and lack of a clear and established regulatory framework. Potential strategies to deal with these problems include the identification and use of sustainable, reproducible and standardised protocols, with the ultimate goal of altering gut microbiome composition. Consequently, establishing an optimal FMT framework is important for the future management of IBD. Therefore, the aim of the present study was to provide consensus-based statements and recommendations regarding the general organisation and criteria required to promote FMT as a recognised strategy for the treatment of IBD.

## METHODS

### Development of the consensus process

The consensus process was developed according to the following steps: selection of expert panel members, identification of key issues and assignment of associated working groups (WGs), development of statements based on best available evidence, achievement of consensus through the Delphi technique, and a face-to-face final meeting to fine tune accrued data and generate a first draft manuscript. Twenty-five consensus members, with proven expertise in the fields of microbiology, immunology, FMT and IBD, were identified and all took part in an expert panel. Based on personal expertise, each member was assigned to one of four WGs: pathogenesis and rationale, FMT donor

selection and biobanking, FMT trials in IBD, and future perspectives. Each WG proposed a list of key issues and developed statements related to the assigned topic(s). For each key issue, best available evidence was obtained through a systematic review of the pertinent literature. Statements were released as expert opinions (EOs).

The elaborated statements were uploaded to an online voting system (<http://scott.armstrong.delphi.stlouisintegration.com/delphi2/>),<sup>17</sup> and disseminated to the panel. Responses from experts were collected, addressed and shared with the panel after each round of review. For each statement, experts were requested to rate their level of agreement: (1) strongly agree, (2) agree with reservation, (3) undecided, (4) disagree, and (5) strongly disagree. Consensus was achieved if at least 80% of respondents expressed strong agreement or agreement with reservation regarding each statement. Statements that did not pass this threshold were revised and rated again in further rounds of voting, until consensus was reached. Panel experts gathered in Rome on 25 June 2022 for refinement and final approval of the overall statements.

## RESULTS

Up to three rounds of voting were implemented to reach consensus for the final accumulated statements. After the first and second rounds, 67% and 79% of statements passed the 80% threshold of agreement, respectively, while 100% of statements achieved the target level after the third round (table 1).

### Pathogenesis and rationale (a)

#### Statement A1

The precise aetiology of IBD is currently unknown; however, its pathogenesis is multifactorial, influenced by genetic susceptibility, host mucosal immune responses and the environment, including diet and the gut microbiome.

*Comment:* IBD, such as Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing inflammatory disorders of the digestive tract resulting from a loss of homeostasis between the intestinal immune system and the gut microbiota in genetically predisposed individuals.<sup>18</sup> Inappropriate mucosal immune responses, due to dysregulation of tolerance to intestinal microbiota or disruption of the epithelial barrier separating microorganisms from underlying tissues, may contribute to the development or perpetuation of IBD.

#### Statement A2

Alterations in composition, relative abundance, diversity and function of gut microbiota (*i.e.*, dysbiosis) promote the development and progression of IBD.

*Comment:* Increasing evidence suggests that the imbalance in gut microbiome composition, or 'dysbiosis', is one of the environmental factors with the greatest impact that can promote the development of IBD, as interactions of the altered microbiota with the host can trigger and promote immune alterations that are associated with IBD.<sup>19</sup> A substantial body of evidence shows that patients with IBD share specific common alterations of the gut microbiome that correlate to the impairment of many functions, including metabolism of short-chain fatty acids, biosynthesis of amino acids, regulation of oxidative stress and the production of toxins,<sup>19</sup> which can separately, or together, contribute to the development of IBD.

