# Supplementary materials

A: Full version of the guideline

B: Glossary

C: Guideline development and conflicts of interest

D: Consultation

E: Continuing Professional Development

F: Lay materials

## A: Full version of the guidelines

A full version of the guideline is available **below**, at HIS website: <https://his.org.uk/resources-guidelines/faecal-microbiota-transplant/> , and on BSG website TBC



## B: Glossary

**Antisecretory medication:** a medication that reduces the normal rate of secretion of a body fluid. In terms of FMT, this medication reduces stomach acid secretion (e.g. proton pump inhibitory and H2-receptor antagonist medications).

**Bookend testing:** A type of screening/assessment which aims to capture changes to donor eligibility, as well as risk factors for pathogen acquisition, in the interval between donor acceptance and donation. Bookend testing should identify asymptomatic pathogen acquisition in the interval between donor acceptance and donation. Depending on donation and screening frequency, this may allow for an exemption from direct testing at, and of, each donation.

**Bowel lavage (prep):** a process which involves an administration of a solution to clean the colon for colonoscopic examination.

***Clostridioides difficile*** (commonly known as *C. diff*): a type of bacterium which causes diarrhoea and inflammation of the colon (known as *C. diff* infection or CDI).

**Complicated CDI:** a severe CDI infection characterized by life-threatening features such as shock, sepsis or colon perforation.

**Engraftment:** a process in which it is evident that bacteria from the stool donor successfully colonised and populated the colon of the recipient.

**Faecal microbiota transplant:** a treatment which involves transfer of healthy bacteria from a stool of a healthy person to the intestine of the patient.

**Fidaxomicin:** a relatively new class of antibiotics which is specifically used for the treatment of *Clostridioides difficile* infections.

**Immunocompetent:** a person with fully functioning immune system

**Immunocompromised:** a person in whom the immune system is not functioning at the optimal level.

**Immunosuppressed:** a person with fully functioning immune system who is undergoing a therapy which slows down the immune system (e.g. post-transplant, autoimmune diseases or cancer chemotherapy).

**Inflammatory bowel disease:** a group of disorders which cause a long-term inflammation of the bowel (intestines). IBD term includes ulcerative colitis and Crohn’s disease.

**Lyophilised:** freeze-dried, a process in which a specimen is frozen and the water is removed.

**Pseudomembranous colitis:** a severe colonic infection in which plaques appear in the colon and combine to form a growth known as pseudomembranes. This form of colitis is usually associated with *Clostridioides difficile* infections.

**Recurrent CDI:** *Clostridioides difficile* infection which initially responded to the antibiotic treatment but which since came back (relapse). Most clinicians consider the infection to be recurrent if it comes back within eight weeks.

**Refractory CDI:** *Clostridioides difficile* infection which did not respond to the antibiotic treatment. This is usually when symptoms persist, although for some patients infection may be cured while they still experience symptoms.

**Sediment:** a portion of the faecal sample which has been centrifuged. After this process, after a short period of time (e.g. 15-30min), contents separate into lighter liquid (see **supernatant**) with the heavier, solid portion of the stool (sediment).

**Slurry:** A mixture of solid matter (which in terms of FMT, come from stool) suspended in water.

**Supernatant:** a portion of the faecal sample which has been centrifuged. After this process, after a short period of time (e.g. 15-30min), contents separate into lighter liquid (supernatant) with the heavier, solid portion of the stool (sediment).

Vancomycin: an antibiotic which is used for treating a wide range of bacterial infections. When taken orally, it is not absorbed into the body, therefore it has an opportunity to act on *Clostridioides difficile.*

## C: Guideline development and conflicts of interest

*Guideline development process*

National Institute of Health and Care Excellence. Developing NICE guidelines: the manual. Process and methods; 2018. Available at: <https://www.nice.org.uk/process/pmg20/chapter/introduction> [last accessed October 2023].

**The Working party members declared following conflicts of interest:**

**BHM** has received consultation honoraria from Ferring Pharmaceuticals, Finch Therapeutics, Summit Therapeutics and speaker fees from Yakult. BHM is also a member of editorial board for Journal of Hospital Infection and Infectious Disease Reports.

