**Journal of Hospital Infection**

The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

--Manuscript Draft--

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<th>JHI-D-18-00499R1</th>
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<td>The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.</td>
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| Corresponding Author: | Benjamin Harvey Mullish, MB BChir  
Imperial College London  
Paddington, London, UNITED KINGDOM |
| Article Type:      | Guidelines |
| Suggested Reviewers: | |
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<table>
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<th>Question</th>
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<td>No, I do not intend to publish Open Access</td>
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Response to Reviewers, Submission JHI-D-18-0499: The use of faecal microbiota transplant as treatment for recurrent and refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

The HIS/BSG working group would like to thank Dr Gray, the editorial team and the reviewers for taking the time to review this guideline. We are glad that the overall tone of the reviews is positive, but note the suggestions made. In response, we have made a number of revisions, which we feel collectively add to the strength of the manuscript.

Thank you for agreeing to not copy edit this paper, so that we can get it online as quickly as possible. We have now corrected the references so that they are in the preferred JHI format, as requested.

Reviewer #1:
I reviewed this as an interested non-expert JHI reader so the following comments are mostly about clarification rather than the finer points of interpreting the literature. The authors are to be congratulated on getting through such an extensive task. I thought it was well-written.
Thank you for this comment.

General comment - there will doubtless be discussions with the Journal about what gets printed and what is referenced online - meanwhile I think a printed version would benefit from a summary table of your recommendations and more prominence to table 2 (donor questioning), tables 3/4 (donor screening) and table 5 (criteria for stool collection).
We note the suggestions for a summary of recommendations from both reviewers. We were also asked at the peer review stage with BSG to include this in the *Gut* version. There is also precedent for this sort of summary in HIS guidelines, e.g. multi-drug resistant Gram-negative bacteria, Wilson *et al*, JHI, 2016. As such, we have added a summary of recommendations. We agree that this adds prominence to the tables in the document.

Specific comments:

8.1.1.1: 'FMT should be offered to patients with recurrent CDI...' - effectively you're saying that this fairly novel, unlicensed, not universally available treatment should be the standard of care, and that any patient with recurrent CDI who is not offered FMT can make a case for negligent treatment. You might intend this - I wouldn't argue - but if so suggest be very clear that this is what you mean. It also conflicts with the later recommendation that before reaching for FMT you should try extended/pulsed van and/or fidax. I think you probably mean a strong recommendation that it 'should be considered'.
The working group cannot make a strong recommendation with the wording 'should be considered', as this is the preferred wording for a 'conditional' recommendation using SIGN terminology. Given the very specific wording required by HIS to ensure NICE terminology is adhered to, we do not feel that there is scope to reword this recommendation. However, the working group are confident that the existing wording clearing conveys the key message.
We do not see that recommendation 8.1.1.1. contradicts 8.1.1.4. 8.1.1.1. purely states that FMT is an appropriate option meriting consideration for certain patients with recurrent CDI, whilst 8.1.1.4. qualifies what prior treatment patients with recurrent CDI should have received prior to receiving FMT.

8.1.1.4: line 32 cites some numbers from ref 68 that don’t look right - 29/209 is not 26.6%

Thank you for spotting this typographical error – this has been corrected (29/109, not 29/209).

8.1.1.4 recommendation i: clumsily worded - could be improved?
The working group agrees this sounds verbose, but this wording is deliberate to try and qualify how ‘recurrent’ CDI should be defined within the context of this document. This was added in response to previous HIS and BSG reviewer comments asking for clearer definition of ‘recurrent CDI’.

8.1.2.3 recommendation i: 'immediate management after endoscopic FMT should be as per endoscopy unit protocol' - not sure what this recommendation achieves, maybe it could be downgraded to the text?

There was strong feeling amongst BSG/ Gut reviewers that this was a helpful recommendation, since it gives guidance to endoscopic units involved in FMT management as to the general management of FMT recipients whilst in the unit.

8.1.2.4/5 Definitions of cure and treatment failure - you acknowledge that there are no standard definitions and suggest that they should be defined case-by-case - but this is to miss an opportunity to offer standard definitions and improve care in future, which is one of the purposes of guidelines - can't you offer authoritative suggestions? The working group had previously considered this suggestion. However, their conclusion was that these definitions were more appropriately made within a specific CDI guideline. This is because the definition of failure or success of FMT should be established concurrently with the definition of failure or success of antimicrobial/ antitoxin treatment to ensure consistency.

8.2.1: you recommend against FMT in patients with anaphylactic food allergy - this was challenged in the consultation with the suggestion that other householders who follow the same restrictions might be suitable donors - that seems like a good idea with some experience behind it but you dismiss it, thereby denying FMT to this minority of patients. Why not make a recommendation to proceed only with great caution? The working group had discussed this topic at length since there is, of course, no published evidence. Their opinion was that even if a patient-selected donor was asked to avoid trigger foods, it may be difficult to gauge how well that donor has complied with the exclusion diet, and/ or how long avoidance of that trigger food is required before they could donate. In the context of patients with true anaphylaxis, the working group therefore felt that the capacity for harm from FMT overall outweighed the chances of benefit.

Also 8.2.1 you raise concerns about performing FMT in patients with decompensated liver disease, but I am unclear why they should be at greater risk from donor faeces than from their endogenous flora?
Patients with decompensated chronic liver disease are clearly at high risk of bacterial sepsis, and in many cases have significant 'leaky gut'. Gut translocation of bacterial content into the portal circulation is the likely source of many septic episodes in such patients. The adverse immunological reaction to these bacteria from the chronically damaged liver may potentiate decompensation episodes. In the opinion of the working group, the theoretical risk of transplanted faecal material translocating into the portal vein and causing adverse outcomes was sufficient to caution on its use in this setting.

8.4.3 you mention in the text that repeated freeze-thawing of donor faeces should be avoided but it's not listed in the good practice points - could it be added here (and thereby make it in to any recommendation summary)?
The working group was of the opinion that the current level of detail provided regarding this topic was sufficient, and that this did not need to be a good practice point.

8.5.1.1: you carefully avoid recommending one of upper vs lower GI administration but these are such different modalities that they must be separable at some level, even if safety/patient experience rather than efficacy. Which do patients prefer? Which is cheaper?
Within the reviewed literature, there was no evidence on whether patients prefer lower or upper GI administration (although there was evidence regarding patients preferring capsule administration to colonoscopy, as described). Cost effectiveness was outside of the remit of the working group. The working group do illustrate where one particular modality may be better suited than another (e.g. caution with upper GI administration in those with swallowing difficulties or large hiatus hernia). As such, the working group do not feel that further clarification is required.

8.5.2.3 recommendation iii: 'FMT via enema should be used as a lower GI option when delivery using colonoscopy or flexible sigmoidoscopy is not possible' - the flexisig option was added in response to a comment from one of those who took part in the consultation exercise but it sits badly with the preceding two recommendations. Suggest make clear that your order of preference goes colonoscopy > flexisig > enema
We think that the wording of this section makes sufficiently clear that flexible sigmoidoscopy is an option when full colonoscopy is considered but not possible.

8.6.6 on non-CDI indications: mention recurrent UTI due to colonisation with virulent uropathogenic strains?
The working group presume that this refers to studies using FMT in attempted decolonisation of the gut with multi-drug resistant organisms (MDRO) responsible for recurrent UTI, e.g. ESBL. However, for the section on non-CDI indications for the use of FMT, only randomised studies were considered; no randomised studies on the use of FMT as gut decolonisation of MDRO were identified (cohort studies only), so these were not considered further.

8.7.5 FMT manufacturing - 'ensure traceability of supply'. In transfusion medicine they talk of 'vein-to-vein traceability'. You could coin a term such as 'bowel-to-bowel traceability' and thereby help ensure that the lessons of transfusion governance are applied here too. There are other possibilities, obviously. Ditto you recommend that donor faeces
documentation is kept for at least 5 years - I think it's 30 years for blood products and it might be sensible to align these.

This section was written after close liaison with the MHRA, given their current role as regulators in the UK for FMT. We have been careful to use the exact terminology given to us by them, and the advice we give regarding documentation is based directly on their guidance.

Table 2 - suggested things to include in donor screening questionnaire - the implication is that different units will make up their own questionnaires along the lines you suggest but without any standardisation of detail - if instead you presented it as a draft of the questionnaire itself you would probably find it was adopted unchanged.

As described at several points in the guideline, we are aware that local factors/ preferences will markedly influence the exact protocols used in practice, including the screening questionnaire. For instance, even amongst the different centres contributing to the working group, some centres exclude all participants with a history of any colonic polyps (even if there is no malignant potential on histology), whilst others only if previous colorectal cancer. As such, we have tried to write a questionnaire that covers the mandatory minimum degree of appropriate donor screening.

Table 3 - blood screening of stool donors - hep A IgM and to a lesser extent hep E IgM are notoriously non-specific - are you suggesting that a positive result would exclude a donor or give rise to further testing? Why do you suggest measuring creatinine and electrolytes? Why CRP and what would you do if not 'normal'?

The working group’s response to this is similar to the last comment, i.e. this is the minimum appropriate screening, and these are recommendations rather than absolutes. Intuitively, most clinicians would agree, for example, that a person with a creatinine level of 500 and/or CRP of 200 would likely have underlying significant disease that may involve the gut microbiota, and would therefore be unsuitable as a donor.

Reviewer #2: JHI-D-18-00499
This manuscript contains an excellent guideline and extensive review of the literature on the use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection, written by a working group representing the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS). I would like to congratulate the authors with the completion of this labour-intensive task.

Thank you for this comment.

I find the methods are sound, the tables and figure appropriate, and the conclusions valid. I note that the manuscript has been through rounds of national (UK) and international consultations as shown in the Additional Appendices, which have led to a significant number of alterations/improvements. The topic is important for the Journal since C. difficile Infection (CDI) continues to cause significant morbidity and mortality primarily as a healthcare-associated infection, and faecal microbiota transplant is relatively new, has proven efficacy, has a number of advantages over conventional treatment options, but is currently available in a minority of hospitals only. The guideline is comprehensive and will be a useful addition to the existing literature.

Thank you for this comment.
However, I believe there is room to improve the clarity and user-friendliness of the guideline. I will attempt to set this out in the following.

**Title:** the title is too long. I recommend removing the text "and other potential indications" for the following reasons: (1) this makes the title more concise, and (2) the manuscript is intended as a guideline and not as a review. The text "and other potential indications" raises the false expectation that the guideline recommends FMT for indications other than treatment for recurrent or refractory CDI, which is explicitly not the case as stated in the recommendation on page 47.

The working group were given the evaluation of the use of FMT in non-CDI indications as a key section of their remit. It clearly forms a considerable section of the text. As such, we feel that it is appropriate for this title to remain unchanged.

**Page 3:** Paragraph "NICE has accredited ....... /accreditation": move this to the Introduction. We were asked to place this paragraph in this position. Please see other HIS guidelines for where a similar approach has been applied, e.g. multi-drug resistant Gram-negative bacteria, Wilson et al, JHI, 2016.

The recommendations and good practice points are graded as "strong", "conditional", and are presented without a grading for one "good practice point".

Thank you for spotting this missed grading – this has been corrected.

Readers of a guideline can broadly be divided in two groups: a group who is mainly interested in reading the recommendations, tables and figures, whilst accepting the considerations and evidence-base at face value, and a smaller group who is interested to meticulously read and consider the considerations and evidence-base that led to all the recommendations, including the reference list. To serve the first group with a user-friendly guideline, I recommend, after Summaries and Introduction, to first list all the recommendations of the guideline with a consecutive number, followed by the sections 'Guideline Development Team', 'Working Party Report', 'Implementation of these guidelines', 'Methodology', and 'Rationale for recommendations'. In the section 'Rationale for recommendations' the recommendations should then be repeated with their list number, followed by the rationale, considerations etc.

We note the suggestions for a summary of recommendations from both reviewers. We were also asked at the peer review stage with BSG to include this in the Gut version. There is also precedent for this sort of summary in HIS guidelines, e.g. multi-drug resistant Gram-negative bacteria, Wilson et al, JHI, 2016. As such, we have added a summary of recommendations.

The manuscript contains a number of "recommendations" and "good practice points". However, since both are graded "strong" or "conditional", except for one good practice point on page 49 which did not receive a grading (why?), I believe that the subtle difference between "recommendation" and "good practice point" is lost on most readers, and hence recommend presenting all as "recommendation". Thus, taking recommendations and good practice points together, I have counted 61 recommendations which I suggest to number, and, as stated above, present as a list immediately after the Summaries and Introduction sections, as follows:
1. FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe-complicated CDI (strong).
2. FMT should be considered in cases of refractory CDI (conditional).
   [Note: I suggest changing this to: FMT should be considered in cases of CDI not responding to other treatment (conditional)]
3. FMT should not be administered as initial treatment for CDI (strong).
4. FMT for recurrent CDI should only be considered after recurrence of symptoms following resolution of an episode of CDI that was treated with appropriate antimicrobials for at least 10 days (conditional).
5. Consider treatment with extended/ pulsed vancomycin and/or fidaxomicin before considering FMT as treatment for recurrent CDI (conditional).
6. For those with severe or complicated CDI, which appears to be associated with reduced cure rates, consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin and bezlotoxumab), before offering FMT (conditional).
7. Further FMT should be offered after initial FMT failure (strong).
8. All FMT recipients should routinely receive follow-up. Clinicians should follow-up FMT recipients for long enough to fully establish efficacy/adverse events, and for at least eight weeks in total (strong).
9. Immediate management after endoscopic administration of FMT should be as per endoscopy unit protocol (strong).
10. Patients should be warned about short term adverse events, in particular the possibility of self-limiting GI symptoms. They should be advised that serious adverse events are rare (strong).
11. After enteral tube administration, patients may have the tube removed and oral water given from 30 minutes post-administration (strong).
12. A decision regarding cure/remission from CDI should be recorded during follow-up. However, this has no uniformly-agreed definition, and should be decided on a case-by-case basis (strong).
13. Treatment failure/recurrence should be defined on a case-by-case basis. Routine testing for C. difficile toxin after FMT is not recommended, but it is appropriate to consider in the case of persistent CDI symptoms/suspected relapse (strong).
14. FMT should be avoided in those with anaphylactic food allergy (strong).
15. FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (strong).
16. FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (strong).
17. Immunocompromised FMT recipients at risk of severe infection if exposed to EBV or CMV should only receive FMT from donors negative for EBV and CMV (strong).
18. FMT should be offered to those with recurrent CDI and inflammatory bowel disease, but patients should be counselled about a small but recognised risk of exacerbation of IBD (strong).
   [Note: to make this unambiguous, I recommend to change to: "FMT should be offered to those with recurrent CDI and concomitant inflammatory bowel disease, but patients should be counselled about a small but recognised risk of exacerbation of IBD (strong)."]
19. FMT should be considered for appropriate patients with recurrent CDI regardless of
other comorbidities (conditional).