**Table 1** Summary of statements approved by the Rome consensus.

Pathogenesis and rationale	
A1	The precise aetiology of IBD is currently unknown; however, its pathogenesis is multifactorial, influenced by genetic susceptibility, host mucosal immune responses and the environment, including diet and the gut microbiome.
A2	Alterations in composition, relative abundance, diversity and function of gut microbiota ( <i>i.e.</i> , dysbiosis) promote the development and progression of IBD.
A3	The gut microbiome of Crohn's disease (CD) and patients with ulcerative colitis (UC) is particularly deficient in <i>Faecalibacterium prausnitzii</i> , which is recognised for its potential anti-inflammatory properties.
A4	The risk of <i>Clostridioides difficile</i> infection in patients with IBD is higher than in the general population.
Donor selection and biobanking	
B1	Suitable donors for experimental faecal microbiota transplantation (FMT) in IBD should submit to blood, as well as stool, testing in agreement with national and international guidelines, currently available for the treatment of <i>C. difficile</i> infection by FMT, and in general, for clinical practice.
B2	Stool donation should be voluntary, and donors should be notified of the potential risks and/or benefits of donating. Moreover, written informed consent must be provided by each patient.
B3	Donors can also be managed through stool banks for experimental use, in agreement with national and international guidelines and regulations available for <i>C. difficile</i> infection and, in general, for clinical practice.
B4	Donor faeces should preferably be collected on site at a stool bank or at the site where the experimental procedure is performed, following national and international guidelines and regulations.
B5	Each donor can be enrolled to contribute different preparations of FMT, in agreement with the experimental protocol.
B6	A registry of donor information should be maintained and stored, in agreement with national and international guidelines and regulations.
B7	Patients should not have direct access to stool banks for the treatment of IBD. Provision of FMT samples should always be under the guidance of a treating healthcare provider, in agreement with national and international guidelines and regulations.
B8	Clear traceability should be available for the complete process of FMT, from faeces collection to FMT sample administration. Therefore, aliquots of each FMT sample should be retained for testing in case unexpected adverse events occur.
B9	A common agreement about the technical aspects of donor FMT preparation will help to provide procedure standardisation and optimisation worldwide, facilitating interpretation of results.
B10	Research is needed to define donor characteristics associated with better clinical response rate and overall outcomes of FMT as a therapeutic option for IBD.
FMT Trials in IBD	
C1	Previously performed randomised controlled trials (RCTs) are, in general, small and methodologically heterogeneous; thus, definitive conclusions cannot be drawn at the present time.
C2	FMT is recommended as a treatment option for both mild and severe recurrent or refractory <i>C. difficile</i> infection in patients with IBD.
C3	FMT may be effective in the induction of remission for mild to moderate UC; however, there is insufficient evidence to recommend FMT as a treatment for UC in routine clinical practice and its use should generally be limited to the research setting.
C4	RCTs suggest that patients with UC who achieve remission following FMT generally do not have sustained remission beyond 1 year after FMT treatment.
C5	Repeated infusions and donor–recipient engraftment are probably important for the therapeutic success of FMT in UC.
C6	An increase in the diversity of gut microbiome composition after FMT is probably a marker of response in UC.
C7	The available data indicate that FMT is low risk for the induction of remission in mild to moderate UC; however, serious adverse events have been reported when using FMT to treat IBD, including exacerbation of disease.

Continued

Table 1 Continued

C8	RCTs have not demonstrated significant differences between FMT and control arms, in terms of disease worsening or symptoms attributable minor or serious adverse events.
C9	After FMT in UC, common adverse events are transient minor gastrointestinal symptoms, such as bloating, diarrhoea and flatulence.
C10	There is insufficient evidence to recommend FMT as a treatment for CD in clinical practice. To date, its use should be limited to the research setting.
C11	There is insufficient evidence to recommend FMT as a treatment for pouchitis in clinical practice. To date, its use should be limited to the research setting.
C12	There are insufficient data on the safety of FMT in CD and pouchitis.
C13	Further research is needed to determine the efficacy and safety of FMT in CD and pouchitis.
<b>Future perspectives</b>	
D1	Future research is needed to identify the optimal characteristics of both FMT donors and recipients for therapeutic use in IBD.
D2	Controlled FMT trials are warranted in order to optimise efficacy in defined phenotypes of IBD.
D3	There is a need to identify biomarkers that predict response to FMT in IBD.
D4	Future research is required to determine the optimal formulation and route of administration for FMT-based therapy in IBD.
D5	Studies are needed to accumulate evidence-based information regarding the use of complementary strategies to improve FMT efficacy.
D6	Studies are required to assess the role of FMT as a stand-alone treatment for IBD or in combination with currently available treatment modalities.