**BM** received speaker fees from New Scientist.

**MNQ** received speaker fees from BMS, Parapharm, Tillots, Jannsen and Takeda.

**AB** declared no conflicts of interest.

**CG** declared no conflicts of interest.

**DM** declared no conflicts of interest.

**RP** declared no conflicts of interest.

**NE** has received speaker fees from a company not related to the topic of this guideline.

**JS** received speaker fees from Takeda, AbbVie, Pfizer and BMS.

**NS** received consultancy fees for advisory board for Pharmacosmos

**BMa** declared no conflicts of interest.

**GK** declared no conflicts of interest.

**SM** declared no conflicts of interest.

**AH** received fees for consultancy and speaker for AbbVie, Arena, Atlantic, Bristol-Myers Squibb, Celgene, Celltrion, Falk, Galapogos, Lilly, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. She also serves on the Global Steering Committee for Genentech.

**CS** is a Chair for the Healthcare Infection Society.

**JK** received consultancy fees from Vedanta Biosciences and Microviable Therapeutics and received a research grant from Vedanta Biosciences. JK is a member/scientific committee of European Helicobacter Microbiota Study group, member of the Scientific Advisory Board of “Microviable Therapeutics”, a member of a steering committee scientific study VE202 for ulcerative colitis (Vedanta Bioscienes) and a founder and board member Netherlands Donor Feces Bank (academic, non-profit)

**PH** Received consultancy and speaker fees from commercial companies and is a Director Modusmedica Ltd (since 2010 onwards)

**TI** received consultancy fees from Ferring and speaker fees from Pharma cosmos. TI is a member BSG/HIS microbiome for health expert panel and a Director of University of Birmingham Microbiome Treatment Centre

**SG** received consultancy honoraria from Enterobiotix and Astra Zeneca, received speaker fees from Tillotts and has investments in biomedical company not related to the topic of this guideline.