... etc. etc., until the last recommendation, currently stated on page 53:

61. Ensure the clinical governance of donor screening (strong).

The 61 recommendations should be organised under a few clear headings, such as
A. Selection of patients
B. Selection of donors
C. Treatment recommendations
D. Laboratory recommendations

E. Clinical and regulatory governance

Thank you for spotting the missed graded good practice point – this has been corrected. The working group were asked by HIS to use SIGN in order to evaluate the reviewed evidence and to remain consistent with NICE methodology in writing the guidelines. This is the reason that ‘recommendation’ vs ‘good practice point’/ ‘strong’ vs ‘conditional’ has been used throughout. After discussion between HIS and BSG, it was agreed that for consistency between both the JHI and Gut versions of these manuscripts, and to ensure adherence with NICE methodology for the JHI version, that we would use the original PICO questions to differentiate sections. See above our comments about a summary of recommendations.

Following the numbered list of recommendations, section 8 can then repeat the number and text of each recommendation from the list, followed by the rationale for the recommendation.

As already discussed, the formatting used in the guideline is at the specific request of HIS.

Finally, I imagine that the editors may choose to select sections 1 to 10, the list of references, figure 1 and tables 1 to 5, appendix 1 and 4, for inclusion in the printed version of the Journal of Hospital Infection, whilst appendix 2, 3, and the Additional Appendices (A, B, C, D, E), to be made available online only. Of course this will be for the editors to decide. The working group are happy to defer this judgement to the Editorial Team.
The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

**Appendix A. Scope**

1. **Guideline title**

The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

1.1. **Short title**

The use of faecal microbiota transplant

2. **The remit**

i. To review the evidence (include randomised trial evidence) for the efficacy of faecal microbiota transplant (FMT) in the treatment of adults (≥18 years), both in *Clostridium difficile* infection (CDI) and in other clinical conditions, and use this to make recommendations about optimal recipient selection and management, donor assessment, material preparation and administration, and other key elements of FMT delivery.

ii. To provide specific guidance about best practice for an FMT service within the context of the regulatory framework for the intervention as it currently exists in the UK and beyond.

Whilst this is not a guideline specifically addressing the management of *Clostridium difficile* infection (CDI), the working group will include consideration of where FMT should be considered within the conventional treatment algorithm of patients with CDI (specifically, in which patients it should be considered, and at which point in their care).

The working group agreed that for the purposes of this guideline, faecal microbiota transplant would be defined as treatment that involves the administration of manipulated whole stool.
There is a growing literature of the use of ‘bacteriotherapy’ originally deriving from healthy donor stool as a potential alternative to FMT (including commensal bacteria, spores, bacteriophages and/ or bacterial proteins or metabolites). However, the working group considered this to still be at the research stage, and would not be considered further.

2.1. Population

2.1.1. Groups that will be covered

Adults (≥18 years) in whom:

i. FMT has been used as treatment for CDI.

ii. FMT has been used as treatment for a non-CDI indication.

Given the variability in the means used to diagnose CDI within different studies, the working group agreed to consider the suitability of the definition used on a study-by-study basis.

2.1.2. Groups that will not be covered

Children and young people (<18 years).

2.2. Healthcare setting

All settings in which National Health Service care is received, and/ or clinical trials are undertaken.

2.3. Clinical management

2.3.1. Key clinical issues that will be covered

a) Appropriate selection of patients with CDI for FMT, and best practice in their management post-FMT.

b) Optimal selection of donors of faecal material, and maintenance of a donor pool.

c) Identification of the preferred means of preparation and administration of FMT to recipients.

d) Evaluation of the safety and efficacy of FMT in treating non-CDI indications.

e) Best practice in the development and delivery of an FMT service.

2.3.2. Clinical issues that will not be covered

a) General management of CDI.
b) General management of non-CDI conditions in which FMT may have a role in therapy.

2.4. Main outcomes

Recommendations for practice

a) Patient/recipient selection, and peri-FMT management
b) Donor selection
c) Preparation and administration of FMT
d) Efficacy and safety of FMT for non-CDI indications
e) Provision of an FMT service

2.5. Economic aspects

Where FMT is being provided under a MHRA license according to Good Manufacturing Practice (GMP) standards, there are significant costs associated with initial setup and maintenance of the service. These include the cost of obtaining the relevant license, laboratory design and equipment to enable quality assurance, storage facilities for samples, etc. However, there is counterbalance to this, as the expectation of the working group is that the publication of this guideline may encourage provision of FMT as treatment for recurrent or refractory CDI. This has consistently been shown to be cost effective in comparison with anti-\textit{C. difficile} antimicrobial therapy\textsuperscript{31–34}, so overall costs associated with treating the condition may actually decrease. Furthermore, there may be changes to the practice of clinicians already offering the service. For example, encouraging the use of healthy unrelated donors (who can provide multiple stool donations after one screening) reduces the cost of screening when compared to the use of an FMT recipient’s relative as donor, who is likely to provide one donation only.

2.6. Status

2.6.1. Scope

This is the final scope.

2.6.2. Timing

The development of the guideline recommendation will begin in July 2017.
3. Related NICE guidance


4. Further information

*Guideline development process*

Additional Appendices

Appendix B. Declarations of interest

B.1. Introduction

All members of the Working Group were required to make formal declarations of interest at the outset, and these were updated throughout the development process. No interests were declared that required any actions.

B.2. Tariq Iqbal

First meeting 19/07/17: no declarations of interest; second meeting 04/10/17: no change.

Third meeting 19/10/17: consultant, advisor or speaker for: Pharmacosmos and Shield Therapeutics.

B.3. Simon Goldenberg (co-chair)

First meeting 19/07/17

Advisory board and/or consultancy and/or speaker fees: Astellas, MSD, Pfizer.

Second meeting 04/10/17; third meeting 19/10/17: no change.

No action required.

B.4. Ailsa Hart

First meeting 19/07/17

Advisory board and/or consultancy and/or speaker fees: AbbVie, Atlantic, Bristol-Myers Squibb, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. Global steering committee for Genentech.

Second meeting 04/10/17; third meeting 19/10/17: no change.

No action required.

No declared conflict of interests for the other participants.
Appendix C.  Clinical evidence tables

C.1.  Reviewed case series of FMT for recurrent or refractory CDI
### Additional Appendices

**Aas et al, Clinical Infectious Diseases, 2003**

<table>
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<tr>
<th>Paper</th>
<th>Study and patient characteristics</th>
<th>Donor characteristics</th>
<th>FMT characteristics</th>
<th>Outcomes</th>
<th>Adverse events</th>
<th>CRD</th>
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<tr>
<td>Case series.</td>
<td>Number of patients: 18.</td>
<td>Donors were 15 family members, and 3 clinical volunteers.</td>
<td>Amount of stool per transplant / administered to patients: 30g stool in 50-70ml normal saline; only 25ml of total administered to patient.</td>
<td>Overall cure within stated follow up period: 83.3% (n=15/18).</td>
<td>Minor GI adverse events: Nil stated.</td>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td></td>
<td>Age (mean): 73+/-9 (range 53-88) years.</td>
<td>Donor demographics: Not defined.</td>
<td>Diluent used to store if frozen: N/A – fresh.</td>
<td>Total follow-up period: 90 days.</td>
<td>Serious adverse events: Nil stated.</td>
<td>Prospectively recruited: No.</td>
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<tr>
<td></td>
<td>Comorbidities: x1 patient with Crohn’s colitis, x1 with leukaemia.</td>
<td>Donor screening: Questionnaire not explicitly stated.</td>
<td>Preparation methods: Homogenised in domestic blender, then coffee filter.</td>
<td>Deaths: x2 - one related to ESRF, one related to COPD.</td>
<td>Loss to follow up explained: Yes.</td>
<td>At least 90% followed up: No - 89%.</td>
</tr>
<tr>
<td></td>
<td>CDI features: Recurrent (at least 2 x laboratory-confirmed CDI after initial antibiotic treatment).</td>
<td>Travel and antibiotic exclusion period: No antibiotics for 6 months prior; nil stated regarding travel.</td>
<td>Time from preparation to transplant (fresh): 6 hours.</td>
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<td></td>
<td>CDI diagnosis confirmation: Cytotoxin A and B positivity.</td>
<td>Screening blood tests: Hepatitis A, B and C, HIV-1/-2, syphilis.</td>
<td>Time period for storage (frozen): N/A.</td>
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<tr>
<td></td>
<td>Pre-FMT antibiotics: Metronidazole +/- vancomycin (not defined).</td>
<td>Screening stool tests: <em>C.difficile</em>, enteric pathogens, ova, cysts and parasites.</td>
<td>Route administered: Upper GI: all nasogatric (18); lower GI: nil; capsules: nil.</td>
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<td>Number of infusions: Single infusion for all patients.</td>
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<td>Bowel purgative: Not described.</td>
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<td>PPI: 20mg omeprazole on day prior to FMT and day of FMT.</td>
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<td>Antimotility: Not described.</td>
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<td>Prokinetics: Not described.</td>
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<td>Time before CDI treatment was stopped before FMT: Continued until day of FMT.</td>
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<td>Donors were identified by the patient or - if not available - provided by the physician.</td>
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<td>Working in healthcare: Not stated.</td>
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<td>Donor demographics: No antibiotics for last three months. Excluded if significant GI disease, metabolic syndrome, chronic illness, immunocompromise, recent travel, and/or high risk lifestyle in last three months.</td>
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<td>Donor screening: Questionnaire - excluded if significant GI disease, metabolic syndrome, chronic illness, immunocompromise, recent travel, high risk lifestyle in last three months.</td>
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<td>Travel and antibiotic exclusion period: Exclusion if travel to an area of high incidence of infectious diarrhoea, and/or antibiotics within past three months.</td>
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<td>Travel and antibiotic exclusion period: Exclusion if travel greater than 100 miles.</td>
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<td>Travel and antibiotic exclusion period: Exclusion if travel to an area of high incidence of infectious diarrhoea and antibiotics for last three months.</td>
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<td>Travel and antibiotic exclusion period: Exclusion if travel to an area of high incidence of infectious diarrhoea.</td>
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<td>Antibiotics within past three months: Exclusion if significant GI disease, metabolic syndrome, chronic illness, immunocompromise, recent travel, high risk lifestyle.</td>
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</table>
| Antibiotics within past three months: Exclusion if significant GI disease, metabolic syndrome, chronic illness, immu...
### Additional Appendices

<table>
<thead>
<tr>
<th>Additional Appendices</th>
<th>Time before CDI treatment was stopped before FMT: Between 3 days prior to FMT and one day prior to FMT.</th>
<th>Stroke, x1 pneumonia; deaths between 19 days to 7 months post-FMT.</th>
</tr>
</thead>
</table>

