European consensus conference on faecal microbiota transplantation in clinical practice

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ABSTRACT
Faecal microbiota transplantation (FMT) is an important therapeutic option for Clostridium difficile infection. Promising findings suggest that FMT may play a role also in the management of other disorders associated with the alteration of gut microbiota. Although the health community is assessing FMT with renewed interest and patients are becoming more aware, there are technical and logistical issues in establishing such a non-standardised treatment into the clinical practice with safety and proper governance. In view of this, an evidence-based recommendation is needed to drive the practical implementation of FMT. In this European Consensus Conference, 28 experts from 10 countries collaborated, in separate working groups and through an evidence-based process, to provide statements on the following key issues: FMT indications; donor selection; preparation of faecal material; clinical management and faecal delivery and basic requirements for implementing an FMT centre. Statements developed by each working group were evaluated and voted by all members, first through an electronic Delphi process, and then in a plenary consensus conference. The recommendations were released according to best available evidence, in order to act as guidance for physicians who plan to implement FMT, aiming at supporting the broad availability of the procedure, discussing other issues relevant to FMT and promoting future clinical research in the area of gut microbiota manipulation. This consensus report strongly recommends the implementation of FMT centres for the treatment of C. difficile infection as well as traces the guidelines of technicality, regulatory, administrative and laboratory requirements.

INTRODUCTION
Faecal microbiota transplantation (FMT) consists of the infusion of faeces from a healthy donor to the GI tract of a recipient patient, in order to treat a specific disease associated with alteration of gut microbiota. A large body of evidence, including randomised controlled trials (RCTs), systematic reviews and meta-analyses, proved clear evidence that FMT is a highly effective treatment against recurrent Clostridium difficile infection (rCDI).1–7 Due to the rising prevalence, severity and mortality of this infection, the therapeutic role played by FMT is therefore important to save human lives and to decrease the economic burden on healthcare systems.8–11 Based on these data, both the European Society for Microbiology and Infectious Disease and the American College of Gastroenterology recommend FMT as a treatment for rCDI.12 13

Beyond the treatment of CDI, FMT has also been investigated in other disorders associated with the alteration of gut microbiota. In particular, studies in humans include RCTs in patients with UC and metabolic syndrome (MS).14–16

The global interest in FMT is increasing, and both doctors and patients are increasingly aware and informed. Although the dissemination of FMT in the clinical practice is restricted by regulatory and bureaucratic issues (principally related to costs, donor programme, safety control),17–19 the FMT practice is booming, ranging from highly organised stool banking programmes to individual treatments with patient-identified directed donors, and even to individual and harmful do-it-yourself practices. Working groups (WGs) from the USA, Austria and France released recommendations on indications and methods of FMT.20–22 Authoritative published guidelines and recommendations have been released as expert opinions rather than evidence-based consensus reports. A rigorous and formal evidence-based process to drive the wide range of FMT practice has not been performed yet.

The aim of this evidence-based consensus report is to define indications and methodology for the use of FMT in the treatment of CDI, to discuss the suitability of FMT for indications other than CDI and to address the minimum requirements needed to implement a FMT centre. The final aim is to encourage and drive the dissemination of the procedure and to promote further clinical research in the area.

METHODS
Consensus development process
The process of development of the consensus conference, aimed at drawing up evidence-based recommendations for the use of FMT in clinical practice, included the following steps: selection of

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METHODS
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The process of development of the consensus conference, aimed at drawing up evidence-based recommendations for the use of FMT in clinical practice, included the following steps: selection of
the expert panel members; identification of main topics and generation of WGs; development of statements according to the best available evidence; development of consensus through the electronic Delphi process and face-to-face meeting to release the final version of statements.

Consensus presidents (GC, AG) and consensus secretary (GI) chose the consensus members based on their expertise in the field of FMT and/or gut microbiota. A total number of 28 experts from 10 European countries constituted the experts panel and had an active role in the development of consensus process. Each member was assigned, according to her/his expertise, to one of the following five WGs: WG-1, indications; WG-2, donor selection; WG-3, preparation of faecal material; WG-4, clinical management and faecal delivery; WG-5, basic requirements for implementing an FMT centre.

Members of each WG elected a chair to coordinate work and to liaise with the consensus presidents and secretary. For each main topic, the consensus presidents and secretary drew up three to six key issues for which members of the corresponding WG were requested to formulate statements after a systematic review of the literature. The quality of evidence and strength of recommendation for each statement were determined according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Definition of the strength of recommendation is given in table 1 and the quality of the published evidence is defined in table 2.

Statements from each WG were edited by the respective chair and then uploaded to an online electronic voting system (http://armstrong.wharton.upenn.edu/delphi2/) by the consensus secretary. The Delphi method was used to achieve a consensus. Several rounds of statements were uploaded and sent out, and the experts’ anonymous responses were collected and shared with the group after each round. The experts were allowed to adjust their answers in subsequent rounds. After multiple rounds, the Delphi method enabled achievement of the ‘correct’ response through consensus.

For each statement, consensus members were requested to rate their level of agreement, among the following: (1) agree strongly; (2) agree with reservation; (3) undecided; (4) disagree; (5) disagree strongly. If the rating was other than ‘agree strongly’, respondents were requested to add some comments to explain their reservation/disagreement, and how to improve the statement. For each statement, the pre-established threshold was reached when the overall result was ≥80%, with the experts agreeing either strongly or with reservation. All statements not reaching 80% of agreement were revised and rated again in further round of voting. To reach consensus, two rounds of electronic votings were run overall.