**HW** declared no conflicts of interest.

## D: Consultation

### Internal consultation

| **Section**  | **Comments** | **Working Party response** |
| --- | --- | --- |
| **Anonymous response, HIS**  |
| 4.1 | “**First episode of CDI***Effectiveness of FMT:* There was weak evidence which suggested that FMT is effective in these patients.29“There was an RCT of FMT for first and second episodes of CDI in Lancet Gastroenterol Hepatol 2022;7:1083-91. I have a few issues with this paper, but it is nonetheless an RCT, which should be considered in my view. | Thank you for this comment. The section here is for first episode of CDI while the paper cited used first and second episode. Unfortunately, it is not possible to separate the data for first and second episode in this study and, therefore, we were not able to use the results to support this evidence statement. However, this study is included in the meta-analysis for the effectiveness, and it is also mentioned in the summary section where we say that the effectiveness is established but FMT is still an invasive and expensive procedure and that we do not currently know if it is justified for these patients.  |
| **Anonymous response, HIS**  |
| 4. Rationale for recommendations | Patients with severe, complicated or fulminant CDI Effectiveness of FMT in patients with severe CDI: There was weak evidence which suggested that FMT is beneficial in this patient group.16Effectiveness of FMT in patients with severe CDI compared to patients with mild/moderate CDI: There was moderate evidence which suggested there was no difference between these two patient groups.17-23 Effectiveness of FMT in patients with refractory or fulminant CDI vs recurrent CDI: There was inconsistent evidence which suggested no difference in effect for these patient groups.24-28 Effectiveness of FMT in patients with pseudomembranous colitis compared to other patients: There was weak evidence, and it is not clear whether in these patients FMT may be less successful.18,21Adverse events in patients with severe, refractory or fulminant CDI: There was weak evidence which suggested there was no increased risk associated with FMT for these types of patients.16,17,24 Adverse events in patients with pseudomembranous colitis: There were no studies.Good practice pointsGPP 1.1: Consider early FMT for patients with severe or complicated CDI who are not responding to antimicrobial therapy.Is the guideline suggesting early FMT for severe or complicated CDI who are not responding to antimicrobial therapy without adequate evidence? | Thank you for this comment. Please note that weak evidence is the quality of the evidence while ‘beneficial’ implies the direction and an observed positive effect. The statements can be interpreted (and this has been summarized further down) as:- evidence is weak but it still suggests that FMT is effective for patients with severe/complicated/fulminant CDI. - evidence was moderate but suggested that FMT is equally effective in patients with severe as well as with mild/moderate CDI- evidence was inconsistent refractory or fulminant CDI but again, suggested that FMT is as effective as for patients with recurrent CDI- evidence is weak but there is a possibility that FMT is less effective for patients with pseudomembranous, which does not imply it is ineffective. - with the volume of the evidence published on FMT, we think that the small number of studies which point out to no effect means that it is unlikely that there is a risk of adverse events from FMT. We think the risk is greater if FMT is not given. Thus, we think there is sufficient evidence to recommend FMT to this type of patients. Please also note that this good practice point (not recommendation) especially states that, for these patients, FMT should be considered earlier than usual.  |
|  | It doesn’t have any comment on the early FMT for fulminant CDI. Does complicated CDI and fulminant CDI have the same meaning in this guideline? | Thank you. We added fulminant CDI to the recommendation.  |
|  | How early is early for FMT in this sentence? | Thank you for this comment. Recommendation 1.3 states to offer FMT for patients who had a second recurrence. However, considering the evidence highlighted in the above response, we think it would not be best to offer FMT earlier than usual. Therefore, for the first or the second episode.  |
| Resolution or improvement of conditions following FMT(P.g 13, line 309) | One dose of FMT may be less effective in patients with pseudomembranous colitis and to achieve a desired effect, these patients could benefit from additional doses. However, clinically, this issue may not be relevant because in practice CDI patients are not routinely assessed for the presence of pseudomembranous colitis.In my own clinical practice, CDI patients are assessed for the presence of pseudomembranous colitis if the patients have severe C.diff colitis features. It should have mentioned clearly which CDI patients are not routinely assessed for the presence of pseudomembranous colitis. | Thank you. We previously discussed this issue at the meetings and the consensus was that, in practice, it is usually not known whether patients have pseudomembranous colitis. In fact, the experience of most of the working party members was that it was discovered only when FMT was delivered via colonoscopy. However, we do not think this changes any of our recommendations. I.e. if a patient does not respond to FMT, we recommend that another FMT is offered. Therefore, clinically, same decisions would be made for patients with and without pseudomembranous colitis.Please note that for this reason, we did not make any recommendations regarding this issue. It is only mentioned in a summary to highlight how the working party interpreted the evidence.  |
| Box 1: Recommended Donor History Questionnaire(P.g 25) | It should include animal exposure/contact including pets. Some GI pathogens including worms can be transmissible from animals to humans.It should also ask the history of worms’ infestations and any anti-helminths agents taken in the screening questions, although stool ocp are tested. | Thank you for your response. We discussed your comment and we do not think this is feasible. This would require the centres to have a different testing schedule. If the testing schedule stays the same regardless of whether there's a different risk and factor question, then there would be no point having the question on the questionnaire. |
| Box 3: Recommended Stool Screening(P.g 26) | Is Multidrug resistant Pseudomonas aeruginosa included in the stool screening for multidrug resistant bacteria?Is screening of Big V carbapenemase producers enough? Does it need to be screened out of Big V like GES and many others? The guideline doesn’t mention which CPEs should be clear from the donor. | Thank you, we think our advice here is adequate. With testing for microorganism, there needs to be a degree of flexibility as to which MDROs are relevant due to different epidemiology and donor risk factors. We therefore think it is up to the centre to think which MDROs are relevant to them. We have added the wording “included but not limited to…” to make it clearer.  |
| **Dr Bin Gao, Tianjin 4th Centre Hospital, Tianjin, China, HIS**  |
| General | Please consider adding inflammatory bowel disease before the IBD and bracketing it in Page 3, and wording IBD directly in Page 10. | Thank you, we changed this.  |
| 6.1, 6.2, GPP 6.1 | Please consider choosing item of 6.2 or GPP 6.1 either, rather than both. | Thank you, we corrected this issue.  |
| 9.2 | 9.2: When offering compassionate use of FMT, the following conditions must be met simultaneously (at once): | Thank you for your comment. We do not think this is necessary. It is clear from the sentence that all conditions must be met which implies that they all need to occur at the same time.  |
|  (P. 6, line 64 | Please consider adding acronym of the term “irritable bowel syndrome” followed within a bracket as IBS used in the following part of the document. | Thank you, we corrected this issue.  |
| P. 8, line 125/144/150 | Please check whether the reference cited here accurately reflect the corresponding text (additional reference needed). | Thank you, we corrected this issue. |
| P. 13, line 325 | Please check whether the reference cited here accurately reflect the corresponding text. | Thank you, we corrected this issue. |
| General | Please consider adding “WHAT’S NEW SINCE 2018 GUIDELINES?” to summarize the document snappily and friendly. | Thank you for this comment. We, in fact, are considering writing an editorial which will highlight these changes.  |
| **CSSC member, BSG** |
|  | A very well written guideline. Excellent, detailed work written in a very clear and systematic way.No concerns | Thank you for your kind comments. |
| **IBD Section Member, BSG** |
|  | no comments from me. I'm happy | Thank you for your kind comments. |
| **CSSC member, BSG** |
|  | Very comprehensive and well written guideline. It would be very helpful if the GRADE rating for each recommendation was clearly visible. | Thank you for your kind comments. |
| **Shanom Ali, UCLH, UK, HIS**  |
| 4.4  | Considerations / Good practice for faecal acquisition, storage and preparation. The volume of cryoprotectant should be proportional to the mass of faecal same to assure consistency in practice. An expected cryopreservant range should be proposed. For general microbiology applications 10-15% is used. For ease of calculation 10% is practical.  E.g. if aiming for a 50g stool, the volume of glycerol would by 5mL. | Thank you, agree that 10-15% needs to be stated. However, we think that this is not the same as 5ml of 100% glycerol per 50g of stool, as this does not account for the volume of diluent used in making a faecal slurry. This should be 10-15% of the final slurry and we added this as a GPP 4.8.GPP 4.8: Where glycerol is used as a cryopreservative, ensure it is at 10-15% final concentration of the prepared faecal material/slurry, with vortexing or other methods used to fully mix the cryopreservative into the material. |
| 4.4  | Since the water content can cause bacterial decay upon freezing, effort to assure the cryoprotectant is mixed into the faecal sample. This will assure the bacterial diversity is protected/maintained as much as possible. | Thank you, this comment is now addressed in GPP 4.8  |
| 4.4  | When collecting faecal samples, efforts to remove as much water should be considered. E.g. by placing onto filter paper. This will help with the cryopreservation stage. | Thank you for your comment. We do not think this is necessary as this is not currently established in clinical practice and it would add another step to processing (extending the processing time) and increase the risk of contamination.  |
| 4.4  | When thawing samples, the temperature difference from -80oC to ambient (#25oC) is a 105oC temperature fluctuation and will cause stress on the bacterial diversity and recovery. This could be eased by initial thawing at refrigeration temperatures before final thaw at room temperature, prior to delivery. Done in this way, samples could remain in a fridge for most part of the process and require only minimal (~10-15 minutes) at ambient. | Thank you for your comment. We are not aware of any data which suggest that this is a problem. Clinically, we know that the practice of leaving the samples at ambient temperature is still effective and it is practical. We think that leaving the samples refrigirated for a prolonged period of time may be more detimental to bacterial viability.  |
| General | For reference, due to environmental legislation and energy consumption consideration, -40oC freezers are being promoted over -80oC freezing.  | Thank you for your comment. We didcussed the freezer temperature in the full text and and we have a research recommendation on this topic.  |