**Statement A3**

The gut microbiome of patients with UC and CD is particularly deficient in *Faecalibacterium prausnitzii*, which is recognised for its potential anti-inflammatory properties.

*Comment:* A growing body of clinical and experimental data indicate that commensal microbiota represent a key player in inflammatory processes that sustain human and experimental IBD.<sup>20</sup> Several reports show decreased microbial diversity, especially in Firmicutes and Bacteroidetes phyla during IBD.<sup>20</sup> Interestingly, *Faecalibacterium prausnitzii*, a member of the Firmicutes phyla, is significantly decreased<sup>21 22</sup> and has well-established anti-inflammatory activities.<sup>22 23</sup> Conversely, Proteobacteria and Actinobacteria are usually elevated in active IBD,<sup>20 24</sup> as well as specific strains of *Escherichia coli*.<sup>21</sup> In this scenario, components of the gut microbiome play a paramount role in IBD, which may represent a disorder associated with bacterial processing. As such, a dysfunctional relationship exists between the gut microbiome and host immune responses, triggering and sustaining chronic inflammation in IBD.

**Statement A4**

The risk of *Clostridioides difficile* infection in patients with IBD is higher than in the general population.

*Comment:* IBD-specific risk factors, such as immunosuppression, severity and extension of inflammation and the observed gut dysbiosis in IBD, are considered to be the main reason(s) for the high risk of *C. difficile* infection in patients with IBD.<sup>25</sup> Increased length of hospitalisation, as well as increased colectomy rate and mortality, are the consequences of concurrent *C. difficile* infection in patients with IBD. Given the potential life-threatening complications of this scenario, screening for *C. difficile* is recommended during IBD flares, and during early therapeutic interventions. Selection of *C. difficile* strains of higher virulence, antibiotic resistance and the increasing rate of recurrent infections make the management of *C. difficile* infection in IBD more challenging. Therefore, an individualised therapeutic

approach is recommended to control *C. difficile* infection during IBD flares.

**Donor selection and biobanking (B)****Statement B1**

Suitable donors for experimental FMT in IBD should submit to blood, as well as stool, testing in agreement with national and international guidelines currently in place for the treatment of *C. difficile* infection by FMT, and in general, for clinical practice.

*Comment:* The main principle of donor screening for the purpose of FMT is to avoid potential transmission of infectious diseases. Blood and stool parameters specified for screening of FMT in *C. difficile* infections have been proved to be safe in several RCTs in patients with UC.<sup>14–16 26–29</sup> A list containing mandatory international parameters to be tested should be available, while others should depend on geographical regions<sup>30</sup> (eg, tropical areas), medical conditions of patients or medical history of donors (eg, history of increased faecal calprotectin). Aside from blood and stool testing, general well-being, diet and psychological status should be monitored through several questionnaires to avoid any potential non-infectious adverse events.

**Statement B2**

Stool donation should be voluntary, and donors should be notified as to the potential risks and/or benefits of donating. Moreover, written informed consent must be provided by each patient.

*Comment:* As procedures for stool collection are non-invasive and can be done in an uncontrolled setting, donors should not be allowed to directly benefit from stool donation in order to avoid fraud with samples. However, donors can be compensated for time and travel expenses, in agreement with national regulations. Additionally, donors should be aware of the risks and benefits of donating, as the screening process might lead to discovery of diagnoses of previously unknown diseases (eg, HIV, colorectal cancer) or predisposition to other diseases (eg, those associated with microbiota alterations). Moreover, donors should be aware that they can withdraw consent at any time.