Afterwards, 22 of 28 (79%) consensus members gathered on 9 July 2016 in Rome for a face-to-face meeting. Before the final conference of the expert panel, each WG had an internal meeting to reach a WG agreement on statements that had not reached consensus at the electronic voting. At the final conference, the chairs presented the respective WG statements to all members in the plenary session and the expert panel voted on each statement by a show of hands. Statements not reaching consensus (<80%) were discussed and either removed or modified and voted again. Finally, the consensus secretary provided a summary of the finalised statements.

Chairs and all WG members provided commentaries and supporting literature for each statement. Finally, all 28 members of the consensus approved the final version of released statements and commentaries.

RESULTS

Indications

Key issue: CDI (clinical pictures of CDI are described in table 3).

FMT for rCDI

Statement: FMT is recommended as treatment option for both mild and severe rCDI. Its implementation in clinical practice is recommended.

Quality of evidence: high.

Strength of recommendation: strong.

Comment: Infusion of faecal microbiota from a healthy donor into a recipient individual with CDI can restore the healthy microbial flora in the diseased colon, leading to the resolution of symptoms. In two open-label RCTs including

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<th>Table 1</th>
<th>Definition of the strength of recommendation and statement</th>
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<tr>
<td><strong>Strength</strong></td>
<td><strong>Definition</strong></td>
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<tr>
<td>Strong</td>
<td>Strongly supports a recommendation for use and/or a statement</td>
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<tr>
<td>Weak</td>
<td>Marginally supports a recommendation for use and/or a statement</td>
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Table 2 Definition of the quality of evidence (QoE)

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<th>QoE</th>
<th>Definition</th>
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<tr>
<td>Strong</td>
<td>Evidence from at least one properly designed RCT</td>
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<tr>
<td>Moderate</td>
<td>Evidence from at least one well-designed clinical trial, without randomisation; from cohort or case–control analytic studies (preferably from more than one centre); from multiple time series</td>
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<tr>
<td>Low</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies or reports of expert committees</td>
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RCT, randomised controlled trial.

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<th>Table 3</th>
<th>Clinical pictures compatible with CDI according to the ESCMID guidelines (modified from Debast et al.)</th>
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<tr>
<td><strong>Clinical picture</strong></td>
<td><strong>Definition</strong></td>
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<tr>
<td>Severe</td>
<td>Episode of CDI with one or more specific clinical (fever, haemodynamic instability, respiratory failure which needs mechanical ventilation, signs and symptoms of peritonitis, signs and symptoms of colonic ischaemia), laboratory (marked leucocytosis, rise in serum creatinine and lactate, marked decrease of serum albumin), radiological (colon distension, colonic wall thickening) or endoscopic (pseudomembranous colitis), symptoms and signs of severe colitis or complicated course of disease</td>
</tr>
<tr>
<td>Recurrent</td>
<td>When CDI recurs within 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment. It is not feasible to distinguish recurrence due to relapse (renewed symptoms from already present CDI) from recurrence due to reinfection in daily practice</td>
</tr>
<tr>
<td>Refractory</td>
<td>CDI that is unresponsive to the antimicrobial treatment, namely persistence of diarrhoea with CD toxin positive or persistent diarrhoea with toxin negative in the absence of other possible causes of diarrhoea (eg, IBS, IBD, non-CDI antibiotic-associated diarrhoea)</td>
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CDI, *Clostridium difficile* infection; ESCMID, European Society for Microbiology and Infectious Disease.
patients with rCDI. FMT showed significantly higher resolution rates than vancomycin (94% and 90% vs 31% and 26%, respectively). Both studies have a small sample of enrolled subjects, as they were stopped early for futility. The excellent efficacy rates (above 80%) of FMT for the treatment of rCDI confirmed afterwards with a larger double-blind RCT, aimed at comparing frozen FMT with fresh FMT (83.5% and 85.1%, respectively at per-protocol analysis). A further double-blind RCT in which FMT using donor stool (heterologous) was compared with FMT using patient’s own (autologous) stool (this latter study was published after the conclusion of this consensus conference).

Moreover, in several systematic reviews and meta-analyses, including both RCTs and non-controlled studies, rCDI resolution rates achieved by FMT ranged between 85% and 89.7%. In all these studies, FMT also showed an excellent safety profile, at least in the short-term follow-up, as only few and almost mild adverse events were reported. Currently, long-term safety data are lacking. In theory, it may be possible to transmit potentially harmful microbiota traits, which may not apper for decades. This possibility should however be envisaged in the context of a favourl risk-benefit ratio, as FMT is a highly efficacious treatment for rCDI and can represent a life-saving treatment for affected patients.

The recurrence of CDI may lead to clinical progression of the disease. Therefore, the recurrence of CDI is more likely to appear as a severe disease rather than a first episode and is associated with a higher mortality. There are several studies that have shown a good efficacy of FMT for severe CDI using a variety of FMT protocols.

Based on this evidence, the panel encourages the use of FMT in clinical practice for the treatment of rCDI. This may also help decrease the associated economic burden on healthcare system, according to recent cost-effectiveness analysis.

FMT for refractory CDI

Statement: FMT can be considered as a treatment option for refractory CDI.

Quality of evidence: low.

Strength of recommendation: strong.

Comment: A recent systematic review found seven non-randomised observational studies in which FMT was used to treat patients with refractory CDI. None of them compared FMT with other therapies, and efficacy rates varied widely among studies (0%–100%; overall resolution rate, 55%). In a recent double-blind RCT aimed at comparing frozen FMT with fresh FMT for the treatment of rCDI, a small portion of patients with refractory CDI were successfully treated with frozen (per-protocol, 100%) and fresh faeces (per-protocol, 67%).