- Giardia
- Cryptosporidium
- Isospora
- H. pylori
- Rotavirus
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 13.</th>
<th>Amount of stool per transplant / administered to patients: 12.5g of stool in 28.5g of product.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 8:5.</td>
<td>Donors were unrelated.</td>
<td>Diluent used to prepare: normal saline - diluted to approx 100-150ml to administer.</td>
</tr>
<tr>
<td>Age (median): 69 (range 59-74) years.</td>
<td>Working in healthcare: Nox</td>
<td>Diluent used to store if frozen: Not clear.</td>
</tr>
<tr>
<td>Comorbidities: Yes - x4 OLT, x1 kidney/ liver transplant, x1 lung transplant, x1 HIV+ with CD4 count of 453. x1 immunocompromised patients with IBS, x1 immunocompetent patient with IBS; no IBD patients.</td>
<td>Donor demographics: As per OpenBiome protocol</td>
<td>Preparation methods: As per OpenBiome protocol.</td>
</tr>
<tr>
<td>CDI features: Not clear if recurrent or refractory. Mean of 4 previous episodes of CDI prior to FMT.</td>
<td>Donor screening: Questionnaire - as per OpenBiome protocol</td>
<td>Time from preparation to transplant (fresh): N/A.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: PCR.</td>
<td>Travel and antibiotic exclusion period: As per OpenBiome protocol</td>
<td>Time period for storage (frozen): As per OpenBiome protocol - not described in paper.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: All patients had previously had oral vancomycin, x7 prev metronidazole (either with or without vancomycin). x5 received fidaxomicin</td>
<td>Screening stools: C. difficile toxin, MC&amp;S, ova, cysts and parasites, H.pylori stool antigen.</td>
<td>Route administered: Upper GI (nasoduodenal): 13; lower GI: 0; capsules: nil.</td>
</tr>
<tr>
<td></td>
<td>Screening bloods: FBC, hepatitis A, B and C, LFTs, HIV, HTLV-1/2, syphilis.</td>
<td>Number of infusions: One routinely, but retreated if relapsed after primary outcome. However - one renal transplant patient received 2 doses of FMT on consecutive days (with successful outcome).</td>
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<td></td>
<td>Bowel purgative: Bowel preparation used - GoLytely (PEG).</td>
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<td>PPI: 40mg pantoprazole night before and morning of procedure.</td>
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<td>Overall cure within stated follow up period: 84.6% (n=11/13) at eight weeks post-FMT.</td>
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<td>Cure with one infusion alone: 100% (n=13/13) at 5 days.</td>
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<td>Total follow up period: Follow up up to 8 weeks described.</td>
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<td>Minor GI adverse events: Several patients transient cramps and/or diarrhoea.</td>
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<td>Minor non-GI adverse events: Nil noted.</td>
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<td>Serious adverse events: x1 patient had episode of CMV reactivation at the time of FMT - thought unrelated. x1 patient had episode of mild transplant rejection two months after FMT - thought unrelated.</td>
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<td></td>
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<td>Deaths: None.</td>
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<td></td>
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<td>Selection/ eligibility reported: Yes.</td>
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<td></td>
<td></td>
<td>Consecutively recruited: Not clearly described.</td>
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<td></td>
<td></td>
<td>Prospectively recruited: No.</td>
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<td></td>
<td></td>
<td>Loss to follow up explained: Yes.</td>
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<td></td>
<td></td>
<td>At least 90% followed up: Yes.</td>
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<tr>
<td>Additional Appendices</td>
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<td>with or after oral vancomycin.</td>
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<td>Antimotility: Loperamide 4mg 1 hour post FMT.</td>
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<td>Prokinetics: Not described.</td>
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<td>Time before CDI treatment was stopped before FMT: See last box.</td>
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<tr>
<td>Case series.</td>
<td>Donors were 45 spouses/partners; 21 relatives; 1 unknown person.</td>
<td>Amount of stool per transplant/administered to patients: 6 tablespoons of stool up to entire donation; 300-700ml of transplant administered.</td>
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<tr>
<td>Number of patients: 77.</td>
<td>Working in healthcare: No.</td>
<td>Diluent used to prepare: Normal saline.</td>
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<tr>
<td>Female: male: 56: 21.</td>
<td>Donor demographics: No antibiotics within past 3 months.</td>
<td>Diluent used to store if frozen: N/A – fresh.</td>
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<tr>
<td>Age (mean): 65+/17 (range 22-87) years.</td>
<td>Donor screening: Questionnaire - not stated.</td>
<td>Preparation methods: Hand blender used to prep.</td>
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<tr>
<td>Comorbidities: Not stated.</td>
<td>Travel and antibiotic exclusion period: Excluded if travel to area of high incidence of infectious diarrhoea, or if antibiotics within past three months.</td>
<td>Time from preparation to transplant (fresh): Within 8 hours.</td>
</tr>
<tr>
<td>CDI features: All recurrent/refractory.</td>
<td>Screening blood tests: HIV-1, HIV-2, hepatitis A, B and C, Syphilis.</td>
<td>Time period for storage (frozen): N/A.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Not clear.</td>
<td>Screening stool tests: <em>Clostridium difficile</em> toxin (if unavailable then EIA), MC&amp;S, <em>Giardia, Cryptosporidium</em>, ova, cysts and parasites, <em>H.pylori</em>, Acid Fast stain for <em>Cyclospora, Isospora</em>.</td>
<td>Route administered: Upper GI: 0; lower GI: all 77 colonoscopic.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: 62 patients had had prior metronidazole, 76 vancomycin (25 tapered vancomycin), 17 rifaximin.</td>
<td>Number of infusions: 77 patients had one (patients that had second not included because given with concurrent vancomycin).</td>
<td>Number of infusions: 77 patients had one (patients that had second not included because given with concurrent vancomycin).</td>
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<tr>
<td></td>
<td>Bowel purgative: All patients given prep but no details.</td>
<td>Cure with one infusion alone: 90.9% (<em>n</em> = 70/77).</td>
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<td>PPI: Not described.</td>
<td>Total follow up period: not clear, but some patients followed-up to 3 years.</td>
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<td></td>
<td>Antimotility: Not described.</td>
<td>Overall cure within stated follow up period: N/A.</td>
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<td></td>
<td>Prokinetics: Not described.</td>
<td>Cure with one infusion alone: 90.9% (<em>n</em> = 70/77).</td>
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<tr>
<td>Minor GI adverse events: Not stated.</td>
<td>Minor non-GI adverse events: Not stated.</td>
<td>Total follow up period: not clear, but some patients followed-up to 3 years.</td>
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<tr>
<td>Selection/eligibility reported: Yes.</td>
<td>Serious adverse events: Nil.</td>
<td>Overall cure within stated follow up period: N/A.</td>
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<tr>
<td>Consecutively recruited: Not clear.</td>
<td>Deaths: x7 deaths (cause unknown in one case, x1 metastatic colorectal cancer (present from pre-FMT), x1 metastatic ovarian cancer, x1 pneumonia (non-enteric organism), x1 MI, x1 stroke, x1 sepsis five months after FMT.</td>
<td>Cure with one infusion alone: 90.9% (<em>n</em> = 70/77).</td>
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<tr>
<td>Prospectively recruited: No.</td>
<td>Loss to follow up explained: Reported but not explained.</td>
<td>Total follow up period: not clear, but some patients followed-up to 3 years.</td>
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<td>At least 90% followed up: No - only 77%.</td>
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<td>Time before CDI treatment was stopped before FMT: 3 days.</td>
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<tr>
<td>Case series.</td>
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<tr>
<td>Number of patients: 42.</td>
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<td>Female: male: 23: 19.</td>
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<td>Age (median): 9 (range 1-18) years.</td>
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<td>Comorbidities: 31% had IBD (x4 Crohn’s, x9 UC); 29% ‘medically complex’, including oncological, metabolic, cardiopulmonary or neurological diagnoses.</td>
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<tr>
<td>CDI features: All children had at least one course of vancomycin. Previously recurrent - at least 2 episodes.</td>
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<tr>
<td>CDI diagnosis: Diarrhoea, haematochezia and/or crampy abdominal pain in combination with positive C. difficile PCR.</td>
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<td>Pre-FMT antibiotics: Not stated.</td>
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<td>Donor: OpenBiome-supplied FMT.</td>
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<td>Working in healthcare: No.</td>
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<tr>
<td>Donor demographics: Not stated.</td>
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<td>Donor screening: Questionnaire: As per OpenBiome protocol.</td>
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<td>Time from preparation to transplant (fresh): None given fresh.</td>
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<td>Time period for storage (frozen): N/A.</td>
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<td>Route administered: Upper GI: 41, nasogastric administration (some children used pre-existing gastrostomy); lower GI: 0; capsules: 1 (1 x 30 capsules).</td>
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<td>Number of infusions: 1 routinely.</td>
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<td>Bowel purgative: Not stated.</td>
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<td>PPI: Rantidine for 24hrs prior to FMT.</td>
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<td>Antimotility: N/A.</td>
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<td>Prokinetics: N/A.</td>
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<tr>
<td>Time before CDI treatment was stopped.</td>
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<tr>
<td>Amount of stool per transplant / administered to patients: 30ml OpenBiome aliquot/ capsule, although not defined re stool quantity.</td>
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<tr>
<td>Diluent used to prepare: As per OpenBiome protocol.</td>
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<tr>
<td>Diluent used to store if frozen: As per OpenBiome protocol.</td>
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<tr>
<td>Preparation methods: As per OpenBiome protocol.</td>
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<tr>
<td>Overall cure within stated follow up period: 71% (n=30/42).</td>
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<td>Cure with one infusion alone: 71% (n=30/42) - remission in 94% (n=16/17) otherwise healthy children, 54% (n=7/13) (54%) with IBD, 75% (n=9/12) medically complex. Success in 71% of children when via NGT, and 67% via gastrostomy (non-significant).</td>
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<td>Minor GI adverse events: 6/47 FMT administrations accompanied by vomiting within 24hrs; self-resolved.</td>
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<td>Minor non-GI adverse events: Nil reported.</td>
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<td>Serious adverse events: Nil reported.</td>
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<td>Deaths: Nil reported.</td>
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<td>Selection/ eligibility reported: Yes.</td>
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<td>Consecutively recruited: Yes.</td>
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<tr>
<td>Prospectively recruited: No.</td>
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<td>Loss to follow up explained: Yes.</td>
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<tr>
<td>At least 90% followed up: Yes.</td>
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before FMT: 48 hours, after minimum of 5 days of vancomycin.
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Donors were age 18 - 50, no medications, BMI 18.5 – 25.</th>
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<tbody>
<tr>
<td>Number of patients: 35.</td>
<td>Working in healthcare: Not stated.</td>
</tr>
<tr>
<td>Age (mean): 43 (range 8 -93) years.</td>
<td>Donor screening: Questionnaire - adapted from US blood bank.</td>
</tr>
<tr>
<td>Comorbidities: IBD in all, 8 on corticosteroids, 3 on Immunomodulators, 11 on biologics.</td>
<td>Time from preparation to transplant (fresh): N/A; given fresh.</td>
</tr>
<tr>
<td>CDI features: Recurrent - at least 2 episodes.</td>
<td>Time period for storage (frozen): Up to 156 days.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Not stated.</td>
<td>Route administered: Upper GI: 5 via nasogastric tube; lower GI: 3 via colonoscopy; capsule: 27 patients.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Not stated.</td>
<td>Number of infusions: Not stated.</td>
</tr>
<tr>
<td></td>
<td>Bowel purgative: Not routinely - just for colonoscopy (4 litres of PEG).</td>
</tr>
<tr>
<td></td>
<td>PPI: 7 on PPI not as premedications.</td>
</tr>
<tr>
<td></td>
<td>Antimotility: Not described.</td>
</tr>
<tr>
<td></td>
<td>Prokinetics: Not described.</td>
</tr>
<tr>
<td></td>
<td>Time before CDI treatment was stopped before FMT: 2 days prior to FMT.</td>
</tr>
<tr>
<td></td>
<td>Amount of stool per transplant / administered to patients: 41g of stool on average.</td>
</tr>
<tr>
<td></td>
<td>Diluent used to prepare: Normal saline.</td>
</tr>
<tr>
<td></td>
<td>Diluent used to store if frozen: Frozen in 10% glycerol.</td>
</tr>
<tr>
<td></td>
<td>Preparation methods: Ambient air.</td>
</tr>
<tr>
<td></td>
<td>Overall cure within stated follow up period: N/A.</td>
</tr>
<tr>
<td></td>
<td>Cure with one infusion alone: Not stated.</td>
</tr>
<tr>
<td></td>
<td>Total follow up period: At least 2 months (range 2 to 6 months).</td>
</tr>
<tr>
<td></td>
<td>Minor GI adverse events: Not specified.</td>
</tr>
<tr>
<td></td>
<td>Minor non-GI adverse events: Not specified.</td>
</tr>
<tr>
<td></td>
<td>Serious adverse events: two required surgery (diverting colostomy and total proctectomy), two developed perianal disease with no prior history of it.</td>
</tr>
<tr>
<td></td>
<td>Deaths: Ni.</td>
</tr>
</tbody>
</table>

Selection/ eligibility reported: No.
Consecutively recruited: No.
Prospectively recruited: No.
Loss to follow up explained: No.
At least 90% followed up: No.

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 22.</th>
<th>Overall cure within stated follow up period: 72.7% (n=16/22) at 2 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 22.</td>
<td>Donors were 13 unrelated, 9 related.</td>
<td>Cure with one infusion alone: 72.7% (n=16/22) (5/10 upper GI (out of 7 analysed), 91.7% (n=11/12) for lower GI (out of 11 analysed)).</td>
</tr>
<tr>
<td>Age (median): Median 71.5 (range 16-92) years.</td>
<td>Donor demographics: No details - just says screening similar to blood donors.</td>
<td>Deaths: x7 (x1 due to CDI, x1 chronic resp disease, x1 related to dialysis, x2 pneumonia, x1 sepsis at ten days post-FMT (aspiration of stool; had been gastroscopic administration), x1 died at home ?cause).</td>
</tr>
<tr>
<td>Comorbidities: x1 IBD (colonoscopic group), x2 patients on chemotherapy, unclear why.</td>
<td>Donor screening: Questionnaire - no details.</td>
<td>Minor GI adverse events: x5 transient constipation/ abdominal discomfort.</td>
</tr>
<tr>
<td>CDI features: Recurrent or refractory.</td>
<td>Time from preparation to transplant (fresh): No stated.</td>
<td>Minor non-GI adverse events: Not stated.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Diarrhoea and toxin testing.</td>
<td>Time period for storage (frozen): No details.</td>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: 19 patients given previous metronidazole, 9 vancomycin (with 13 both together).</td>
<td>Route administered: Upper GI: nasoduodenal in 10; lower GI: colonoscopic in 12.</td>
<td>Consecutively recruited: Yes.</td>
</tr>
<tr>
<td></td>
<td>Number of infusions: 1 FMT.</td>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td></td>
<td>Bowel purgative: 3l of PEG if colonoscopic administration.</td>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td></td>
<td>PPI: PPI if upper GI administration.</td>
<td>At least 90% followed up: Yes.</td>
</tr>
<tr>
<td></td>
<td>Antimotility: Not described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prokinetics: Metoclopramide just prior to upper GI administration.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amount of stool per transplant / administered to patients: 60g stool average (35-75g), 250ml total once mixed with saline (100 - 300ml range).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diluent used to prepare: Normal saline.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diluent used to store if frozen: Not stated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preparation methods: Some fresh, some frozen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time from preparation to transplant (fresh): No stated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time period for storage (frozen): No details.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Travel and antibiotic exclusion period: Excluded if antibiotics within past six months.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Screening bloods: No details.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Screening stools: No details.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall cure within stated follow up period: 72.7% (n=16/22) at 2 months.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cure with one infusion alone: 72.7% (n=16/22) (5/10 upper GI (out of 7 analysed), 91.7% (n=11/12) for lower GI (out of 11 analysed)).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor GI adverse events: x5 transient constipation/ abdominal discomfort.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor non-GI adverse events: Not stated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serious adverse events: See deaths.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deaths: x7 (x1 due to CDI, x1 chronic resp disease, x1 related to dialysis, x2 pneumonia, x1 sepsis at ten days post-FMT (aspiration of stool; had been gastroscopic administration), x1 died at home ?cause).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Selection/ eligibility reported: Yes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consecutively recruited: Yes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prospectively recruited: No.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss to follow up explained: Yes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At least 90% followed up: Yes.</td>
<td></td>
</tr>
</tbody>
</table>
Time before CDI treatment was stopped before FMT: 12-24 hrs.
### Additional Appendices

**Costello et al, Alimentary Pharmacology and Therapeutics, 2015**

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Donors were 4 healthy volunteers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 20.</td>
<td>Working in healthcare: No.</td>
</tr>
<tr>
<td>Female: male: not stated.</td>
<td>Donor demographics: No details.</td>
</tr>
<tr>
<td>Age(median): 69 years.</td>
<td>Donor screening: Questionnaire - adapted from US blood bank.</td>
</tr>
<tr>
<td>Comorbidities: Not stated.</td>
<td>Travel and antibiotic exclusion period: Excluded if travel to diarrhoea-endemic areas within 6 months and/or used antibiotics for 3 months.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Not stated.</td>
<td>Number of infusions: 17 patients had 1, 3 patients had 2.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Conventional therapy with metronidazole, vancomycin and/or fidaxomicin had failed in all.</td>
<td>Screening stool tests: <em>C difficile</em> toxin B PCR, routine MC&amp;S, faecal <em>Giardia</em> antigen, faecal <em>Cryptosporidium</em>, Acid-fast stain for <em>Cyclospora, Isospora</em>, ova, cysts and parasites, <em>H pylori</em> fecal antigen.</td>
</tr>
</tbody>
</table>

| Amount of stool per transplant / administered to patients: Not stated. |
| Diluent used to prepare: Normal saline. |
| Diluent used to store if frozen: 10% glycerol. |
| Preparation methods: Anaerobically prepared. |
| Time from preparation to transplant (fresh): all frozen. |
| Time period for storage (frozen): 16 patients had stool stored for < 2 months. 4 patients had stool stored > 2 months. |
| Route administered: Upper GI: 1; lower GI: 19; capsule: nil. |
| Number of infusions: 17 patients had 1, 3 patients had 2. |
| Bowel purgative: Not reported. |
| PPI: Not reported. |
| Antimotility: Not reported. |
| Prokinetics: Not reported. |
| Time before CDI treatment was stopped before FMT: Not reported. |

| Overall cure within stated follow up period: 85% (n=17/20). |
| Cure with one infusion alone: 85% (n=17/20). |
| Total follow up period: Minimum 3 months (but up to 14 months). |

| Minor GI adverse events: None. |
| Minor non-GI adverse events: None. |
| Serious adverse events: None. |
| Deaths: None. |