**Statement B3**

Donors can also be managed through stool banks for experimental use in agreement with national and international guidelines and regulations available for *C. difficile* infection, and in general, for clinical practice.

*Comment:* Stool banks are able to process stool donations in a standardised manner, which is appropriate for further clinical and experimental procedures in IBD. In stool banks, donors are rigorously screened before stool administration to patients, FMT preparation is standardised, and both the cost and time needed to prepare FMT samples are potentially reduced compared with the clinical setting. Moreover, stool banks possess expertise, and may therefore contribute to optimisation of the quality of FMT samples, in general. Finally, stool banks may provide access to FMT samples for IBD centres that are unable to provide this service.

**Statement B4**

Donor faeces should preferably be collected on site at a stool bank or at the site where the experimental procedure is performed, following national and international guidelines and regulations.

*Comment:* Donors should receive clear instructions about how to collect stool, preferably on site or at a stool bank. When this is not possible, the collected stool should be stored at 4°C and shipped to the clinical site or stool bank within



6 hours after collection, where it should be processed by trained personnel.<sup>4 31 32</sup>

#### Statement B5

Each donor can be enrolled to contribute different preparations of FMT, in agreement with the experimental protocol.

*Comment:* Donor faeces can be used to prepare different preparations of FMT (eg, fresh vs frozen samples, and single vs multiple donors per preparation). So far, frozen FMT samples are recommended over fresh preparations, mainly due to safety. Frozen FMT samples can be quarantined until full donor screening is completed at the end of the donation period. For fresh FMTs, the material is administered before fulfilment of the complete screening process. Therefore, for fresh FMTs, more regular donor laboratory screening has been suggested.<sup>32 33</sup>

#### Statement B6

A registry of donor information should be maintained and stored, in agreement with national and international guidelines and regulations.

*Comment:* Registration of donor information related to the FMT process should be regulated by national and international healthcare authorities. Information from donors and recipients should be stored for at least 10 years, or in agreement with national and international regulations. These data should be provided to the stool bank in order to attain long-term safety data.

#### Statement B7

Patients should not have direct access to stool banks for the treatment of IBD. Provision of FMT samples should always be under the guidance of a treating healthcare provider, in agreement with national and international guidelines and regulations.

*Comment:* Access to stool banks should be restricted to healthcare providers, as FMT administration requires documentation and suitable follow-up to encounter any potential adverse events, which can only safely occur under the supervision of a physician. Therefore, it is inappropriate for patients to have direct access to stool banks.

#### Statement B8

Clear traceability should be available for the complete process of FMT, from donor screening to faeces collection and FMT sample administration. Therefore, aliquots of each FMT sample should be retained for testing in case unexpected adverse events occur.

*Comment:* All steps of the FMT process should be registered, and aliquots of donor samples should be retained and stored at  $-80^{\circ}\text{C}$  in order to allow back tracing, in case any unexpected adverse event (eg, infection with pathogens) occurs. Drug-resistant *E. coli* transmission after FMT has been reported, indicating the importance of retaining donor stool for further analysis after possible adverse events, and guarantees prompt intervention in such cases.<sup>34</sup>

#### Statement B9

A common agreement regarding the technical aspects of donor FMT preparation will help to provide procedure standardisation and optimisation worldwide, facilitating interpretation of results.

*Comment:* FMT has shown promising results, especially in UC, despite heterogeneous study designs. Variations in protocols include different routes of FMT infusion (eg, nasoduodenal, rectal, oral), frequency of administration, control placebos (eg,

water, autologous faecal material) and endpoint measurements. Dose standardisation regarding frozen faecal material preparations, storage and administered volume will facilitate interpretation and comparison of future FMT studies, including the resulting outcomes.

#### Statement B10

Research is needed to define donor characteristics associated with better clinical response rate and overall outcomes of FMT as a therapeutic option for IBD.