Moreover, refractory CDI often arises as a severe disease, which may be a life-threatening condition. As FMT appears to be an effective treatment of severe CDI, it can also be considered an effective therapeutic option in CDI that is unresponsive to the usual antimicrobial treatment. However, further studies will need to consolidate this evidence.

FMT for the first episode of CDI

Statement: There is insufficient evidence to recommend FMT as a treatment for the first episode of CDI.

Quality of evidence: low.

Strength of recommendation: weak.

Comment: A recent systematic review found that FMT was used to treat an initial episode of CDI in a very small (n=7) number of patients, with discrepant results. These data come from two small case series of patients with refractory or severe first episode of CDI. In addition, a preliminary report showed that treatment with FMT after the first episode of CDI can decrease mortality in patients infected with the 027 strain in comparison to FMT performed after recurrence. However, additional studies will need to establish if FMT is more cost-effective than antibiotics for the treatment of the first episode of CDI.

Other indications

The experts panel took into account other clinical indications for a possible use of FMT in the clinical practice, such as IBD, IBS, metabolic disorders, paediatrics, but for none of them emerged an evidence-based recommendation to use FMT except that in a context of research (see online supplementary 1).

Donor selection

Key issue: collection of medical history

General recommendations

Statement: Potential donors for FMT have to undergo, at the beginning of the selection process, a medical interview to exclude history and risk factors (see box 1).

Quality of evidence: low.

Strength of recommendation: strong.

Comment: The main objective of donor selection is to reduce and prevent any adverse event related to the infused faecal material. Therefore, the panel recommends general exclusion criteria for donor selection before performing FMT, regardless of indications. As a first step, all potential donors should undergo a general questionnaire (preferably written) focused on their medical history and lifestyle habits to identify the risk factors. This is extremely relevant to exclude issues not detectable through blood and stool testing. To reduce the risk of donor comorbidities, individuals aged <60 years should be preferred. However, this indication cannot be mandatory in order not to foreclose the use of intimate healthy partners merely because of age. The panel chose the exclusion criteria shown in box 1 because they are the requirements of the European Commission for the selection of allogenic living donors of human tissue transplants. In addition, further exclusion criteria, especially those related to the presence of GI disorders, or drugs which may impair microbiota, were considered, based on available evidence. Indeed, the use of these or similar exclusion criteria assured, as shown in several RCTs, large case series and systematic review, the occurrence of no or few adverse events related to the infusion of donors’ material, as also stated in the French National Guidelines of FMT for the treatment of rCDI.

Statement: Screened donors have to undergo a further interview on the same day of the donation, in order to check any recently onset potentially harmful issue (see box 2).

Quality of evidence: low.

Strength of recommendation: strong.

Comment: To ensure the safest possible procedure, the panel recommends a further check of recent history and risk factors of selected and laboratory screened donors on the same day of donation. The above recommendation is supported by excellent safety data from several RCTs, and is also reported in the French National Guidelines of FMT for rCDI.
Guidelines

Box 1 Key issues to select potential donors at the preliminary interview

INFECTION DISEASES
- History of, or known exposure to, HIV, HBV or HCV, syphilis, human T-lymphotropic virus I and II, malaria, trypanosomiasis, tuberculosis
- Known systemic infection not controlled at the time of donation
- Use of illegal drugs
- Risky sexual behaviour (anonymous sexual contacts; sexual contacts with prostitutes, drug addicts, individuals with HIV, viral hepatitis, syphilis; work as prostitute; history of sexually transmittable disease)
- Previous receipt of tissue/organ transplant
- Previous (<12 months) reception of blood products
- Recent (<6 months) needle stick accident
- Recent (<6 months) body tattoo, piercing, earring, acupuncture
- Recent medical treatment in poorly hygienic conditions
- Risk of transmission of diseases caused by prions
- Recent parasitosis or infection from rotavirus, Giardia lamblia and other microbes with GI involvement
- Recent (<6 months) travel in tropical countries, countries at high risk of communicable diseases or traveller’s diarrhoea
- Recent (<6 months) history of vaccination with a live attenuated virus, if there is a possible risk of transmission
- Healthcare workers (to exclude the risk of transmission of multidrug-resistant organisms)
- Individual working with animals (to exclude the risk of transmission of zoonotic infections)

GI, METABOLIC AND NEUROLOGICAL DISORDERS
- History of IBS, IBD, functional chronic constipation, coeliac disease, other chronic GI disorders
- History of chronic, systemic autoimmune disorders with GI involvement
- History of, or high risk for, GI cancer or polypsis
- Recent appearance of diarrhoea, hematochezia
- History of neurological/neurodegenerative disorders
- History of psychiatric conditions
- Overweight and obesity (body mass index >25)

DRUGS THAT CAN IMPAIR GUT MICROBIOTA COMPOSITION
- Recent (<3 months) exposure to antibiotics, immunosuppressants, chemotherapy
- Chronic therapy with proton pump inhibitors

Box 2 Issues to address on the same day of donation to check any recently onset of harmful events

- Newly appeared GI signs and symptoms, for example, diarrhoea, nausea, vomiting, abdominal pain, jaundice
- Newly appeared illness or general signs as fever, throat pain, swollen lymph nodes
- Use of antibiotics or other drugs that may impair gut microbiota, new sexual partners or travels abroad since the last screening
- Recent ingestion of a substance that may result harmful for the recipients
- Travel in tropical areas—contact with human blood (sting, wound, showing, piercings, tattoos)—sexual high-risk behaviour
- Diarrhoea (more than three loose or liquid stools per day) among members of the entourage (including children) within 4 weeks of donation

An alternative way, without exploiting the questionnaire, is to collect donor stools just after the results of the exams, and freeze and store them, if the centre has expertise in managing frozen material and has the availability of authorised stool bank facilities.