<p>| Selection/ eligibility reported: Yes. |
| Consecutively recruited: Yes. |
| Prospectively recruited: No. |
| Loss to follow up explained: Yes. |
| At least 90% followed up: Yes. |</p>
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Donors were spouses or close relative.</th>
<th>Amount of stool per transplant / administered to patients: 50g in 500mls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 23.</td>
<td>Donor working in healthcare: No.</td>
<td>Diluent used to prepare: Normal saline.</td>
</tr>
<tr>
<td>Female: male: 14: 9.</td>
<td>Donor demographics: Not stated.</td>
<td>Diluent used to store if frozen: N/A - fresh.</td>
</tr>
<tr>
<td>Age (median): 66 years (range 25-99) years (including 8 additional patients treated with 'bacteriotherapy').</td>
<td>Donor screening: Questionnaire – asked regarding current and previous GI diagnoses/ symptoms.</td>
<td>Preparation methods: Anaerobically prepared.</td>
</tr>
<tr>
<td>Comorbidities: 3 with diabetes mellitus, 1 with microscopic colitis.</td>
<td>Travel and antibiotic exclusion period: Definitely an antibiotic use restriction but not clearly stated.</td>
<td>Time from preparation to transplant (fresh): Not stated.</td>
</tr>
<tr>
<td>CDI features: All recurrent.</td>
<td>Screening blood tests: HIV-1 and -2, hepatitis C virus, and hepatitis B surface antigen.</td>
<td>Time period for storage (frozen): N/A.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Culture and/or toxin EIA.</td>
<td>Screening stool tests: <em>Salmonella</em>, <em>Shigella</em>, <em>Campylobacter</em>, enterohemolytic <em>Escherichia coli</em>, and <em>Clostridium difficile</em>.</td>
<td>Route administered: Upper GI: nil; ower GI: 23 (enema/rectal catheter); capsules: nil.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Metronidazole and/or vancomycin used in all patients beforehand.</td>
<td>Number of infusions: 22 patients received 1 FMT, 1 patient received 2 FMTs.</td>
<td>Number of infusions: 22 patients received 1 FMT, 1 patient received 2 FMTs.</td>
</tr>
<tr>
<td>Overall cure within stated follow up period: 65% (n=15/23).</td>
<td></td>
<td>Cure with one infusion alone: 65% (n=15/23).</td>
</tr>
<tr>
<td>Minor GI adverse events: None.</td>
<td></td>
<td>Total follow up period: Median follow up of 18 months (range 0-201 months).</td>
</tr>
<tr>
<td>Minor non-GI adverse events: None.</td>
<td></td>
<td>Deaths: None.</td>
</tr>
<tr>
<td>Serious adverse events: None.</td>
<td></td>
<td>At least 90% followed up: Yes.</td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
<td></td>
<td>Selection/eligibility reported: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
<td></td>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
<td></td>
<td>At least 90% followed up: Yes.</td>
</tr>
</tbody>
</table>
### Case series

**Number of patients:** 67  
**Female:** male: 39:28  
**Age (mean/standard deviation):** Mean 45.42 (+/-17.33) years.  
**Comorbidities:** x5 PSC, x4 liver transplant, x3 end stage liver disease, concurrent IBD in all (x35 Crohn’s, x31 UC, x1 indeterminate colitis).  
**CDI features:** recurrent or refractory.  
**CDI diagnosis confirmation:** Return of diarrhoea and positive CDI testing within 12 weeks of FMT.  
**Pre-FMT antibiotics:** metronidazole in 47 patients, vancomycin in 63, vancomycin taper in 38 patients, fidaxomycin in 7, rifaxamin in 7.  
**Donors were patient-directed donor or unrelated healthy volunteers.**  
**Donors working in healthcare:** not stated.  
**Donor demographics:** As per Bakken et al, *Clin Gastroenterol Hepatol*, 2011.  
**Travel and antibiotic exclusion period:** Excluded as donor if travel within last 6 months where diarrheal illnesses are endemic or risk of travelers diarrhea is high, and/or use of antibiotics within 3 months.  
**Screening blood tests:** HIV -1&-2, hepatitis A, B and C, syphilis.  
**Number of infusions:** 53 patients received one infusion, 14 received 2 infusions.  
**Bowel purgative:** Standard bowel preparation, but not specified.  
**PPI:** If upper GI administration, PPI on the evening before and morning of the procedure.  

### Amount of stool transplant

- **Lower GI:** 25-50ml  
- **Upper GI:** 250-500ml  
- **Diluent used to prepare:** Preservative-free normal saline or 4% milk.  
- **Diluent used to store if frozen:** N/A – fresh.  
- **Preparation methods:** Household blender, homogenized and removal of particle matter with gauze/urine strainers in a Biohazard Level 2 facility.  
- **Time from preparation to transplant (fresh):** Certainly within 24 hours, and preferably within 6 hours.  
- **Time period for storage (frozen):** N/A.  
- **Route administered:** Upper GI: nil; lower GI: 67 (colonoscopy or sigmoidoscopy); capsule: nil.  
- **Number of infusions:** 53 patients received one infusion, 14 received 2 infusions.  
- **Bowel preparation:** Standard bowel preparation, but not specified.  
- **PPI:** If upper GI administration, PPI on the evening before and morning of the procedure.

### Overall cure within stated follow up period

- **90%** (**n=60/67**) within 3 months.  
- **Cure with one infusion alone:** 79% (**n=53/67**).  
- **Total follow up period:** average length 10.4 (range 3-36) months.  

### Minor GI adverse events

- IBD flare, managed as outpatient.  
- Minor non-GI adverse events: x4 pneumonia.  
- Serious adverse events: x1 colectomy for refractory IBD, x7 hospitalised, x2 CDI recurrence, x2 IBD exacerbation, x1 small bowel obstruction, x1 CMV colitis.  

### Deaths

- None.

### Selection/ eligibility reported

- Yes.  
- Consecutively recruited: No.  
- Prospectively recruited: No.  
- Loss to follow up explained: N/A.  
- At least 90% followed up: N/A.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Antimotility: Loperamide optional for lower GI administration.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Prokinetics: Not stated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time before CDI treatment was stopped before FMT: 24-48 hrs.</td>
</tr>
</tbody>
</table>
**Additional Appendices**

<table>
<thead>
<tr>
<th>Fischer et al, American Journal of Gastroenterology, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case series.</strong></td>
</tr>
<tr>
<td>Number of patients: 328.</td>
</tr>
<tr>
<td>Female: male: 241: 87.</td>
</tr>
<tr>
<td>Age (mean/ standard deviation): 61.4 (+/-19.3) years.</td>
</tr>
<tr>
<td>Comorbidities: 77 immunocompromised (x3 CVID, x3 selective IgA deficiency, x71 immunosuppressants (20 for solid organ transplant, 29 for IBD, 6 for rheumatoid arthritis, 2 for SLE, 1 for pemphigoid, 1 for chronic obstructive airway disease, 1 for psoriasis)), x11 chemotherapy for malignancy, x63 IBD (25 UC, 33 Crohn’s), x118 diverticulosis.</td>
</tr>
<tr>
<td>CDI features: Recurrent disease in 87.2% and severe or severe-complicated in 12.8%.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Postive stool <em>C difficile</em> toxin or</td>
</tr>
<tr>
<td>Donors were 130 (40%) patient-directed donors, and 198 universal (60%).</td>
</tr>
<tr>
<td>Donor working in healthcare: Not stated.</td>
</tr>
<tr>
<td>Donor demographics: Not stated.</td>
</tr>
<tr>
<td>Donor screening: Questionnaire – depended upon individual centre.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Depended upon individual centre.</td>
</tr>
<tr>
<td>Screening blood tests: Depended upon individual centre.</td>
</tr>
<tr>
<td>Screening stool test: Depended upon individual centre.</td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: Not specified.</td>
</tr>
<tr>
<td>Diluent used to prepare: Not specified.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: Both fresh and frozen, but specific details not given.</td>
</tr>
<tr>
<td>Preparation methods: Dependent upon individual centre.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Dependent upon individual centre.</td>
</tr>
<tr>
<td>Time period for storage (frozen): Dependent upon individual centre.</td>
</tr>
<tr>
<td>Route administered: Not specified (‘predominantly colonoscopy’).</td>
</tr>
<tr>
<td>Number of infusions: Dependent upon individual centre.</td>
</tr>
<tr>
<td>Bowel purgative: Not specified.</td>
</tr>
<tr>
<td>PPI: Not specified.</td>
</tr>
<tr>
<td>Antimotility: Not specified.</td>
</tr>
<tr>
<td>Prokinetics: Not specified.</td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: Dependent upon each centre.</td>
</tr>
<tr>
<td>Overall cure within stated follow up period: 1 month 81.4% (n=267/328).</td>
</tr>
<tr>
<td>Cure with one infusion alone: Not specified.</td>
</tr>
<tr>
<td>Total follow up period: Not specified.</td>
</tr>
<tr>
<td>Minor Gi adverse events: Not specified.</td>
</tr>
<tr>
<td>Minor non-Gi adverse events: Not specified.</td>
</tr>
<tr>
<td>Serious adverse events: Not specified.</td>
</tr>
<tr>
<td>Deaths: Not specified.</td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: No.</td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Loss to follow up explained: N/A.</td>
</tr>
<tr>
<td>At least 90% followed up: N/A.</td>
</tr>
</tbody>
</table>
Additional Appendices

PCR.

Pre-FMT antibiotics:
vancomycin.
### Additional Appendices

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 57.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 34: 23.</td>
<td></td>
</tr>
<tr>
<td>Age (median): Median 72 (range 25-99) years.</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: x7 toxic megacolon, x12 acute kidney injury (x3 needing dialysis), x10 with hypovolaemic/ septic shock, x7 mental status changes, x4 on mechanical ventilation. x10 patients had inflammatory bowel disease (x5 with Crohn’s and x5 with ulcerative colitis) and x10 patients were on immunosuppressive medications.</td>
<td></td>
</tr>
<tr>
<td>CDI features: Severe, recurrent and severe-complicated.</td>
<td></td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Positive stool <em>C. difficile</em> PCR.</td>
<td></td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Included vancomycin,</td>
<td></td>
</tr>
<tr>
<td>Donors were screened patient-selected donors for first 29 patients, whilst next 28 from OpenBiome stool bank.</td>
<td></td>
</tr>
<tr>
<td>Donors working in healthcare: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Donor demographics: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Donor screening: Questionnaire – for patient-selected donors, this was as for Bakken <em>et al</em>, <em>Clin Gastroenterol Hepatol</em>, 2011; for OpenBiome, as per OpenBiome protocol.</td>
<td></td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: For patient-selected donors, this was as for Bakken <em>et al</em>, <em>Clin Gastroenterol Hepatol</em>, 2011; for OpenBiome, as per OpenBiome protocol.</td>
<td></td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): 6 hours.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): As per OpenBiome protocols.</td>
<td></td>
</tr>
<tr>
<td>Route administered Upper GI: nil; lower GI: 57 via colonoscopy or sigmoidoscopy.</td>
<td></td>
</tr>
<tr>
<td>Screening blood tests: For patient-selected donors, this was as for Bakken <em>et al</em>, <em>Clin Gastroenterol Hepatol</em>, 2011; for OpenBiome, as per OpenBiome protocol.</td>
<td></td>
</tr>
<tr>
<td>Screening stool tests: For patient-selected donors, this was as for Bakken <em>et al</em>, <em>Clin Gastroenterol Hepatol</em>, 2011;</td>
<td></td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: As per Fischer <em>et al</em>, <em>Alim Pharm Ther</em>, 2015 or OpenBiome.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to prepare: As per Fischer <em>et al</em>, <em>Alim Pharm Ther</em>, 2015 or OpenBiome.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to store if frozen: As per Fischer <em>et al</em>, <em>Alim Pharm Ther</em>, 2015 or OpenBiome.</td>
<td></td>
</tr>
<tr>
<td>Preparation methods: As per Fischer <em>et al</em>, <em>Alim Pharm Ther</em>, 2015 or OpenBiome.</td>
<td></td>
</tr>
<tr>
<td>Overall cure within stated follow up period: 91% (n=52/57), i.e. 100% severe CDI (n=19/19), and 87% (n=33/38).</td>
<td></td>
</tr>
<tr>
<td>Minor GI adverse events: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Deaths: x7 unrelated deaths, x4 CDI-related deaths.</td>
<td></td>
</tr>
<tr>
<td>Cure with one infusion alone: 52.6% (n = 30/57).</td>
<td></td>
</tr>
<tr>
<td>Total follow up period: Up to 6 months.</td>
<td></td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
<td></td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
<td></td>
</tr>
<tr>
<td>Prospectively recruited: Yes.</td>
<td></td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
<td></td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
<td></td>
</tr>
<tr>
<td>fidaxomicin, rectal vancomycin, intravenous metronidazole.</td>
<td>for OpenBiome, as per OpenBiome protocol.</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
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</tr>
</tbody>
</table>
Additional Appendices

Fischer et al, Alimentary Pharmacology and Therapeutics, 2015

Case series.
Number of patients: 29.
Female: male: 17: 12.
Age (mean/ standard deviation): Overall, mean 65.2 (+/-17.9) years (range 25-92 years); mean 60.8 (range 26-87) years in severe; 67.6 (range 60-78) years in severe-complicated.

Comorbidities: x3 Crohn's, x2 UC, x1 hypogammaglobulinaemia, x1 ESKD, x1 ESLD, x1 renal transplant, x1 liver transplant, x4 on immunosuppressive meds. 12/19 of pts treated in ITU at the time with following complications: x5 patients with toxic megacolon (caecal diam >12cm or rectosigmoid> 6.5cm diameter); x7 AKI and hypovolaemic/septic shock, x4 of which required vasopressors, x3 with change in mental status, x2 patients ventilated. x22 with

Donors were either patient selected-donor, or universal donors. If patient-directed, same donor used for subsequent FMTs if required. 44 FMTs in all - patient-selected for 16 FMTs, universal donor for 28 FMTs.

Donors working in healthcare: Not described.

Donor demographics: Not clear.


Travel and antibiotic exclusion period: As per Bakken et al, Clin Gastroenterol Hepatol, 2011.

Screening blood tests: As per Bakken et al, Clin Gastroenterol Hepatol, 2011.

Screening stool tests: As per Bakken et al, Clin Gastroenterol Hepatol, 2011.

Amount of stool per transplant / administered to patients: 50-200g of stool.

Diluent used to prepare: 300ml of saline.

Diluent used to store if frozen: N/A – all fresh.

Preparation methods: No additional details.

Time from preparation to transplant (fresh): Six hours.

Time period for storage (frozen): N/A.

Route administered: Upper GI: nil; lower GI: flexible sigmoidoscopy or colonoscopy either proximal or distal to the splenic flexure at the discretion of the endoscopist. In practice – proximal to the splenic flexure in 18 FMTs, distal in 26.

Number of infusions: As many as per protocol until end point. 16 x 1 FMT (7 severe, 9 complicated), 11 x 2nd FMT (3 severe, 8 compl), 2 x 3rd FMT (0 severe, 2 complicated).

N.B. Oral vancomycin (125 mg every 6 hours) was resumed 24–48 hours after FMT for a minimum of 5 days if there were pseudomembranes present at colonoscopy. For patients who did not

Overall cure within stated follow up period: By 3 months, 62% (n=18/29) in remission.

Cure with one infusion alone: 70% (n=7/10) in severe arm; 47% (n=9/19) in severe-complicated arm.

Total follow up period: Up to 3 months.

Minor GI adverse events: Not stated.
Minor non-GI adverse events: Not stated.
Serious adverse events: Nil.
Deaths: x2 deaths by 1 month; x1 death from sepsis within 24 hours of FMT; death following colectomy after 3x failed FMT in patient who was six weeks post-OLT. By 3 months – x2 further deaths from CDI recurrence, x1 death from cirrhosis, x1 death from heart failure, x1 death from respiratory failure, x1 death from aspiration.