### External consultation

TBC

## E: Continuing Professional Development

1. When should treatment of CDI with FMT be considered?
	1. When a patient is diagnosed with CDI and has risk factors for recurrence
	2. After first recurrence
	3. After two or more CDI recurrences.
	4. After first recurrence of refractory CDI
	5. FMT can be offered to any patient with FMT.
2. Why should cancer patients not receive FMT for treatment of CDI?
	1. FMT is not effective in this group of patients
	2. They are at high risk of experiencing severe adverse events
	3. They can receive treatment but only after cancer treatment has ended
	4. Cancer patients cannot be transported to facilities where FMT is given
	5. There is no reason to suggest that cancer patients cannot receive FMT
3. Which route of FMT administration is less likely to be successful for treatment of CDI?
	1. Colonoscopy
	2. Enema.
	3. Upper GI to stomach
	4. Upper GI to duodenum
	5. Oral capsules.
4. Which donor factors make FMT less effective for treatment of CDI?
	1. Age.
	2. Mismatched sex
	3. Microbiota composition
	4. Presence of MDRO
	5. None of the above
5. For which conditions, other than CDI, FMT may be considered?
	1. Ulcerative colitis
	2. Crohn’s disease
	3. IBS
	4. MDRO
	5. Obesity

## F: Lay materials

Please follow the link below for useful information on FMT:

[**FAECAL MICROBIOTA TRANSPLANTATION**](https://gutscharity.org.uk/advice-and-information/health-and-lifestyle/faecal-microbiota-transplantation-fmt/)

**gutscharity.org.uk/info/FMT**