Recommendations for specific situations
See online supplementary 1.

Key issue: testing for donor selection

General recommendations

Statement: Suitable donors for FMT should undergo both blood and stool testing at most 4 weeks before donation (see box 3). If there are no changes in donor’s health and specific circumstances, testing may be repeated up to 8 weeks.

Quality of evidence: low.
Strength of recommendation: strong.

Comment: The primary purpose of donor testing is to check the donor for infectious diseases potentially transmittable to the recipient. The selected blood and stool exams were shown to achieve an excellent safety profile in several RCTs of FMT.1–3 7 14–16 36 Some testing should be mandatory, with others as options, according to geographical areas (eg, human T-lymphotropic virus types I and II antibodies, or Strongyloides stercoralis), clinical conditions of recipients (eg, cytomegalovirus IgG, viral capsid antigen IgG, bacterial culture for Vibrio cholera and Listeria monocytogenes, antigens and/or acid fast-staining for Isospora and Microsporidia in the case of immunosuppressed recipients) or medical history of donors (eg, calprotectin). Although for some potential pathogen (such as human T-lymphotropic virus) there is no knowledge on transmission via FMT, the panel has expanded the boundaries of screening tests in order to ensure maximum safety profile to patients. Part
of blood testing, moreover, is required by the European Commission for the selection of allogenic living donors of human tissue transplants and by the French National Guidelines of FMT for rCDI.20 35

Most of the complications reported in the literature are principally related to the route of administration of faecal infusion and not to transmission of infection. However, there is poor evidence suggesting a precise deadline of donor testing before donation.

Specific situations
See online supplementary 1.

Key issue: choice of donors
Statement: Related or unrelated donors can be selected when FMT is performed to treat CDI. For other indications, the choice may be driven by specific needs.

Quality of evidence: moderate.
Strength of recommendation: strong.

Comment: According to the available evidence, there is no significant difference between patient-selected and anonymous healthy donors in terms of FMT outcomes, at least for rCDI, as shown by a meta-analysis. The use of both related and unrelated donors for FMT provided excellent rates of rCDI resolution in several RCTs and large case series.1 2 36 37 Nevertheless, randomised studies comparing directly these categories of donors are still lacking. The use of unrelated healthy donors may be useful in FMT centres, with large volume of patients, to satisfy FMT requests. The availability of a stool bank in those centres is of utmost importance. Choice of related or unrelated donors might be driven by specific needs (eg, specific FMT indications, such as when there is a potential advantage of choosing unrelated donor to treat conditions with a pathogenic genetic basis; or in particular research designs). Finally, the advantage of excluding either related (eg, for IBD) or unrelated (eg, for paediatrics) donors still needs additional research to be addressed.

Preparation of faecal material

Key issue: stool handling and fresh faeces preparation
Statement: A minimum set of general steps has to be followed for the preparation of fresh faeces (see box 4).

Quality of evidence: moderate.
Strength of recommendation: strong.

Comment: The general steps (box 4) recommended by this statement are based on what has been described, but never...
rigorously tested. There are no reported studies comparing different preparation protocols of fresh faecal material, but the protocols used in different studies are comparable and allow good/moderate evidence of suitable protocols of fresh faecal preparation for FMT treatment of rCDI. The treatment efficacy with all considered protocols has been over 80%. When reported, fresh faeces have been used for transplant within 6 hours after evacuation or on the same day. Both anaerobically and aerobically prepared samples are efficient in treatment of rCDI. This could be due to the fact that a considerable part of the bacterial genera of healthy microbiota produce resilient spores allowing interindividual transfer of at least a proportion of oxygen-sensitive intestinal bacteria. Given that these spore-forming bacteria typically represent about one-third of gut bacteria, and that disorders associated with microbiota alteration, such as IBS or IBD, are typically defined by lower abundance of anaerobic bacteria, it is rational to expect that the anaerobic processing of samples would be relevant for FMT success in the treatment of these disorders.

The amount of used faecal material varies from study to study, with most studies using 50 g of faeces; nevertheless, recently, even 30 g of faecal material were shown to be sufficient for successful FMT. However, the panel recognises that stool weight is a highly imperfect measure of microbiota quantity and acknowledge that there is wide variability in microbial content in stool between individuals and even different donations.

Moreover, the panel recommends faecal material to be diluted with sterile saline solution (0.9%) with three to five times larger volume of solvent (eg, 30 g of faeces to be diluted in 150 mL of saline). In some studies, water has been successfully used as a solvent of faecal material (eg, Satokari et al.). Although it has been reported that the preference should be given to saline as this solvent enables better preservation of microbes, conclusive comparative studies are missing. After homogenisation, the solids should be strained using gauze, tea strainer or similar device and suspension should be poured into a sterile container.