Selection/ eligibility reported: Yes.
Consecutively recruited: Yes.
Prospectively recruited: Yes.
Loss to follow up explained: Yes.
At least 90% followed up: Yes.
### Additional Appendices

<table>
<thead>
<tr>
<th>pseudomembranes at first FMT.</th>
<th>improve by days 6–7, the vancomycin was stopped, and bowel prep was administered if no ileus was present. The next day (day 7–8), a repeat FMT, from the same donor as the first FMT if patient-directed, was performed by sigmoidoscopy or colonoscopy. If pseudomembranes were present, oral vancomycin was resumed for an additional 5 days. If no pseudomembranes were detected, antibiotics were not resumed following the repeat FMT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI features: 9 patients with first episode of CDI; all others with previous episodes.</td>
<td>Bowel purgative: Split dose 4l Golytely if no ileus/obstruction.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Diarrhoea (at least 3 loose stools/day) and positive toxin.</td>
<td>PPI: Not described.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Not stated.</td>
<td>Antimotility: Not described.</td>
</tr>
<tr>
<td></td>
<td>Prokinetics: Not described.</td>
</tr>
<tr>
<td></td>
<td>Time before CDI treatment was stopped before FMT: 12-24hr prior to FMT.</td>
</tr>
</tbody>
</table>
Garborg et al, Scandinavian Journal of Infectious Diseases, 2010

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 40.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 21: 19.</td>
<td>Age (mean): Mean age 75 (range 53-94) years.</td>
</tr>
<tr>
<td>Comorbidities: x1 Wegener’s, x1 AML.</td>
<td>Repeated courses of antibiotics, not formally described.</td>
</tr>
<tr>
<td>CDI features: Not described.</td>
<td>CDI diagnosis confirmation: Diarrhoea and + C difficile toxin (testing for A and B).</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: All patients had had at least two courses of oral metronidazole (500mg three times daily) or vancomycin (125mg po four times daily).</td>
<td>Donors were close relatives/household members.</td>
</tr>
<tr>
<td>Donors working in healthcare: No.</td>
<td>Donor demographics: Not stated.</td>
</tr>
<tr>
<td>Donor screening: Questionnaire - “Symptoms of GI disease or history of chronic infectious disease”.</td>
<td>Screening bloods: Hepatitis A, B and C, HIV.</td>
</tr>
<tr>
<td>Screening stools: MC&amp;S, Yersinia. No routine parasite screening (“low prevalence in Norway”).</td>
<td>Amount of stool per transplant / administered to patients: 50-100g.</td>
</tr>
<tr>
<td>Diluent used to prepare: 250ml sterile normal saline.</td>
<td>Diluent used to store if frozen: All fresh.</td>
</tr>
<tr>
<td>Preparation methods: Stool placed on gauze pad and strained; flushed with saline; drawn up into syringes ready for administration.</td>
<td>Overall cure within stated follow up period: 835 (n=33/40).</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Same day.</td>
<td>Cure with one infusion alone: 73% (n=29/40) (28 in duodenum, 1 in colon).</td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A.</td>
<td>Total follow up period: Up to 80 days.</td>
</tr>
<tr>
<td>Route administered: Upper GI: OGD with delivery in distal duodenum; 38; lower GI: Colonoscopy; 2.</td>
<td>Minor GI adverse events: Not stated.</td>
</tr>
<tr>
<td>Number of infusions: One at baseline; follow up if ‘did not respond’ although not specifically defined.</td>
<td>Minor non-GI adverse events: Not stated.</td>
</tr>
<tr>
<td>Bowel purgative: Not mentioned, even for colonoscopy.</td>
<td>Serious adverse events: Not stated.</td>
</tr>
<tr>
<td>PPI: Not stated.</td>
<td>Deaths: x5 deaths within 3 weeks - 2 months post-FMT but none attributable to FMT. x2 deaths attributed to ‘frailty’, x1 advanced Wegener’s, x1 AML/ antibiotics, one patients with advanced cardiovascular disease who had fulminant colitis, underwent colectomy, but died.</td>
</tr>
<tr>
<td>Antimotility: Not stated.</td>
<td>Prokinetics: Not stated.</td>
</tr>
<tr>
<td>Prokinetics: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Additional Appendices</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: Evening prior to FMT.</td>
<td></td>
</tr>
</tbody>
</table>
### Additional Appendices

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 29.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 6: 23.</td>
<td></td>
</tr>
<tr>
<td>Age (mean/ standard deviation): 80.1 (+/- 6.49) years (13 patients 70-79, 14 patients 80-89, 2 patients &gt; 90 years).</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: x8 patients with diabetes mellitus.</td>
<td></td>
</tr>
<tr>
<td>CDI features: No specific details - purely symptoms &gt; 6 months, failed at least 3 antibiotic regimens.</td>
<td></td>
</tr>
<tr>
<td>CDI diagnosis confirmation: At least three unformed stools in 24 hour and positive stool <em>C difficile</em> test by toxin (by ELISA) or toxin gene B (by PCR). All patients here defined RCDI by symptoms &gt; 6 months and at least x3 failed antibiotics.</td>
<td></td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Not indicated.</td>
<td></td>
</tr>
</tbody>
</table>

| Donors were patient-selected family or friends. | Amount of stool per transplant / administered to patients: 450cc - 270cc via colonoscopy AND 180cc into jejunum via enteroscopy. |
| Donors working in healthcare: | | Diluent used to prepare: Saline - whole stool sample (>30g) mixed with 50-70ml of sterile saline, made up to 5 x 90cc aliquots. |
| Donor demographics: Not stated. | Diluent used to store if frozen: Fresh. |
| Donor screening: Questionnaire – peptic ulcer disease/GORD, IBS, IBD, polyps, malignancy, antibiotic use/ hospitalisation within past 3 months. | Preparation methods: Stool mixed with saline, homogenised in blender for <4 minutes, filtered x2 with coffee filter paper. |
| Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within the past three months. | Time from preparation to transplant (fresh): Within 6 hours. |
| Screening bloods: HIV, HTLV-I/-II, syphilis enzyme immunoassay, hepatitis A immunoglobulin M, hepatitis B surface antigen, hepatitis C antibody, and *Helicobacter pylori* antibody. | Time period for storage (frozen): N/A. |
| Screening stools: MC&S/ ova, cysts and parasites x3, *Cryptosporidium, Microspora, C difficile* toxin. | Route administered: Enteroscopy into jejunum AND colonoscopy in all 29 patients. |
| Bowel purgative: Not described. | Number of infusions: 1 FMT per patient (combined upper and lower GI administration). |
| PPI: 20mg omeprazole evening before/morning of procedure. | Antimotility: Not described. |

| Overall cure within stated follow up period: 100% (n=29/29). | Minor GI adverse events: Bloating 10% (n=3/29). |
| Cure with one infusion alone: 100% (n=29/29). | Minor non-GI adverse events: Fever 7% (n=2/29) (transient for one day). |
| Total follow-up period: Reported 25.37 +/- 12.8 months follow-up (range 8-50 months). | Serious adverse events: None. |
| In addition - researchers report 60% weight gain, 40% stable weight, 75% improved 'failure to thrive' (defined as decrease of weight >10% from baseline, with no improvement despite medical treatment of CDI and nutritional treatment). | Deaths: None. |
| Loss to follow up explained: N/A. | At least 90% followed up: Yes. |

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Girotra et al, *Digestive Diseases and Sciences*, 2016

- Selection/ eligibility reported: Yes.
- Consecutively recruited: Yes.
- Prospectively recruited: No.
<table>
<thead>
<tr>
<th>Prokinetics: Not described.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time before CDI treatment was stopped before FMT: &gt;12 hours.</td>
</tr>
</tbody>
</table>

Case series.
Number of patients: 133.
Female: male: 86: 47.
Age (median): Median 75 (IQR 59.5 - 81.5) years.
Comorbidities: x3 chemotherapy, x19 immunosuppressants, x5 solid organ transplant, x1 allogenic stem cell transplant, x43 GI comorbidities (no details).
CDI features: Median of 3 recurrences (IQR 1-4); no specific details re recurrent vs refractory confirmation.
Pre-FMT antibiotics: x4 metronidazole only, x13 vancomycin only, x2 fidaxomicin only, x61 metronidazole/ vancomycin, x8 vancomycin/ fidaxomicin, x34 metronidazole/ vancomycin/...

Donors working in healthcare: not stated
Donor demographics: Not stated
Donor screening: Questionnaire - not stated.
Travel and antibiotic exclusion period: Not stated.
Screening blood tests.: Rapid plasma reagin and fluorescent Treponema antibody-absorbed.
Screening stool tests: Not stated.

Amount of stool per transplant / administered to patients: Not stated.
Diluent used to prepare: Not stated.
Diluent used to store if frozen: Yes, in some cases - no details given.
Preparation methods: Not stated.
Time from preparation to transplant (fresh): Not stated.
Time period for storage (frozen): Not stated.
Screening stool tests: Not stated.
Screening blood tests: Not stated.
Screening stool tests: Not stated.
Preparation methods: Not stated.

Bowel purgative: Yes - 117 (no details given).
PPI: Yes - 31 (no details given).
Antimotility: Yes - 31 (no details given).
Prokinetics: Not stated.
Time before CDI treatment was stopped before FMT: Not stated.

Overall cure within stated follow up period:
Primary cure on day 30 and 90 was achieved in 84.2% (n=101/120) and 78.3% (n=72/92).
Cure with one infusion alone: No diarrhoea at 30 days in 84.2% (n=101/120); no diarrhoea at 90 days in 78.3% (n=72/92).
Total follow up period: Median follow up 141 days (IQR 50-353 days).

Minor GI adverse events: x5 nausea, x3 abdominal pain, 2 belching, x2 vomiting, x2 'food intolerance', x1 IBS.
Minor non-GI adverse events: x3 fever, x2 throat discomfort.
Serious adverse events: x1 aspiration pneumonia, x1 haemorrhage (during endoscopy - no details), x1 loss of tooth, x1 polyneuropathy, x1 weight gain > 10kg in 12 months post-FMT.
Deaths: x7 died during follow up, x2 within 90 days of FMT. In x6 cases, definitely not related to CDI (in one patient, recurrence of CDI one week after FMT contributed to her death (but

Selection/eligibility reported: Yes.
Consecutively recruited: Not clear.
Prospectively recruited: No.
Loss to follow up explained: No.
At least 90% followed up: Yes.
| fidaxomicin, x11 | unknown. | stroke described as primary cause of death. |
### Additional Appendices

**Hamilton et al, American Journal of Gastroenterology, 2012**

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Donors were standard donors for 33 FMTs, and individual donors for 10 FMTs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 43.</td>
<td>Donors working in healthcare: Not stated.</td>
</tr>
<tr>
<td>Age (mean/standard deviation): Mean 59 (+/- 21) years.</td>
<td>Donor screening: Questionnaire - before recruitment, the donors were required to submit available medical records and have a separate medical history interview away from the recipient patient. The history included assessment of infectious risk, including identification of known risk factors for HIV and hepatitis, current communicable diseases, and recent travel to areas of the world with a higher prevalence of diarrheal illnesses.</td>
</tr>
<tr>
<td>Comorbidities: x14 IBD patients.</td>
<td>Preparation methods: Stool from individual donors was passed through stainless steel tea strainers; stool from universal donors was transported on ice to the lab, and processed within 2 hours. Material was weighed and homogenised in commercial blender under nitrogen gas. Slurry then passed through 2.0, 1.0, 0.5 and 0.25mm stainless steel lab sieves. The resulting material was then centrifuged at 6000 x g for 15 minutes and resuspended to one-half the original volume in normal saline.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Toxin positive with at least two subsequent recurrences.</td>
<td>Time period for storage (frozen): 1-8 weeks.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: All had vancomycin, 17 patients had addition of vancomycin and 2 weeks of rifaximin (one of these 17 had 4 weeks of rifaximin); 3 patients took 2-4 weeks of nitazoxanide.</td>
<td>Route administered: Upper GI: nil; lower GI: colonoscopy (with majority into terminal ileum or caecum, with a small proportion into other colonic areas) in all 43; capsules: nil.</td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: 50g.</td>
<td>Number of infusions: 1x FMT in 37</td>
</tr>
<tr>
<td>Diluent used to prepare: 250ml sterile, non-bacteriostatic normal saline.</td>
<td>Overall cure within stated follow up period: 95% (n=41/43) within 2 months follow-up.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: 10% glycerol.</td>
<td>Cure with one infusion alone: 86% (n=37/43).</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: All had vancomycin, 17 patients had addition of vancomycin and 2 weeks of rifaximin (one of these 17 had 4 weeks of rifaximin); 3 patients took 2-4 weeks of nitazoxanide.</td>
<td>Total follow up period: 2 months following FMT.</td>
</tr>
<tr>
<td>Minor GI adverse events: ~1/3 of patients reported flatulence and excessive bowel movements within fortnight following procedure.</td>
<td>Minor non-GI adverse events: None.</td>
</tr>
<tr>
<td>Serious adverse events: None.</td>
<td>Deaths: None.</td>
</tr>
<tr>
<td>Selection/eligibility reported: Yes.</td>
<td>Consecutively recruited: Yes.</td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
<td>Loss to follow up explained: No.</td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
<td></td>
</tr>
</tbody>
</table>
### Additional Appendices

<table>
<thead>
<tr>
<th>Screening blood tests</th>
<th>Patients, 2x FMT in 6 patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV, hepatitis B/C, RPR, LFTs.</td>
<td>Bowel purgative: Yes - GoLYTELY or Moviprep.</td>
</tr>
<tr>
<td>Screening stool tests: Clostridium difficile toxin B PCR, MC&amp;S, ova, cysts and parasites, Giardia, Cryptosporidium, H pylori antigen.</td>
<td>PPI: Not described.</td>
</tr>
<tr>
<td></td>
<td>Antimotility: Not described.</td>
</tr>
<tr>
<td></td>
<td>Prokinetics: Not described.</td>
</tr>
<tr>
<td></td>
<td>Time before CDI treatment was stopped before FMT: 2 days.</td>
</tr>
</tbody>
</table>
Hefazi *et al*, Mayo Clinic Proceedings, 2017