*Comment:* Research is mandatory to identify donor markers to achieve optimal therapeutic efficacy and overall success of FMT in IBD. Therefore, microbiota,<sup>35</sup> dietary patterns (questionnaires)<sup>36 37</sup> and other aspects, such as drug use,<sup>38</sup> family medical history,<sup>32</sup> psychological status<sup>39</sup> and genetic background,<sup>40–42</sup> should be characterised to identify potential trends in improved clinical outcomes. Aside from specific donor markers, donor-recipient engraftment should also be investigated.<sup>43</sup>

### FMT trials in IBD (C)

#### Statement C1

Previously performed RCTs are, in general, small and methodologically heterogeneous; thus, definitive conclusions cannot be drawn at the present time.

*Comment:* After being successfully used for the treatment of *C. difficile* infection, FMT has also been investigated in patients with UC, first in non-randomised studies,<sup>11–13</sup> and then in RCTs,<sup>14–16</sup> both with promising results, although there were substantial differences in FMT procedures and measured outcomes. Indeed, although these studies and subsequent meta-analyses<sup>44–47</sup> highlight satisfactory remission rates following donor FMT administration, published and/or available RCTs are generally small and methodologically heterogeneous, as they differ in timing, number and route of faecal infusions, characteristics of donor faeces versus controls (shams) for FMT, making the resulting outcomes difficult to interpret as a whole, with definitive conclusions unable to be drawn.

#### Statement C2

FMT is recommended as a treatment option for both mild and severe recurrent or refractory *C. difficile* infection in patients with IBD.

*Comment:* FMT is effective for the treatment of recurrent *C. difficile* infection in patients without IBD,<sup>48</sup> as well as in patients with UC and CD.<sup>49 50</sup> However, studies in patients with UC report that UC flares could not be prevented by single-dose FMT. There is insufficient evidence to recommend FMT as a treatment for the first episode of *C. difficile* infection in IBD.

#### Statement C3

FMT may be effective in the induction of remission in mild to moderate UC; however, there is insufficient evidence to recommend FMT as a treatment for UC in routine clinical practice and its use should generally be limited to the research setting.

*Comment:* To date, FMT has shown promising results for the induction of remission in mild to moderate patients with UC. However, these studies were performed in cohorts of patients with UC with a relatively small sample size, as well as variations among study designs,<sup>14–16</sup> making comparisons among studies difficult to reconcile. For this reason, there are insufficient available data to support the routine clinical use of FMT to induce remission in patients with UC. However, the experts agreed that FMT might be used under specific circumstantial conditions,

which should be considered on a case-by-case basis and discussed in detail with all parties concerned.

#### Statement C4

RCTs suggest that patients with UC who achieve remission following FMT generally do not have sustained remission beyond 1 year after FMT treatment.

*Comment:* FMT studies in UC lack long-term follow-up data regarding the efficacy and persistence of treatment.<sup>51</sup> Therefore, a more sustained follow-up with disease monitoring is needed in regard to time after treatment. The available data<sup>14–16</sup> suggest that relapse is likely, and that maintenance therapy may be mandatory in order to achieve long-term efficacy. However, the number of infusions, as well as dosing should be further investigated for both induction and maintenance therapies.

#### Statement C5

Repeated infusions and donor–recipient engraftment are probably important for the therapeutic success of FMT in UC.

*Comment:* Data from available RCTs performing FMT in UC<sup>14–16 26 27</sup> suggest that repeated infusions are important; however, there is no consensus at present regarding the minimum number of administrations needed for FMT success. Additionally, efficacy of FMT in UC appears to also be recipient-dependent,<sup>14</sup> suggesting that donor–recipient engraftment is critical. Aside from identification of donor markers that may be important for FMT success, recipient markers and their importance for interplay with donor faecal material/faecal antigens should also be investigated.

#### Statement C6

An increase in the diversity of gut microbiome composition after FMT is probably a marker of response in UC.