**Guidelines**

**Box 4 Minimum general steps to follow for the preparation of fresh and frozen faecal material**

**FRESH FAECAL MATERIAL**
- Fresh stool should be used within 6 hours after defecation
- To protect anaerobic bacteria, the storage and preparation should be as brief as possible
- Until further processing, the stool sample can be stored at ambient temperature (20°C–30°C)
- Anaerobic storage and processing should be applied if possible
- A minimum amount of 30 g of faeces should be used
- Faecal material should be suspended in saline using a blender or manual effort and sieved in order to avoid the clogging of infusion syringes and tubes
- A dedicated space, disinfected using measures that are effective against sporulating bacteria, should be used
- Protective gloves and facial masks should be used during preparation

**FROZEN FAECAL MATERIAL**
- At least 30 g of donor faeces and 150 mL of saline solution should be used
- Before freezing, glycerol should be added up to a final concentration of 10%
- The final suspension should be clearly labelled and traceable, and stored at −80°C
- On the day of faecal infusion, faecal suspension should be thawed in a warm (37°C) water bath and infused within 6 hours from thawing
- After thawing, saline solution can be added to obtain a desired suspension volume
- Repetitive thawing and freezing should be avoided

**Key issue: preparation and defrosting of frozen faecal material**

**Statement:** Frozen faecal material can be used for FMT. A minimum set of general steps has to be followed for the preparation of frozen material (see box 4).

**Quality of evidence:** moderate.

**Strength of recommendation:** strong.

**Comment:** The FMT approach based on frozen faeces is essential for the development of a stool bank and is the optimal way to standardise the FMT process and to allow the availability of stool on demand, without delays associated with new screening. Comparative RCTs have shown similar efficiency of FMT performed with fresh and frozen faecal samples for the treatment of rCDI. Similar to fresh samples, preparation of frozen faecal suspensions under normal air or under oxygen-free atmosphere yielded similar resolution rate. For indications other than rCDI, anaerobic preparation might be more relevant, as indicated by higher resolution rates achieved with anaerobically prepared samples when compared with aerobically prepared faecal suspensions. The panel recommends to use at least 30 g of donor faeces and 150 mL of saline solution. Before freezing, glycerol should be added up to a final concentration of 10%. Glycerol protects microbial cells from damage induced by freezing. On the contrary, the use of ethanol is still controversial. Despite encouraging phase I findings, ethanol-treated mix of sporulating bacteria failed to treat rCDI in a phase II study. It is plausible that ethanol, beyond killing pathogens, can also severely alter the composition of commensal microbiota, possibly eliminating critical elements such as bacteria-phages, fungi and non-sporulating bacterial components.

The final suspension should be clearly labelled and traceable (using codes similar as for blood and tissue transplantation) and stored at −80°C. Storing at −20°C might be feasible, but should be avoided since it allows some enzymes to be active, which can lead to degradation of sensitive microbial populations (eg, Bacteroidetes). Nevertheless, further studies are needed to show the optimal storage temperature of the frozen samples.

On the day of faecal infusion, faecal suspension should be thawed in a warm (37°C) water bath. After thawing, saline solution could be added to obtain a desired suspension volume. The
thawed faecal material should be infused within 6 hours after defrosting. Since microbial cells are sensitive after defrosting, repetitive thawing and freezing should be avoided and frozen samples should be prepared in doses needed for each infusion procedure.

**Key issue: microbiota analysis of donors and recipients**
See online supplementary 1.

### Clinical management and faecal delivery

**Key issue: recipient preparation**

#### Antibiotics

**Statement:** Patients with rCDI should be treated with vancomycin or fidaxomicin at least for 3 days before FMT. Antibiotics should be stopped 12–48 hours before faecal infusion.

**Quality of evidence:** moderate.

**Strength of recommendation:** strong.

**Comment:** In patients with rCDI preinfusion use of metronidazole, vancomycin or fidaxomicin should be performed for at least 3 days,1 3 17 20 – 22 in order to repress the abundance of intestinal *C. difficile*. However, antibiotics should be stopped 12–48 hours before stool application.

In emergencies, if frozen donor samples are immediately available, bridging therapy with antibiotics can be dispensed.

In indications other than rCDI, for example, IBD, there are no high quality data to support any recommendation, even though antibiotic pretreatment could potentially increase clinical response.61

#### Bowel lavage

**Statement:** Recipients should be prepared with bowel lavage by polyethylene glycol before procedure when FMT is performed by upper route or by colonoscopy.

**Quality of evidence:** low.

**Strength of recommendation:** weak.

**Comment:** For delivery by colonoscopy, recipients receive a conventional colon lavage routinely given prior to colonoscopic examination.2 17 20 21 As bowel lavage is able to reduce the abundance of *C. difficile*, it is also reasonable to suggest it also when FMT is performed via upper GI tract.1 2 3 17 20 21 32 33 However, there is some report showing high success rate of FMT performed via upper GI tract and without prior bowel lavage.34 For delivery via enema, no preparation instructions have been developed. In particular, with a large RCT to treat rCDI by FMT, Lee *et al* obtained high cure rates using enema faecal delivery without colon lavage prior the procedure.3

**Key issue: routes of faecal delivery**

#### FMT via colonoscopy

**Statement:** When possible, donor stools should be infused into the right colon via the working channel of the colonoscope. In cases of severe colitis, faecal suspension can be disposed in the left colon for safety reasons.

**Quality of evidence:** high.

**Strength of recommendation:** strong.

**Comment:** Different routes of faecal delivery have been reported. Many systematic reviews and meta-analyses reported that colonoscopy achieved higher resolution rates of rCDI and similar safety profile than other routes of delivery.4 5 Depending on the general condition of the recipient, donor stool can be applied to the right or to the left colon.2 7 26 31 55 It does not seem to be very essential to dispose the suspension in multiple, smaller portions as it will distribute by gut peristalsis anyway. An amount of 200–500 mL of faecal suspension obtained from 20 to 100 g faeces can be delivered safely to the colon in contrast to other sites.2 26 37 45 56

#### FMT via enema

**Statement:** FMT can be applied by enema. Patients should be instructed to hold the infused material for at least 30 min and to remain supine to minimise the urge to defecate. The procedure could be repeated.3

**Quality of evidence:** low.

**Strength of recommendation:** strong.

**Comment:** Enema as route of administration have been reported in rCDI, in paediatric patients as well as in critical ill patients when colonoscopy was contraindicated.13 In other indications than rCDI, some study protocols implicate repeated enemas to increase clinical success.15 The enema route of administration may offer some advantages, as it is widely available and does not require costly devices. It is less invasive than other routes.