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 23.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median): 66 (range 23-88) years.</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: x13 patients had haematological malignancy (x4 diffuse large B cell lymphoma, x2 Hodgkin’s lymphoma, x1 chronic myeloid leukaemia, x1 follicular lymphoma, x1 stage IV cutaneous T cell lymphoma, x1 B cell acute lymphocytic leukaemia, x1 hairy cell leukaemia, x1 chronic lymphocytic leukaemia, x1 severe aplastic anaemia); x1 with active disease at time of FMT, x2 with recent chemotherapy use, x2 with neutropenia within 12 weeks prior to FMT, x10 patients with solid organ malignancy (x4 breast, x2 anal, x1 colon, x1 pancreatic, x1 tonsillar, x1 non-small.</td>
<td></td>
</tr>
<tr>
<td>Donors: Fresh stool from family/ friends in 10 patients, frozen stool from standard donors in 13 patients.</td>
<td></td>
</tr>
<tr>
<td>Donor working in healthcare: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Donor demographics: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Number of infusions: 1 FMT.</td>
<td></td>
</tr>
<tr>
<td>Bowel purgative: Not stated.</td>
<td></td>
</tr>
<tr>
<td>PPI: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Antimotility: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Prokinetics: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: 24 hours.</td>
<td></td>
</tr>
</tbody>
</table>

| Amount of stool per transplant / administered to patients: ~50g. |
| Diluent used to prepare: 250ml normal saline. |
| Diluent used to store if frozen: Not stated. |
| Time from preparation to transplant (fresh): Not stated. |
| Time period for storage (frozen): Not stated. |
| Route administered: Upper GI: nil; lower GI: All 23 patients received FMT via colonoscopy into caecum. |
| Number of infusions: 1 FMT. |
| Bowel purgative: Not stated. |
| PPI: Not stated. |
| Antimotility: Not stated. |
| Prokinetics: Not stated. |
| Time before CDI treatment was stopped before FMT: 24 hours. |

| Overall cure within stated follow up period: 92% (n=11/12) of haematological malignancy patients (other patient died), and 80% (n=8/10) solid malignancy patients. |
| Cure with one infusion alone: 86% (n=19/22) by primary outcome criteria. |
| Total follow up period: x1 CLL patient recurred at 22 months post-FMT in context of ibrutinib and coamoxiclav; successfully treated with 10 days of metronidazole. x1 tonsillar cancer patient had CDI recurrence at 14 months after exposure to cefalexin; successfully treated with 10 days of metronidazole. |
| Minor GI adverse events: x3 chronic diarrhoea for at least six months (despite negative *Clostridium difficile* laboratory tests), x8 transient diarrhoea, x3 abdominal cramps, x2 faecal urgency, x2 constipation, x1 nausea. |
| Minor non-GI adverse events: None. |
| Serious adverse events: None. |
| Deaths: x1 death after cardiac arrest of Hodgkin’s lymphoma patient at day 5 (multiple medical comorbidities thought likely cause, not FMT); x2 deaths at > 60 days related to the underlying malignancy progressing. |

Selection/ eligibility reported: Yes. 
Consecutively recruited: Yes. 
Prospectively recruited: No. 
Loss to follow up explained: Yes. 
At least 90% followed up: Yes.
### Additional Appendices

| Cell lung, x5 with metastasis at time of FMT, x3 recent chemotherapy use, x1 with recent neutropenia. Other comorbidities include x1 COPD, x1 ESKD on haemodialysis, x1 graft versus host disease (on immunosuppression), x1 granulomatosis with polyangiitis (Wegener’s) on immunosuppression, x1 hypogammaglobulinaemia on intravenous immunoglobulin, x1 inflammatory arthritis on corticosteroids. |
|---|---|---|
| CDI features: All recurrent. CDI diagnosis confirmation: Not explicitly defined, but definitions of recurrent, severe and complicated CDI as per American College of Gastroenterology. Pre-FMT antibiotics: All given additional vancomycin until 24hrs | vancomycin then 10 days of fidaxomicin. N.B. in all - x10 more chemotherapy courses and x8 more antibiotic courses after FMT. |
prior to FMT. Median of 2.5 standard treatment courses per patient (defined as at least 10 days of metronidazole, vancomycin or fidaxomicin), \( x \) previous vancomycin taper, and \( x \) total treatment courses for CDI.)
<table>
<thead>
<tr>
<th>Hirsch et al, BMC Infectious Diseases, 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case series.</strong></td>
</tr>
<tr>
<td><strong>Number of patients:</strong> 19.</td>
</tr>
<tr>
<td><strong>Female:</strong> 13: <strong>Male:</strong> 6.</td>
</tr>
<tr>
<td><strong>Age (mean):</strong> 61 (range 26-92) years.</td>
</tr>
<tr>
<td><strong>Comorbidities:</strong> x3 IBS, x2 diabetes mellitus, x1 diverticulitis, x1 lymphoma, x1 acute myeloid leukaemia, x1 renal cancer, x1 chronic renal failure.</td>
</tr>
<tr>
<td><strong>CDI features:</strong> Refractory and recurrent (2 or more episodes).</td>
</tr>
<tr>
<td><strong>CDI diagnosis confirmation:</strong> Not stated.</td>
</tr>
<tr>
<td><strong>Pre-FMT antibiotics:</strong> metronidazole, vancomycin +/or fidaxomicin.</td>
</tr>
<tr>
<td><strong>Amount of stool per transplant / administered to patients:</strong> 2.3g.</td>
</tr>
<tr>
<td><strong>Diluent used to prepare:</strong> 350ml in 0.9% normal saline.</td>
</tr>
<tr>
<td><strong>Diluent used to store if frozen:</strong> 15% glycerol.</td>
</tr>
<tr>
<td><strong>Preparation methods:</strong> Strict environmental control &lt;6 hours after defaecation. All sterile, wet weight of stool was homogenised in 350ml 0.9% normal saline and aliquoted; samples were then centrifuged at 200 x g for 10 mins. Supernatant was decanted and centrifuged at 4600 x g for 15 minutes. supernatant removed and pellet re-suspended in 0.9% normal saline with glycerol. The typical concentration was 0.5g/ml. The resulting FMT slurry was put in 5-10ml syringes and frozen at -80°C.</td>
</tr>
<tr>
<td><strong>Time from preparation to transplant (fresh):</strong> N/A.</td>
</tr>
<tr>
<td><strong>Time period for storage (frozen):</strong> 1-3 weeks at -80°C; prior to use, syringes were transferred to -20°C and used within six weeks.</td>
</tr>
<tr>
<td><strong>Route administered:</strong> Nil upper or lower GI; all capsules. Aliquots of 0.4 mL of FMT slurry were dispensed into Size 1 acid-resistant hypromellose capsules.</td>
</tr>
<tr>
<td><strong>Overall cure within stated follow up period:</strong> 68% (n=13/19).</td>
</tr>
<tr>
<td><strong>Cure with one infusion alone:</strong> 68% (n=13/19) at 90 days.</td>
</tr>
<tr>
<td><strong>Total follow up period:</strong> Primary outcome assessed at 90 days, whilst secondary outcome assessed at 6 weeks after this.</td>
</tr>
<tr>
<td><strong>Minor GI adverse events:</strong> x5 abdominal pain (x4 self-resolved; x1 required opiates and was hospitalised).</td>
</tr>
<tr>
<td><strong>Minor non-GI adverse events:</strong> None.</td>
</tr>
<tr>
<td><strong>Serious adverse events:</strong> None.</td>
</tr>
<tr>
<td><strong>Deaths:</strong> x1 died from respiratory failure after failing FMT treatment.</td>
</tr>
<tr>
<td><strong>Selection/ eligibility reported:</strong> Yes.</td>
</tr>
<tr>
<td><strong>Consecutively recruited:</strong> Not clear.</td>
</tr>
<tr>
<td><strong>Prospectively recruited:</strong> No.</td>
</tr>
<tr>
<td><strong>Loss to follow up explained:</strong> No.</td>
</tr>
<tr>
<td><strong>At least 90% followed up:</strong> Yes.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Number of infusions:</td>
</tr>
<tr>
<td>Bowel purgative:</td>
</tr>
<tr>
<td>PPI:</td>
</tr>
<tr>
<td>Antimotility:</td>
</tr>
<tr>
<td>Prokinetics:</td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT:</td>
</tr>
<tr>
<td>Case series.</td>
</tr>
</tbody>
</table>
Additional Appendices

| Time before CDI treatment was stopped before FMT: FMT given on last 1 or two days of CDI treatment. |
### Case series.

- **Number of patients:** 27.
- **Female:** male 13:14.
- **Age (mean):** 69.4 (range 26-87) years.
- **Comorbidities:** Not specified.
- **CDI features:** Recurrent and refractory.
- **CDI diagnosis confirmation:** (1) Laboratory-confirmed *C. difficile* toxin using EIA with no other cause for diarrhea; (2) refractory CDI (defined as ongoing diarrhea despite antimicrobial treatment) or recurrent CDI (defined as symptom resolution for at least 2 days after discontinuation of treatment with recurrence of diarrhea).
- **Pre-FMT antibiotics:** All had at least prior metronidazole; 19 had subsequent vancomycin monotherapy. 8 had

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Amount of stool per transplant / administered to patients: 150g of stool.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donors were two healthy volunteers.</td>
<td>Diluent used to prepare: 300mls sterile water.</td>
</tr>
<tr>
<td>Donors working in healthcare: Not specified.</td>
<td>Diluent used to store if frozen: N/A.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded if used antibiotics within last 6 months.</td>
<td>Time period for storage (frozen): N/A – fresh.</td>
</tr>
<tr>
<td>Screening blood tests: Hepatitis B surface antigen, hepatitis C antibody, <em>Helicobacter pylori</em> and syphilis serologic markers, HIV types -1 and -2, and HTLV types -I and -II.</td>
<td>Route administered: Upper GI: nil; lower GI: 27 via retention enema.</td>
</tr>
<tr>
<td>Number of infusions: 1 enema in 22 patients, 2 enemas in 5 patients.</td>
<td>Total follow up period: Mean follow-up of 427.3 days after transplant.</td>
</tr>
<tr>
<td>Bowel purgative: Not specified.</td>
<td>Overall cure within stated follow up period: 81% (n=22/27).</td>
</tr>
<tr>
<td>PPI: Not specified.</td>
<td>Cure with one infusion alone: 81% (n=22/27).</td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: At least 24 hours before.</td>
<td>Serious adverse events: Not specified.</td>
</tr>
<tr>
<td>Deaths: Not specified.</td>
<td></td>
</tr>
</tbody>
</table>

### Donors were two healthy volunteers.

- **Travel and antibiotic exclusion period:** Excluded if used antibiotics within last 6 months.
- **Screening blood tests:** Hepatitis B surface antigen, hepatitis C antibody, *Helicobacter pylori* and syphilis serologic markers, HIV types -1 and -2, and HTLV types -I and -II.
- **Screening stool tests:** Stool was processed for enteric bacterial pathogens, *C. difficile* toxin, and ova and parasites.

### Amount of stool per transplant / administered to patients: 150g of stool.

- **Diluent used to store if frozen:** N/A.
- **Preparation methods:** Not specified.
- **Time from preparation to transplant (fresh):** Not specified.
- **Time period for storage (frozen):** N/A – fresh.
- **Route administered:** Upper GI: nil; lower GI: 27 via retention enema.
- **Number of infusions:** 1 enema in 22 patients, 2 enemas in 5 patients.
- **Bowel purgative:** Not specified.
- **PPI:** Not specified.
- **Antimotility:** Not specified.
- **Prokinetics:** Not specified.
- **Time before CDI treatment was stopped before FMT:** At least 24 hours before.

### Overall cure within stated follow up period: 81% (n=22/27).

- **Cure with one infusion alone:** 81% (n=22/27).
- **Minor GI adverse events:** Not specified.
- **Minor non-GI adverse events:** Not specified.
- **Serious adverse events:** Not specified.
- **Deaths:** Not specified.

### Selection/ eligibility reported: Yes.

- **Consecutively recruited:** Yes.
- **Prospectively recruited:** No.
- **Loss to follow up explained:** Yes.
- **At least 90% followed up:** Yes.
| combination metronidazole and vancomycin therapy. |   |   |   |
Case series.  
Number of patients: 26.  
Female: male: 24:2.  
Age (mean): 59 years.  
Comorbidities: Not stated.  
CDI features: Recurrent.  
Mean duration of diagnosis of CDI prior to FMT of 12.6 (range 4 to 84) months.  
CDI diagnosis confirmation: Not stated.  
Pre-FMT antibiotics: All had previous treatment with metronidazole, and repeated tapering courses of vancomycin. Some patients had prior *Saccharomyces boulardii* or *Lactobacillus* GG. Pre-FMT, all had 2 weeks of metronidazole or vancomycin, discontinued 2-3 days before FMT.  
Donors were family members in 25 cases, and friend in 1 case.  
Donor working in healthcare: No.  
Donor demographics: Not specified.  
Donor screening: Questionnaire – asked regarding known exposure to HIV within 12 months, high-risk sexual behaviours, use of illicit drugs, tattoo within 6 months, incarceration within 12 months, risk factors for Creutzfeldt-Jakob disease, GI comorbidities, recent ingestion of allergen, systemic autoimmunity, chronic pain syndromes.  
Travel and antibiotic exclusion period: No antibiotics for preceding 90 days.  
Screening blood tests: blood for hepatitis A, B and C, HIV-1&2, Treponema pallidum.  
Screening stool tests: Stool for culture for bacteria, stain for ova and parasites, *C difficile* toxin A and B.  
Amount of stool per transplant / administered to patients: "6.8 tablespoons of donor stool".  
Diluent used to prepare: 1 litre of sterile water passed through gauze. Aliquoted in 60ml syringes.  
Diluent used to store if frozen: N/A – fresh.  
Preparation methods: As above.  
Time from preparation to transplant (fresh): 6 hours prior to transplant.  
Time period for storage (frozen): N/A.  
Route administered: Upper GI: nil; lower GI: all 26 via colonoscopy; capsules: nil.  
Number of infusions: not explicitly stated but implies single infusion for all patients.  
Bowel purgative: PEG bowel prep night before transplant.  
PPI: Not stated.  
Antimotility: Not stated.  
Prokinetics: Not stated.  
Time before CDI treatment was stopped: Overall cure within stated follow up period: 92.3% (n=24/26).  
Cure with one infusion alone: 92.3% (n=24/26).  
Total follow up period: follow up of mean 10.7 months (ranged from 2-30 months).  
Minor GI adverse events: Mild diarrhoea post-FMT in x3 patients.  
Minor non-GI adverse events: No.  
Serious adverse events: No.  
Deaths: No.  
Selection/ eligibility reported: Yes.  
Consecutively recruited: Yes.  
Prospectively recruited: No.  
Loss to follow up explained: Yes.  
At least 90% followed up: Yes.
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>before FMT: 2-3 days.</td>
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<tr>
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</tbody>
</table>
Case series.
Number of patients: 80.
Female: male 42: 38.
Age (mean): N.B. 75 adults, and 5 children.
Mean age of adults: 53 (range 20-88) years; mean age of paediatric patients: 10.9 (range 6.5–16) years.
Comorbidities: x36 IBD, x19 solid organ transplant, x3 HIV/AIDS, x7 cancer, x4 rheumatoid arthritis, x1 adrenal insufficiency, x6 cirrhosis, x1 ESKD, x1 panhypopituitarism, x1 end-stage COPD, x1 ESKD with allograft failure, x1 SJogrens.
CDI features: Both refractory and recurrent patients included as well as severe/complicated disease.
CDI diagnosis: Not clearly specified.
Pre-FMT antibiotics:

| Amount of stool per transplant / administered to patients: Varied by centre. |
| Diluent used to prepare: Varied by centre. |
| Diluent used to store if frozen: Varied by centre. |
| Preparation methods: Varied by centre. |
| Time from preparation to transplant (fresh): Varied by centre. |
| Time period for storage (frozen): Varied by centre. |
| Route administered: Not specified. |
| Number of infusions: 85% (n=68/80) had single FMT, 15% (n=12/80) had >1 FMT. |
| Bowel purgative: Varied by centre. |
| PPI: Varied by centre. |
| Antimotility: Varied by centre. |
| Prokinetics: Varied by centre. |
| Time before CDI treatment was stopped before FMT: Varied by centre. |

Overall cure within stated follow up period: 89% (n=71/80) within a minimum of 12 weeks.
Cure with one infusion alone: 78% (n=62/80).
Total follow up period: 12 weeks post-FMT.