*Comment:* Aside from clinical outcomes, such as clinical and endoscopic remission, microbial markers, including alterations (ie, increase) in microbiome diversity, should be evaluated and correlated with FMT success or failure in future investigation. These markers could be used to predict response in patients and this has the potential to personalise treatment towards precision medicine approaches.

#### Statement C7

The available data indicate that FMT is low risk for the induction of remission in mild to moderate UC; however, serious adverse events have been reported when using FMT to treat IBD, including exacerbation of disease.

*Comment:* Assessment of patient safety in the performed RCTs shows good outcomes, with very limited adverse events, most of which are associated with the mode of administration. In general, nasoduodenal delivery results in relatively more adverse events than an enema via rectal delivery<sup>14–16 52</sup>; thus, the latter has been generally accepted as a safer route of delivery. To date, however, long-term FMT safety data in patients with UC are lacking.

In fact, serious adverse events have been observed in RCTs in a limited number of patients (<10%). These include aspiration and suspected small bowel perforation when FMT is performed by upper GI administration.<sup>26</sup> The most frequent severe adverse event related to the FMT procedure is suggested to be disease worsening requiring hospitalisation and, in limited cases, colectomy. In the trial by Costello *et al* disease worsening was observed in 2 of 43 patients receiving autologous FMT and in 1 of 38 patients receiving FMT from the donor. In Moayyedi's

trial, 2 of 38 patients enrolled presented patchy inflammation and abscesses. Other significant severe adverse events were pneumonia, *C. difficile* infection or other forms of enterocolitis.<sup>14–16</sup>

#### Statement C8

RCTs have not demonstrated significant differences between FMT and control arms, in terms of disease worsening or symptoms attributable to minor or serious adverse events.

*Comment:* FMT trials in UC have commented on adverse events<sup>11–16</sup>; however, as no significant differences between control and treatment arms have been identified, these adverse events are suggested to be the result of the administration procedure, rather than the processed, donor faecal material, itself.

#### Statement C9

After FMT in UC, common adverse events are transient minor gastrointestinal symptoms, such as bloating, diarrhoea and flatulence.

*Comment:* Minor adverse events in FMT trials are observed in up to 83% of patients and include gastrointestinal symptoms, such as transient diarrhoea, borborygmus, abdominal pain, bloating and flatulence. Transient fever has been reported as well.<sup>53</sup> Most adverse events resolve spontaneously within days after the procedure.

#### Statement C10

There is insufficient evidence to recommend FMT as a treatment for CD in clinical practice. To date, its use should be limited to the research setting.

*Comment:* Very limited data are available for FMT in CD, consisting mainly of case reports and pilot studies, rather than large RCTs.<sup>54 55</sup> These studies show adverse events, consisting of mostly GI symptoms, with disease flares reported as serious adverse events related to FMT. A pilot study by Vermeire *et al* showed no difference at week 8 after FMT in six patients with refractory CD.<sup>35</sup> In addition, assessing the effects of FMT in the maintenance of remission in CD, Sokol *et al* reported a non-significant lower incidence of flares in the FMT group compared with sham.<sup>54</sup> Further research should consist of optimising induction and maintenance of remission in this patient population. Large sized RCTs are mandatory to recommend FMT as a viable treatment approach in CD patients.

#### Statement C11

There is insufficient evidence to recommend FMT as a treatment for pouchitis in clinical practice. To date, its use should be limited to the research setting.

*Comment:* Dysbiosis is believed to also occur in patients with pouchitis.<sup>56</sup> Currently, there only a limited number of studies have used FMT for the management of pouchitis. However, within the published literature and case reports, the procedure was mostly reported to be safe, yet not effective. Similar to the RCTs of FMT in UC, the studies performed were also heterogeneous, and evaluated different outcome measurements. Thus, further investigation and optimisation of protocols are required to determine the potential use of FMT in pouchitis.<sup>57–62</sup>

#### Statement C12

There are insufficient data on the safety of FMT in CD and pouchitis.