#### FMT via upper GI tract

**Statement:** FMT can be performed via upper GI tract. The faecal suspension can be delivered through the working channel of a gastroscope, or through nasogastric, nasojejunal or gastrostomy tube. Patients must be kept in a 45° upright position for 4 hours after infusion in order to prevent aspiration.

**Quality of evidence:** high.

**Strength of recommendation:** strong.

**Comment:** When applied to the upper GI tract, total volumes of inserted bacterial suspension are much lower, about 25–50 mL compared with lower GI tract application.57 Volumes up to 500 mL have been placed via nasojejunal tubes over a longer period (2–3 min/50 mL).1

The peri-interventional use of prokinetics and proton pump inhibitors (PPIs) has been reported in case of upper GI delivery.20 58 59 However, their beneficial use has not been proven yet.

Due to side effects and gut microbiota modifying effects of prokinetics and PPIs, their use should be considered cautiously.60 61

Protocols using capsules containing faecal preparations for oral administration are up to now under investigation, with mixed results.62–64 This approach could expand the availability of FMT therapy in terms of accessibility and patient desirability. However, conclusive results are lacking, as comparative trials have not been performed yet.

**Key issue: safety considerations**

**Statement:** FMT appears to be safe even in immunocompromised and critically ill patients regardless the route of delivery. In case of critically ill patients, faecal infusion by enema(s) should be preferred.

**Quality of evidence:** low.

**Strength of recommendation:** strong.

**Comment:** FMT has been performed in elderly,65 immunocompromised66 67 as well as in critically ill patients, via upper and lower GI tract. However, the rate of serious adverse events in recipients who received FMT via upper GI tract seems to be higher. Aspiration pneumonia due to nausea and vomiting by a nasogastric or nasojejunal tube has been reported.3 37 68 Fever has been observed both after via-upper GI and (less frequently) after via-colonoscopy infusion.38 58 59 67 68 In the study by Moayyedi *et al*,13 rectal abscesses after via-enemas infusion of faeces or placebo were reported in patients with UC. However, perianal disease in UC is also known to occur regardless of FMT.69
Key issue: repeated faecal infusion

Statement: Faecal infusion can be repeated in case of treatment failure or clinical recurrence of CDI.

Quality of evidence: high.

Strength of recommendation: strong.

Comment: In severe CDI infection, especially in colitis with endoscopic evidence of pseudomembranes, repetition of faecal infusion had been necessary to induce clinical remission.\(^2\) 0\(^{32}\) 70\(^{72}\) Success of FMT may also depend on the amount of delivered faecal suspension, which can be increased by multiple infusions.\(^3\) Factors negatively influencing the outcome of FMT might be low volume of donor stool, severe colitis and/or ongoing antibiotic treatment and route of delivery, together with frequency of CDI-related hospitalisation.\(^7\)

Stool from another donor should be considered in case of failed clinical resolution despite multiple infusions.

In other indications than rCDI, such as IBD, repeated FMTs have been reported to increase the success rate.\(^14\) 15\(^{51}\) 73\(^76\) Nevertheless, in many other potential indications than rCDI proven standard procedures are lacking.

Key issue: monitoring of patients (adverse events and efficacy outcomes)

Short-term monitoring of patients for adverse events

Statement: Recipients should be monitored for the occurrence of possible acute complications related to the procedure.

Quality of evidence: low.

Strength of recommendation: weak.

Comment: Infection control practices of patients with rCDI should be performed as recommended by international guidelines.\(^12\) 13 according to disease severity and comorbidities. The need for hospitalisation of patients with other underlying diseases depends on the diagnosis and clinical condition. When repeated faecal infusions are necessary, provided that the patient’s condition is good, further applications can be performed in an outpatient setting.\(^15\) The duration of the observation period has not been defined yet, as it depends on the route of delivery, the underlying diseases and the general condition of the patient.\(^72\)

Most common short term adverse events after FMT due to CDI have been described as diarrhoea, abdominal cramps, belching, constipation, fever as well as Gram-negative bacteraemia and perforation.\(^1\) 42\(^65\) In IBD, diarrhoea, abdominal bloating and cramping, fever and deterioration of disease have been reported.\(^51\) 58\(^77\) 78 Mortality has been reported as an outcome due to aspiration during sedation after FMT via colonoscopy.\(^79\) Another patient died after regurgitation of faecal material infused into the duodenum under general anaesthesia.\(^57\) After delivering donor stool via a pre-existing nasogastric tube, another patient developed septic shock and toxic megacolon and died after colonic resection.\(^60\) Finally, a patient had a severe septic shock due to the faecal aspiration following endoscopic peroral jejunal FMT.\(^54\)

Long-term monitoring of patients for adverse events

Statement: Periodicity and length of follow-up for long-term adverse events are not determined. Follow-up should include clinical and analytical data.

Quality of evidence: low.

Strength of recommendation: weak.