Minor GI adverse events: x3 self-limiting diarrhoea, x3 bloating and abdominal discomfort, x1 Crohn’s flare, x1 nausea, x1 minor mucosal tear at colonoscopy.
Minor non-GI adverse events: x1 fever, x1 hip pain, x1 pertussis.
Serious adverse events: x10 hospitalization (x1 for fever, encephalopathy and pancytopenia; x1 abdo pain post FMT, x3 IBD flares (x2 Crohn’s, x1 UC), x1 stroke, x1 colectomy, x1 fall and sustained hip fracture, x1 influenza B and diarrhoea, x1 catheter infection.
Deaths: x2 deaths (x1 pneumonia and x1 aspiration after...
| Vancomycin 67 (84%), fidaxomicin 23 (29%), rifaximin 13 (16%), metronidazole 55 (69%). |  |  | sedation for colonoscopic FMT). |
### Additional Appendices

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 272.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 189: 83.</td>
<td></td>
</tr>
<tr>
<td>Age (mean/ median/ standard deviation): Mean 57.2 (+/- 19.2) years; median 59.0 (range 16-100) years.</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: x10 dialysis, x22 established Crohn’s, x21 established UC, x15 lymphocytic colitis, x5 diagnosed with Crohn’s during colonoscopy for FMT, x1 diagnosed UC by x14 newly-diagnosed lymphocytic colitis. x13 reclassified in terms of IBD. x8 solid organ recipients, x30 patients without IBD were taking biologics (anti-TNF, rituximab), immunomodulators (methotrexate, purine analogues), and/or corticosteroids.</td>
<td></td>
</tr>
<tr>
<td>CDI features: All patients had at least two</td>
<td></td>
</tr>
<tr>
<td>Donors working in healthcare: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Screening blood tests: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to prepare: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to store if frozen: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Route administered: Upper GI: nil; lower GI: colonoscopy (272); capsule: nil.</td>
<td></td>
</tr>
<tr>
<td>Number of infusions: One routinely, more than one if required - specific criteria not defined.</td>
<td></td>
</tr>
<tr>
<td>Bowel purgative: Yes - all had purgative on day prior to procedure (as per Hamilton et al, Am J Gastroenterol, 2012).</td>
<td></td>
</tr>
<tr>
<td>Overall cure within stated follow up period: 74% (n= 32/43) in IBD patients and 92.2% (n=211/229) in non-IBD patients.</td>
<td></td>
</tr>
<tr>
<td>Cure with one infusion alone: 74% (n= 32/43) in IBD patients and 92.2% (n=211/229) in non IBD patients.</td>
<td></td>
</tr>
<tr>
<td>Total follow up period: Up to 6 years.</td>
<td></td>
</tr>
<tr>
<td>Minor GI adverse events: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Minort non-GI adverse events: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events: 25.6% (n=11/43) of IBD patients diagnosed with FMT-related flare. x2 patients hospitalised with IBD flare within two months of FMT. Clearance of CDI by FMT generally associated with improved control of IBD over the long term. x6 patients struggled with IBD despite optimisation of immunosuppressive treatment, x3 of whom underwent colectomies.</td>
<td></td>
</tr>
<tr>
<td>Deaths: Nil.</td>
<td></td>
</tr>
</tbody>
</table>

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Khoruts et al, Clinical Gastroenterology & Hepatology, 2016

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Group 1 (IBD) x68 patients (age 57.6 years) and Group 2 (non-IBD) x204 patients (age 57.2 years)

- **Group 1**
  - Number of patients: 68
  - Age (range): 16-100 years
  - Comorbidities: x10 dialysis, x22 established Crohn’s, x21 established UC, x15 lymphocytic colitis, x5 diagnosed with Crohn’s during colonoscopy for FMT, x3 diagnosed UC by newly-diagnosed lymphocytic colitis, x15 reclassified in terms of IBD. x8 solid organ recipients, x30 patients without IBD were taking biologics (anti-TNF, rituximab), immunomodulators (methotrexate, purine analogues), and/or corticosteroids.
  - CDI features: All patients had at least two.
  - Donors working in healthcare: As per Hamilton et al, Am J Gastroenterol, 2012.
  - Travel and antibiotic exclusion period: As per Hamilton et al, Am J Gastroenterol, 2012.
  - Screening blood tests: As per Hamilton et al, Am J Gastroenterol, 2012.
  - Amount of stool per transplant / administered to patients: As per Hamilton et al, Am J Gastroenterol, 2012.

- **Group 2**
  - Number of patients: 204
  - Age (range): 16-100 years

---

**Selection/ eligibility reported:** Yes.

**Consecutively recruited:** Yes.

**Prospectively recruited:** No.

**Loss to follow up explained:** Yes.

**At least 90% followed up:** Yes.
<p>| spontaneous relapses of CDI following initial episode, defined as recurrence within three months of discontinuation of anti-CDI antibiotics treatment in conjunction with diarrheal symptoms. | CDI diagnosis confirmation: Positive stool testing within two months of FMT - not clearly defined. | Pre-FMT antibiotics: x206 patients had had prior metronidazole, x270 vancomycin, x69 fidaxomicin, x71 rifaximin, x104 probiotics. | PPI: Not described. Antimotility: Not described. Prokinetics: Not described. Time before CDI treatment was stopped before FMT: 2 days. |</p>
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 61.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 40:21.</td>
<td></td>
</tr>
<tr>
<td>Age (mean): 84 (range 66-101) years.</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: Not Specified.</td>
<td></td>
</tr>
<tr>
<td>CDI features: Some patients refractory/recurrent; some during first CDI.</td>
<td></td>
</tr>
<tr>
<td>CDI diagnosis confirmation: PCR that detects toxin and B genes, and toxin C gene deletion that characterises 027.</td>
<td></td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Patients divided into 'tardive transplant' (i.e. only after x3 antibiotic failures) or 'early transplant' (during first week of infection during first treatment, accompanied by antibiotics). Antibiotics were for non-severe disease: metronidazole.</td>
<td></td>
</tr>
</tbody>
</table>

Donors were preferentially healthy family members, but also used healthy volunteer students and residents. Donor working in healthcare: Yes - some residents. Donor demographics: BMI<30, exclude active cancer, diarrhoea, current immunosuppressive drugs, antibiotics within past three months. Donor screening: Questionnaire: As above. Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within past three months. Screening blood tests: HIV, hepatitis A, B, C, E, active CMV, active EBV, Treponema pallidum, HTLV. Screening stool tests: MC&S, parasites, toxigenic C difficile. |

Amount of stool per transplant / administered to patients: >30g. Diluent used to prepare: Whole stool mixed with 400ml normal saline, homogenised for 10 minutes. Diluent used to store if frozen: N/A – fresh. Preparation methods: 10 minutes of homogenisation in blender, filtered, put into a syringe at room temperature. Time from preparation to transplant (fresh): <6 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: Via nasogastric tube in 61 patients; nil lower GI or capsules. Number of infusions: In early FMT arm - one FMT routine; but offered 2nd FMT if relapse. Bowel purgative: 4l Klean Prep/ two glasses of Fast Prep day before FMT. PPI: No - but used 200ml 1.4% bicarbonate 15 minutes before FMT. Antimotility: Not specified. Prokinetics: Not specified. Overall cure within stated follow up period: Global death rate of 19% (n=3/16) in early transplant arm (day 20, day 37, day 166), 67% (n=2/3) died in arm of those treated by tardive transplant (day 28, day 54). None of these patients died with evidence of CDI. Cure with one infusion alone: 33% (n=1/3) treated by tardive FMT dead at day 31; 4.2% (n=1/16) treated by early FMT dead at day 31. Total follow up period: No details on absolute length of follow-up. Minor GI adverse events: x24 diarrhoea (resolved day 1 after FMT), x1 nausea. Minor non-GI adverse events: Not specified. Serious adverse events: x1 acute heart failure - no details. Deaths: 3/16 in early transplant arm (vs 29/45 treated by abx only or tardive transplant). No sign of CDI at time of death (days 20, 37, 166).
orally three times a day for 14 days, then vancomycin 125mg four times a day for 14 days, then fidaxomicin 200mg twice a day for 10 days; for severe disease (defined as AKI, paralytic ileus, or peritoneal fluid), used vancomycin and metronidazole for primary infection, then fidaxomicin if relapse/failure.

Time before CDI treatment was stopped before FMT: Not specified.
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Donors were volunteers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 94</td>
<td>Donor working in healthcare: Not specified</td>
</tr>
<tr>
<td>Female: male: 53: 41.</td>
<td>Donor demographics: Not specified</td>
</tr>
<tr>
<td>Age (mean): Mean 71.8 (range 24-95) years.</td>
<td>Donor screening: Questionnaire - describes use of questionnaire but no details given - “similar to the Full Length Donor History Questionnaire documents (US Food and Drug administration, DHQ version 1.3, May 2008”</td>
</tr>
<tr>
<td>Comorbidities: x3 IBD, x3 post-renal transplant.</td>
<td>Travel and antibiotic exclusion period: Not specified</td>
</tr>
<tr>
<td>CDI features: Some patients refractory (defined as ongoing diarrhea despite treatment with at least 5 days of oral vancomycin, 125mg four times daily), or recurrent (symptom resolution for at least two days after the discontinuation of treatment with recurrence of diarrhoea.</td>
<td>Screening blood testss: HIV-1/-2, HTLV-1 and -2, Hepatitis A IgG/M, hepatitis B surface antigen, hepatitis C antibody, Treponema pallidum.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Toxin positive by enzyme immunoassay or polymerase chain reaction.</td>
<td>Screening stools: Ova, cysts and parasites, MC&amp;S, C difficile toxin, norovirus, adenovirus, rotavirus.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Average of 2.1 previous anti-CDI antibiotic</td>
<td>Bowel purgative: Not specified.</td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: Not specified.</td>
<td>PPI: Not specified.</td>
</tr>
<tr>
<td>Diluent used to prepare: 300ml water.</td>
<td>Antimotility: Not specified.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: N/A – fresh.</td>
<td>Prokinetics: Not specified.</td>
</tr>
<tr>
<td>Preparation methods: Homogenisation of stool in water using a disposable spatula.</td>
<td>Time before CDI treatment was stopped before FMT: Not specified.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Not specified.</td>
<td>Overall cure within stated follow up period: At 6 months – 87% (n=81/94) in remission after FMT.</td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A.</td>
<td>Cure with one infusion alone: 47.9% (n=45/94) with single FMT in remission at 6 months.</td>
</tr>
<tr>
<td>Route administered: Upper GI: nil; lower GI: retention enema in all 94 patients; nil capsules.</td>
<td>Total follow up period: 24 months.</td>
</tr>
<tr>
<td>Number of infusions: No fixed number - as many as required to achieve remission. No clear definition of non-response.</td>
<td>Minor GI adverse events: &quot;10% experienced transient constipation and excess flatulence post-FMT&quot;.</td>
</tr>
<tr>
<td>Minor non-GI adverse events: None described.</td>
<td>Serious adverse events: None described.</td>
</tr>
<tr>
<td>Deaths: 75% (n=6/8) patients not responding to FMT died (not clear when). All &quot;over 70 years of age&quot;, with multiple underlying significant comorbidities and passed away due to critical illnesses; none had deaths attributable to FMT or directly due to CDI.</td>
<td>Selection/eligibility reported: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
<td>Prospectively recruited: No.</td>
</tr>
</tbody>
</table>
| Loss to follow up explained: Yes. | At least 90% followed up: Yes.
Additional Appendices

courses (range 1-4), specifically: x74 metronidazole courses (79.3%), x71 vancomycin (75%), x14 vancomycin taper (15.2%), x3 probiotic monotreatment (0.03%), x16 concomitant metronidazole/vancomycin (17.4%).
Case series.
Number of patients: 15.
Female: male: 14: 1.
Age (median): 81.5 (range 68-95) years.
Comorbidities: no haematological or IBD.
CDI features: Relapsing defined as recurrence of loose stool following successful antibiotic treatment in a patient with previous toxin positive CDI.
CDI diagnosis confirmation: Not specified.
Pre-FMT antibiotics: All had had previous metronidazole and vancomycin; x3 patients tapering vancomycin and intravenous immunoglobulin.

| Donors were healthy related volunteers. |
| Working in healthcare: Yes – in three cases where relatives could not be identified. |
| Donor demographics: Not specified. |
| Donor screening: HIV-1/2, HTLV-1 and -2, hepatitis A IgG/M, hepatitis B surface antigen, hepatitis C antibody, Treponema pallidum. |
| Questionnaire: Yes, but not specified. |
| Travel and antibiotic exclusion period: Not specified. |
| Screening stools: Ova, cysts and parasites, MC&S, C difficile toxin. |

Amount of stool per transplant administered to patients: 30g.
Diluent used to prepare: 0.9% normal saline.
Diluent used to store if frozen: N/A – fresh.
Preparation methods: Stool sample prepared in less than 6 hours; add 50-70ml of normal saline, homogenise with handheld stool blender, gradually advance speed, continue for 2-4 mins until smooth, filter suspension in coffee filter paper.
Time from preparation to transplant (fresh): 6 hours.
Time period for storage (frozen): Not applicable.
Route administered: Upper GI: All 15 patients received FMT via nasogastric tube; lower GI and capsules: nil.
Number of infusions: 1 FMT per patient routinely, repeat if required.
Bowel purgative: Not given.
PPI: Omeprazole 20mg eve before and on morning.
Antimotility: Not given.

Overall cure within stated follow up period: 84% (n=15/18) “resolution”.
Cure with one infusion alone: 884% (n=15/18) “resolution”.
Total follow-up period: 90 days.
Minor GI adverse events: x1 diarrhoea.
Minor non-GI adverse events: Nil.
Serious adverse events: Nil.
Deaths: x2 (not felt related to FMT).

Selection/ eligibility reported: Yes.
Consecutively recruited: Yes.
Prospectively recruited: No.
Loss to follow up explained: Yes.
At least 90% followed up: Yes.
<table>
<thead>
<tr>
<th>Prokinetics: Not given.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time before CDI treatment was stopped before FMT: Stopped on the evening before FMT.</td>
</tr>
</tbody>
</table>
Donors: 61 donors were close relatives/ other household members; in 9 cases, healthy volunteers.

Amount of stool per transplant / administered to patients: 20-30ml stool.

Diluent used to prepare: 100-200ml water; 100ml of suspension administered to caecum.

Diluent used to store if frozen: N/A – all fresh.

Preparation methods: Not specified.

Travel and antibiotic exclusion period: Excluded as donor if any antibiotic use within past six months; no details of travel restrictions.

Screening stool tests: C difficile culture/ tox A/ B; MC&S, ova cysts and parasites.

Donors working in healthcare: Not specified.

Donor demographics: Not specified.

Donor screening: Questionnaire - "No antibiotics and no intestinal symptoms within 6 months".