*Comment:* Based on the lack of large RCTs and long-term follow-up data, no conclusions can be drawn at the present time for the safety of FMT in CD and pouchitis.<sup>57–62</sup>

**Statement C13**

Further research is needed to determine the efficacy and safety of FMT in CD and pouchitis.

*Comment:* Further research and optimisation of FMT in CD and pouchitis are required to evaluate efficacy and to generate (long-term) safety data in order to bring FMT into the clinical setting.<sup>57–62</sup>

**Future perspectives (D)****Statement D1**

Future research is needed to identify the optimal characteristics of both FMT donors and recipients for therapeutic use in IBD.

*Comment:* FMT has been shown to be a promising treatment strategy for UC. However, efficacy rates appear to be influenced by donor-specific, recipient-specific and procedure-specific characteristics. Moreover, donor–patient engraftment has gained more support in favour of identifying a universal ‘super donor’. As such, further research is required to define ideal patient and donor characteristics and their optimal engraftment.

**Statement D2**

Controlled FMT trials are warranted in order to optimise efficacy in defined phenotypes of IBD.

*Comment:* Future studies should take strictly defined patient phenotypes into account when considering outcomes of FMT in IBD. These studies have the potential to identify specific phenotypes that are associated with a positive response, or lack of response, after FMT administration.

**Statement D3**

There is a need to identify biomarkers that predict response to FMT in IBD.

*Comment:* Aside from identifying possible optimal characteristics of donors and recipients and patient phenotypes, the identification of immunological and microbial biomarkers to predict response to treatment is required in order to avoid loss of time, cost and adverse events, due to non-responsive FMT therapy. Such biomarkers could be detected with 16S rRNA amplicon sequencing, shotgun metagenomic sequencing, proteomics and/or transcriptomic analyses. By identifying such biomarkers, there is the potential to design more targeted strategies for FMT treatment of IBD, evolving towards a more precision-based, personalised medicine approach.<sup>63</sup>

**Statement D4**

Future research is required to determine the optimal formulation and route of administration for FMT-based therapy in IBD.

*Comment:* An optimal dose to increase FMT efficacy has not yet been established. To date, nasoduodenal tube delivery, as well as FMT infusion via colonoscopy or rectal enema, have been the most studied routes of administration in IBD. However, a recent study<sup>28</sup> has leveraged the use of oral capsules containing lyophilised faecal microbiota as their delivery system. This route of administration is less invasive and therefore may be looked on more favourably by patients. More RCTs are needed to optimise dose and route of administration.

**Statement D5**

Studies are needed to accumulate evidence-based information regarding the use of complementary strategies to improve FMT efficacy.

*Comment:* Success rates of modulating the gut microbiome composition by FMT could be improved by complementary

strategies, such as a supportive anti-inflammatory diet, in both donors and recipients,<sup>64</sup> by optimising pre-FMT bowel preparation, by pretreatment with antibiotics, as well as by probiotic, prebiotic, synbiotic and postbiotic supplementation.

**Statement D6**

Studies are required to assess the role of FMT as a stand-alone treatment for IBD or in combination with currently available treatment modalities.

*Comment:* Aside from evaluating complementary strategies (D5), further studies are also warranted to investigate the combination of FMT with, for example, currently used concomitant IBD therapies, ranging from corticosteroids to biological agents and JAK inhibitors. This combinatorial approach, targeting both the immune response and gut microbiome composition, might lead to greater remission rates than each strategy on its own. Moreover, the prevention of onset and/or postoperative recurrence should be investigated, as well as the effects of FMT on cancer treatments and vice versa.