Comment: To date, there are not enough long-term follow-up data to estimate potential FMT-related diseases. A single case of weight gain has been reported, as well as the development of peripheral neuropathy, Sjögren’s disease, idiopathic thrombocytopenic purpura and rheumatoid arthritis.\(^37\) 81 There are other anecdotal reports about improvement of non CDI-related diseases after FMT as IBS, chronic constipation, antibiotic-induced non-infectious colitis as well as extraintestinal diseases as Parkinson’s disease, multiple sclerosis and idiopathic thrombocytopenic purpura.\(^82\) 83\(^84\) However, causality to FMT remains unclear. The transmission of malignant, autoimmune, metabolic or neuropsychiatric diseases have been discussed and at least partially shown in animal models.\(^84\) Patients with CDI are known to be at high risk of postinfectious IBS.\(^85\) However, the role of FMT in this context has to be elucidated.

The implementation of registry data collections can effectively deal the issue of long-term monitoring of patients for adverse events.

Monitoring of patients for efficacy outcomes

Statement: Patients receiving FMT for CDI should be followed up for at least 8 weeks.

Quality of evidence: low.

Strength of recommendation: strong.

Comment: Treatment response implies clinical improvement,\(^13\) as reduction of stool frequency and improvement of stool consistency, as well as amelioration of other parameters of disease severity as laboratory parameters, radiological and/or endoscopic findings. Repetition of C. difficile testing in stool samples is generally not recommended, as toxins might stay positive for weeks. In clinical practice, it is not rational to distinguish between recurrence and relapse of CDI.

Basic requirements for implementing an FMT centre

Key issue: clinical requirements and facilities

Statement: Development of referral FMT centres for the treatment of CDI in clinical practice is encouraged. Centres should be implemented in hospitals with appropriate expertise and facilities.

Quality of evidence: moderate.

Strength of recommendation: strong.

Comment: CDI is the most common cause of diarrhoea in inpatients, and is increasing in incidence, morbidity, mortality and likelihood to recur.\(^8\) On the other hand, CDI not responding to standard therapy is a complex disease requiring clinical expertise. FMT achieved significant advantage over standard antibiotic therapy for the management of rCDI in RCTs,\(^1\) 2 and is clearly recognised as a reliable and cost-effective treatment for this burdensome disease.\(^6\) 9\(^9\) 11 Therefore, the dissemination of the FMT procedure and the establishment of FMT services into clinical setting could be useful practices to reduce the healthcare burden of rCDI,\(^43\) as advocated by physicians interested into gastroenterology and infectious diseases.\(^3\) 5\(^19\) 86\(^-\)89\(^9\) The development of an FMT centre service could fill the therapeutic gap for the management of the life-threatening rCDI by ensuring the optimal standardisation of the FMT process.

Statement: In order to establish an FMT centre, actively involved members are encouraged to undergo a specific training on FMT processes.

Quality of evidence: low.

Strength of recommendation: strong.

Comment: As with other technical procedures, a specific training period is required before performing FMT. Therefore, physicians who are going to implement FMT in their centre are encouraged to undergo a prior training. Essentially, training on FMT is composed of three parts: clinical training, which includes donor and patient selection, and patient management after FMT; delivery training, which includes the learning of...
different routes of delivery (eg, enema, colonoscopy, nasoduodenal/nasojejunal tube, etc) and microbiological training (preparation of fresh and frozen faecal material).

Statement: The assemblage of a multidisciplinary team, including gastroenterologists, microbiologists and infectious disease physicians, is encouraged to build an FMT centre.

Quality of evidence: low.
Strength of recommendation: strong.

Comment: There are no published data supporting this statement, and evidence comes from opinions of the expert panel, based on clinical experience, descriptive case studies or reports of expert committees. Nevertheless, the panel strongly believes that the development of a multidisciplinary team, composed of gastroenterologists, microbiologists and infectious disease physicians, will be extremely useful to build an FMT referral centre, because it would gather different and complementary expertises.

Statement: The availability of several facilities (including endoscopy service, clinical ward and outpatient clinic) is mandatory to implement an FMT centre. FMT can be performed within either inpatient or outpatient setting.

Quality of evidence: low.
Strength of recommendation: strong.

Comment: There are no published data supporting this statement and evidence comes from opinions of the expert panel, based on clinical experience, descriptive case studies or reports of expert committees. Provided that the patient’s condition is stable, faecal infusion can be performed in an outpatient setting. The panel strongly believes that several facilities are needed to build an FMT referral centre, to offer FMT to both patients with mild and severe CDI, to manage potential adverse events related either to the procedure or to the infused material and to easily follow-up patients after FMT.

Statement: A clinical governance dealing with administrative issues of FMT is recommended to develop an FMT centre.

Quality of evidence: low.
Strength of recommendation: strong.

Comment: There are no published data supporting this statement and evidence comes from opinions of the expert panel, based on clinical experience, descriptive case studies or reports of expert committees. The panel believes that the implementation of a clinical governance within the FMT centre would be extremely useful to deal with administrative issues related to FMT (eg, reimbursements, authorisations), and to overcome all bureaucratic and organisational barriers that may prevent the development and the work of the centre itself.

Key issue: microbiological requirements and facilities
Statement: FMT centres need to have an access or be part of the facility that allows safe processing of human samples (biosafety level 2) including aliquoting, storage and preparation of faeces. Stool banking is encouraged.

Quality of evidence: low.
Strength of recommendation: strong.

Comment: There are no evidence-based data supporting the recommendation of high-quality microbiological requirements for building an FMT Centre. Current recommendations include expert opinions from the expert panel and existing general recommendation including guidelines for safe work practice.

One of the key functions of the FMT centre is the management of blood and faecal samples from either donor or recipients. C. difficile is a pathogen with a biosafety level 2 (cabinet with high-efficiency particulate air filter) and according, safety requirements and recommendation need to be implemented.

Material processing (fresh faeces, bank of frozen and stored faeces) and safety precautions have to adhere to basic principles for safe preparation of human material, including: rigorous protocols in securing the materials; maintenance of standard operating procedures (SOPs) for the processing; use of certified laboratory testing; definition of quality control tests and standards for the release of the final product.

There are numerous advantages associated with the implementation of stool banks (such as the OpenBiome initiative in the USA). A frozen stool bank allows faecal donors to be recruited and thoroughly screened ahead of time, in a methodical manner, without time pressure and with the potential advantage to reduce the costs associated with donor screening as one donor can serve for multiple FMT donations. Furthermore, the accumulation of expertise and the standardisation of FMT processing ultimately allow optimising the quality control, a greater potential for rigour of testing and the coordination of research activities/outcomes monitoring. Finally, stool banks may improve the accessibility of FMT to centres that otherwise would be unable to provide the service due to inadequate resources to conduct donor recruitment/screening and FMT processing.

Statement: FMT procedure and donor screening documentation should be stored for at least 10 years (unless local requirements consider longer retention period) in order to archive donor material in case of future adverse events.

Quality of evidence: low.
Strength of recommendation: strong.

Comment: Management of the records related to the FMT procedure should be regulated by local health organisation. FMT procedure and donors’ and recipients’ records should be stored for at least 10 years. This may differ according to local requirements, and longer storage time could be needed. The records of the FMT centre will provide access to the long-term safety data.

Samples of donor faeces before the processing and before the administration to recipients should be stored for a possible microbiological evaluation and qualitative and quantitative characterisation due to safety reasons. The frozen samples should be stored in adequate facilities (or, when specifically regulated, by authorised facilities) and should be clearly labelled with the code of the donor and the date of donation.

Key issue: regulatory requirements
Statement: Appropriate FMT registries should be implemented, in order to collect data concerning indications, procedure, effectiveness and safety profiles.

Quality of evidence: low.
Strength of recommendation: strong.

Comment: There are no published data supporting this statement, and evidence comes from opinions of the expert panel, based on clinical experience or on reports of expert committees. Recently, the American Gastroenterological Association established a National Institutes of Health-funded registry to track patient outcomes associated with FMT, with the ultimate objective to protect the well-being of patients and guide further scientific exploration in the field. Such a registry would serve as a source of short-term and long-term information about the clinical practice of FMT in the USA.

FMT has not undergone traditional regulatory approval process of pharmaceutical products with sequential testing leading to large phase III trials assessing efficacy and safety prior to clinical utilisation. Therefore, the panel believes that the creation of registries to be kept at the local (hospital) and/or at the regional, national or international competent authorities is relevant to collect data and could be useful to deal with outcomes and safety issues related to FMT. In order to trace causality of
FMT and newly developed diseases, traceability by keeping appropriate registries would be a wise process to learn about potential long-term side effects.

Statement: Specific national rules for the classification of FMT should be followed to implement an FMT centre.

Quality of evidence: low.

Strength of recommendation: strong.

Comment: A commonly acknowledged regulatory classification for FMT has not been established yet in Europe. Several countries have introduced some national rules and others require to be compliant to the European directive 2004/23 on quality and safety of tissues and cells.94

As FMT falls under the category of ‘Substance of Human Origin’ like cells, tissues, milk, etc., the most important requirements should be followed, as for example an adequate facility.

Activities and responsibilities for processing and testing the raw material, for use of equipment, for preservation and storage and for release and distribution of FMT, should be described in SOPs.

CONCLUSIONS

This consensus indicates that the only clinical indication with sufficient evidence of benefit from the implementation of FMT in clinical practice is CDI (see online supplementary 2). The consensus panel strongly recommends the implementation of FMT centres for the treatment of CDI in adults.

CDI is the most common cause of infectious diarrhoea among hospitalised patients, and, despite advances in both drug treatment and infection control practices, complications rates (such as sepsis, toxic megacolon, death) continue to increase, mainly due to treatment failure and recurrence of infection. Therefore, CDI may represent a considerable therapeutic challenge for clinicians. The clinical burden of rCDI is intuitively tied to a commensurate economic burden, which is principally due to the increased duration of hospitalisation or re-admission and the management of complications.

On the other hand, although FMT has been shown to achieve excellent cure rates with few serious adverse events, physicians together with hospital organisations are not ready yet to offer this option of treatment to such patients because a series of technical, logistical and bureaucratic issues have hampered the development of an FMT capability at many hospitals. This mainly occurs because a clear global regulation is still lacking, particularly in Europe.

We believe that the results obtained by this evidence-based consensus conference are important because they reiterate the need to make use of the FMT for the treatment of CDI, establish technical guidelines of the procedure and mostly indicate basic requirements for an organisative model, which is essential to implement FMT in the clinical practice within an appropriate safety control and clinical governance (see online supplementary 2). At last, this can help to make a life-saving treatment option for patients widely available, with a profitable impact on the healthcare system.

Moreover, there is no strong evidence-based recommendation for the use of FMT in other clinical conditions, although interesting findings come from the application of FMT for the treatment of UC,15 MS,16 IBS17 and, more recently, graft-versus-host disease.18 Therefore, the experience resulting from an FMT approach to CDI could be translated in terms of scientific information, technical know-how and knowledge dissemination platforms to other research areas, with the ultimate goal of understanding the role that may be played by FMT, in the future, in other clinical conditions.

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Contributors GC, GI and AG planned the meeting and established the main topics. All panel members were involved in developing the statements with supporting evidence and drafted the text of discussion relevant to their statements. GC wrote the initial draft of the manuscript. All panel faculties read and revised the manuscript for important intellectual content and approved the final manuscript.

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