**DISCUSSION**

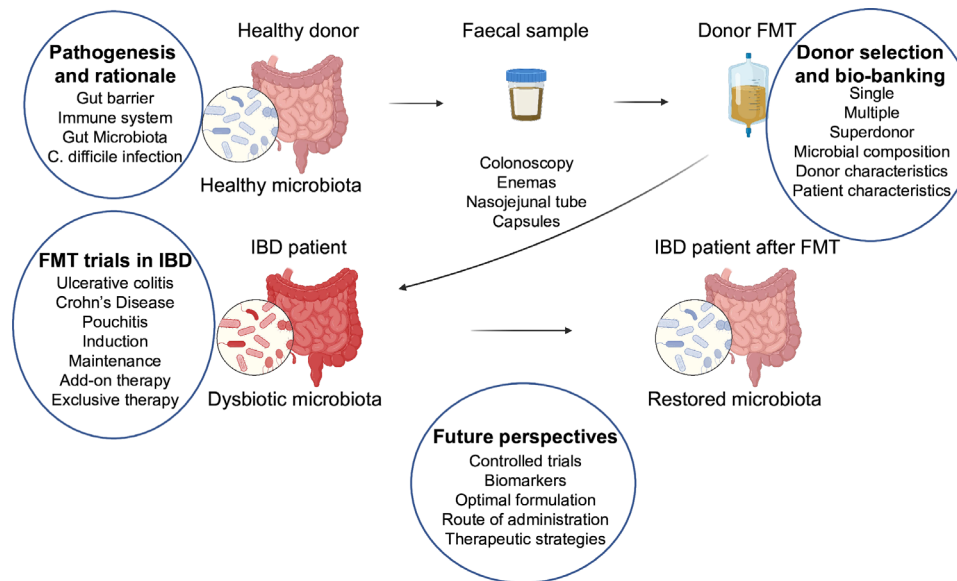
The authors of this manuscript, representing an international group of experts in various aspects of IBD, agree that further research is warranted before promoting FMT as a recognised strategy for the treatment of IBD. The procedure is generally accepted to be safe in patients with IBD, particularly in UC (figure 1). Most of the complications reported in the literature are primarily related to the route of administration of faecal infusion, and not to transmission of infection. Nevertheless, to avoid the burden of adverse events, donors should be rigorously screened by following the international guidelines already available for FMT treatment in *C. difficile* infection.<sup>32 65 66</sup>

In addition, stool banks should be put into operation to facilitate FMT research, and the possibility of compassionate use to treat IBD should be considered by implementing permanent donor enrolment, screening of donor faecal material by microbiota characterisation and donor health status, as well as optimising storage of faecal material samples.<sup>32</sup> Moreover, stool banks should register all donor and patient data in order to allow efficient traceability and monitor changes in health state (eg, remission/flares, psychological status) after FMT administration.

Several FMT pilot studies and RCTs have been performed for the treatment of IBD, but using heterogeneous study designs. The available results, especially in UC, are promising, but appear to be donor- and patient-dependent.<sup>14–16</sup> Yet, to bring FMT into the daily GI practice, further research is needed to optimise both short- and long-term success rates and to further evaluate safety. This approach should identify optimal route of administration, dose, frequency, donor–recipient engraftment, patient phenotype, together with the identification of immunological and microbiome biomarkers for FMT response. Taken together, this approach will aid in the standardisation of FMT and its clinical application to treat UC. For CD and pouchitis, further research is mandatory to evaluate the (long-term) safety, and efficacy, of its use. Nonetheless, this line of research could highly benefit from steps taken to optimise its use in UC.

Future work includes rigorous characterisation of donor microbiota, as well as investigating the effects on IBD recipients before and after FMT, which could be leveraged to maximise FMT efficacy, and to clarify mechanisms of action. Further increasing FMT efficacy by investigating supportive diets in both donors and recipients, bowel preparation, antibiotics pretreatment, probiotic, prebiotic, synbiotic and postbiotic support, as





**Figure 1** Faecal microbiota transplantation (FMT) pathway in IBD: from healthy donor to restored gut microbiota in patients with disease.

well as combination therapy with concomitant IBD therapy is of primary importance. Moreover, identifying specific microbiota strains associated with prediction of FMT success, could lead to the development of well-defined single- or multi-strain probiotics.

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