Cure with one infusion alone: 94% (n=66/70) (100% (n=34/34) of those with non-027, 89% (n=32/36) with 027) within 12 weeks.

Number of infusions: 1 FMT.

Time from preparation to transplant (fresh): 6 hours.

Current blood tests: Hepatitis B surface antigen, Hepatitis C antibody, HIV-1/2 , Treponema pallidum plasma reagin test; total blood count, C-reactive protein, creatinine, liver enzymes.

Time before CDI treatment was stopped before FMT: Average of 36 hours.

Bowel purgative: 4l PEG (Colonsteril).

PPI: Not specified.

Prokinetics: Not specified.

Overall cure within stated follow up period: 94% (n=66/70) (100% (n=34/34) of those with non-027, 89% (n=32/36) with 027) within 12 weeks.

Minor GI adverse events: Not specified.

Minor non-GI adverse events: Not specified.

Serious adverse events: Not specified.

Deaths: x4 patients infected with 027 did not respond to FMT and died within 3 months. 10 other patients died of 'unrelated illnesses' during one year of follow-up.

Selection/ eligibility reported: Yes.

Consecutively recruited: Not clear.

Prospectively recruited: No.

Loss to follow up explained: Yes.

At least 90% followed up: Yes.
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Amount of stool per transplant / administered to patients: Not specified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 201.</td>
<td>Diluent used to prepare: Not specified.</td>
</tr>
<tr>
<td>Female: male: 125: 76.</td>
<td>Diluent used to store if frozen: Not specified.</td>
</tr>
<tr>
<td>Age (mean/ standard deviation): Mean age 66.6 (+/-18.3) years.</td>
<td>Preparation methods: Not specified.</td>
</tr>
<tr>
<td>Comorbidities: x37 cancer, x30 immunosuppressed, x26 CKD. Immunosuppressed defined as chemotherapy within 1 year of FMT, HIV with CD4 &lt; 200, or prednisolone use greater than or equal to 20mg for more than 1 month.)</td>
<td>Time from preparation to transplant (fresh): Not specified.</td>
</tr>
<tr>
<td>CDI features: 61 with refractory, 140 with recurrent.</td>
<td>Time period for storage (frozen): Not specified.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Positive toxin or polymerase chain reaction.</td>
<td>Route administered: Upper Gi: nasogastric tube x 76, PEG x5; lower Gi: x45 enema, x75 colon; capsules: nil.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Not specified.</td>
<td>Number of infusions: Some people received multiple FMT procedures - repeat FMTs within 90 days of previous FMT were still maintained as a 'single infection unit'.</td>
</tr>
<tr>
<td>Donor demographics: not specified.</td>
<td>PPI: Not specified.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Not specified.</td>
<td>Prokinetics: Not specified.</td>
</tr>
<tr>
<td>Screening blood tests: Not specified.</td>
<td>Overall cure within stated follow up period: 88% (n=176/201) over 90 days.</td>
</tr>
<tr>
<td>Screening stool tests: Not specified.</td>
<td>Cure with one infusion alone: 73.1% (n=147/201).</td>
</tr>
<tr>
<td></td>
<td>Total follow-up period: Each patient for 90 days.</td>
</tr>
<tr>
<td></td>
<td>Minor GI adverse events: Not specified.</td>
</tr>
<tr>
<td></td>
<td>Minor non-GI adverse events: Not specified.</td>
</tr>
<tr>
<td></td>
<td>Serious adverse events: Not described.</td>
</tr>
<tr>
<td></td>
<td>Deaths: 18 deaths in cohort but no clear timeframe, and not clear if any related to FMT. Described as mortality rate of 6.25% in response group, 28% in failure rate.</td>
</tr>
<tr>
<td></td>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td></td>
<td>Consecutively recruited: Yes.</td>
</tr>
<tr>
<td></td>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td></td>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td></td>
<td>At least 90% followed up: Yes.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Additional Appendices**

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 201.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 124: 77.</td>
<td></td>
</tr>
<tr>
<td>Age (mean/ standard deviation): Mean 68.79 (+/−16.78) years for x181 non-IBD patients, mean 46.9 (+/−19.97) for the x20 IBD patients.</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: 13/20 IBD patients were immunosuppressed (no further details); no further specific details about immunosuppression.</td>
<td></td>
</tr>
<tr>
<td>CDI features: Recurrent CDI in 13/20 of IBD patients, primary refractory in 7/20. 1.90 (+/−1.02) CDI infections in past three months for IBD patients, 1.79 (+/1.17) CDI infections in past three months for non-IBD patients.</td>
<td></td>
</tr>
<tr>
<td>CDI diagnosis confirmation: GDH first, then toxin A and B; PCR</td>
<td></td>
</tr>
<tr>
<td>Donors were typically family members, but small number of unrelated universal donors. Amongst IBD cohort - 6 patients had family members as donor, universal donor in other 14.</td>
<td></td>
</tr>
<tr>
<td>Donor working in healthcare: Not defined.</td>
<td></td>
</tr>
<tr>
<td>Donor demographics: Not defined.</td>
<td></td>
</tr>
<tr>
<td>Donor screening: Questionnaire - not defined.</td>
<td></td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Not defined.</td>
<td></td>
</tr>
<tr>
<td>Screening blood tests: Not defined.</td>
<td></td>
</tr>
<tr>
<td>Screening stool tests: Not defined.</td>
<td></td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: Not defined.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to prepare: Not defined.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to store if frozen: Not defined.</td>
<td></td>
</tr>
<tr>
<td>Preparation methods: Not defined.</td>
<td></td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Not defined.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): Not defined.</td>
<td></td>
</tr>
<tr>
<td>Route administered: Upper GI: 5 nasogastric (IBD patients only; not described re non-IBD patients) Lower GI: 13 colonoscopy (IBD patients only; not described in non-IBD patients); 2 retention enema (IBD patients only; not described re non-IBD patients) (15).</td>
<td></td>
</tr>
<tr>
<td>Number of infusions: Any relapse beyond 90 days was defined as 'new infection'. However, not made clear if patients given more than one FMT.</td>
<td></td>
</tr>
<tr>
<td>Bowel purgative: Not described.</td>
<td></td>
</tr>
<tr>
<td>PPI: Not described.</td>
<td></td>
</tr>
<tr>
<td>Antimotility: Not described.</td>
<td></td>
</tr>
<tr>
<td>Prokinetics: Not described.</td>
<td></td>
</tr>
<tr>
<td>Overall cure within stated follow up period: As per primary outcome - difficult to give more specific information than already given.</td>
<td></td>
</tr>
<tr>
<td>Cure with one infusion alone: 87.3% (n=158/181) in non-IBD, 75% (15/20) in IBD; but 17.15 (n=31/181) non-IBD relapse within 90 days/ 13.9% (n=25/180) beyond 90 days, and 25% (n=5/20) IBD relapse within 90 days/ 20% (n=4/20) beyond 90 days. 3/5 failures in IBD arm had newly-diagnosed IBD, other had severe active disease.</td>
<td></td>
</tr>
<tr>
<td>Minor GI adverse events: None.</td>
<td></td>
</tr>
<tr>
<td>Minor non-GI adverse events: None.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events: None.</td>
<td></td>
</tr>
<tr>
<td>Deaths: None.</td>
<td></td>
</tr>
<tr>
<td>Total follow up period: At least 90 days.</td>
<td></td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
<td></td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
<td></td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
<td></td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
<td></td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
<td></td>
</tr>
</tbody>
</table>

Meighani et al, *Digestive Diseases and Sciences, 2017*
### Additional Appendices

<table>
<thead>
<tr>
<th>Used if discordance.</th>
<th>Time before CDI treatment was stopped before FMT: No specific details.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-FMT antibiotics: Not defined for non-IBD; for IBD, 15 vancomycin alone, 5 vancomycin and oral metronidazole.</td>
<td></td>
</tr>
</tbody>
</table>


**Additional Appendices**

**Patel et al, Mayo Clinic Proceedings, 2013**

<table>
<thead>
<tr>
<th>Case series.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 31.</td>
</tr>
<tr>
<td>Female: male: 17: 14.</td>
</tr>
<tr>
<td>Age (mean/ standard deviation): Mean 61.26 (+/- 19.34) years.</td>
</tr>
<tr>
<td>Comorbidities: x5 diverticulosis, x5 IBS, x3 UC, x1 Crohn’s, x1 gastroparesis, x1 colonoal fistula, x3 prev sigmoid surgery for diverticulitis, x2 subtotal colectomy with ileosigmoid anastomosis, x1 left hemicolectomy with colostomy, x3 long term corticosteroids, x2 hypogammaglobulinaemia, x1 OLT, x1 renal transplant, x1 long term methotrexate.</td>
</tr>
<tr>
<td>CDI features: Recurrent - mean +/- SD number of confirmed relapses before FMT of 4 +/- 1.4 (range 2-7) episodes.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: At least 3x unformed stools/ day, at</td>
</tr>
<tr>
<td>Working in healthcare: Not stated.</td>
</tr>
<tr>
<td>Donor demographics: No stated age/ BMI limits.</td>
</tr>
<tr>
<td>Donor screening: Questionnaire - exclude if: chronic GI disease, active peptic ulcer disease, GORD requiring daily PPI, IBS, IBD, history of colon polyps/ cancer, antibiotics or hospitalisation in past three months.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: No stated travel restrictions; excluded as donor if antibiotic use within past 3 months.</td>
</tr>
<tr>
<td>Screening blood tests: hepatitis A IgM, HBsAg, HBC IgG/M, hepatitis C antibody, HIV, 1/-2 antibody, HTLV-1/-2 antibody, RPR/ syphilis EIA.</td>
</tr>
<tr>
<td>Number of infusions: One initially.</td>
</tr>
<tr>
<td>Bowel purgative: Yes - PEG day before FMT.</td>
</tr>
<tr>
<td>PPI: Not described.</td>
</tr>
<tr>
<td>Antimotility: 4mg loperamide either pre- or immediately after colonoscopy.</td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: Whole stool - median transplanted weight of 115g (range 18-397g).</td>
</tr>
<tr>
<td>Diluent used to prepare: Normal saline - &quot;added in 100ml increments until mixture suitable for instillation through working channel of colonoscope&quot;. Median volume of FMT 360 (range 180-900) ml.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: N/A – fresh.</td>
</tr>
<tr>
<td>Preparation methods: Blender/ pitcher.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Six hours; kept at room temperature until processing.</td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A.</td>
</tr>
<tr>
<td>Route administered: Upper GI: nil; lower GI: colonoscopy (31); capsule: nil.</td>
</tr>
<tr>
<td>Overall cure within stated follow up period: At 3 months – 91.3% (n=21/23) said diarrhoea no longer present; at 1 year, 100% (n=6/6) reported maintained improvement or resolution.</td>
</tr>
<tr>
<td>Cure with one infusion alone: Of 29 with diarrhoea – 24.1% (n=7/29) reported improvement and 75.9% (n=22/29) resolution of diarrhoea by median time of three days.</td>
</tr>
<tr>
<td>Total follow up period: One year.</td>
</tr>
<tr>
<td>Minor GI adverse events: Not described.</td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not described.</td>
</tr>
<tr>
<td>Serious adverse events: Microperforation - caused by biopsy of an area of presumed ischaemic small bowel injury during the FMT procedure; managed conservatively.</td>
</tr>
<tr>
<td>Deaths: x1 death at three months - directly related to recently diagnosed metastatic pancreatic cancer, not related to FMT.</td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: Yes, implied that were.</td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td>At least 90% followed up: Yes - at least as far as primary outcome.</td>
</tr>
</tbody>
</table>
### Additional Appendices

<table>
<thead>
<tr>
<th>Least 2 x toxin positive episodes previously to participate.</th>
<th>Microsporidia smear, <em>C difficile</em> toxin (PCR or EIA).</th>
<th>Prokinetics: Not described. Time before CDI treatment was stopped before FMT: Antibiotics continued until 4 hours before prep (i.e. stopped day prior to FMT).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-FMT antibiotics: All 31 previous methotrexate, all 31 previous vancomycin, 6 previous fidaxomicin, 10 previous rifaximin, 23 prior probiotic.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Additional Appendices
- Least 2 x toxin positive episodes previously to participate.
- Pre-FMT antibiotics: All 31 previous methotrexate, all 31 previous vancomycin, 6 previous fidaxomicin, 10 previous rifaximin, 23 prior probiotic.
- Microsporidia smear, *C difficile* toxin (PCR or EIA).
- Prokinetics: Not described.
- Time before CDI treatment was stopped before FMT: Antibiotics continued until 4 hours before prep (i.e. stopped day prior to FMT).
Pathak et al, Clinical & Experimental Gastroenterology, 2013

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Donors were preferably family/first degree relatives; family used in all cases here.</th>
<th>Amount of stool per transplant/administered to patients: About 6-8 tablespoons.</th>
<th>Minor GI adverse events: Not stated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 12.</td>
<td>Working in healthcare: Not specifically addressed.</td>
<td>Diluent used to prepare: 1l of tap water.</td>
<td>Minor non-GI adverse events: Not stated.</td>
</tr>
<tr>
<td>Female: male: 8: 4.</td>
<td>Donor demographics: Not given.</td>
<td>Diluent used to store if frozen: N/A - all fresh.</td>
<td>Serious adverse events: Not stated.</td>
</tr>
<tr>
<td>Age (mean): Mean 71.9 (range 37 – 90) years.</td>
<td>Donor screening: Questionnaire - exposure to HIV, hepatitis, STDs; high risk sexual behaviour; drug use, tattoos/piercings, imprisonment, other high risk behaviour; known current communicable disease; GI morbidities including IBD or GI malignancy; antibiotic use within 90 days.</td>
<td>Preparation methods: No specific details.</td>
<td>Deaths: x1 death. Patient with perforated appendix; developed rCDI; didn't respond to six months of anti-CDI treatment, went to ITU. Donor was husband - no screening, and no response to colonoscopic FMT. For 2nd FMT, used healthy volunteer donor FMT via nasoduodenal tube - responded. Urinary tract infection at nursing home few months later – antibiotic treatment precipitated further CDI. Further sepsis, returned to ITU -</td>
</tr>
<tr>
<td>Comorbidities: x1 UC, 1 renal transplant, x1 left colon adenocarcinoma and diverticulitis; x1 ruptured appendix; x2 ventilator-dependent.</td>
<td>Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within last 90 days.</td>
<td>Time from preparation to transplant (fresh): 6 hours.</td>
<td>Selection/eligibility reported: Yes.</td>
</tr>
<tr>
<td>CDI features: Recurrent; full details not given.</td>
<td>Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within last 90 days.</td>
<td>Time period for storage (frozen): N/A.</td>
<td>Consecutively recruited: Yes, implied that were.</td>
</tr>
<tr>
<td>Two of the patients had had recurrent CDI treated with FMT 'many years ago'.</td>
<td>Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within last 90 days.</td>
<td>Route administered: Upper GI: nasoduodenal tube (1; as a second FMT); lower GI: colonoscopy (12).</td>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Not specifically defined.</td>
<td>Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within last 90 days.</td>
<td>Number of infusions: 1 FMT initially.</td>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: All vancomycin, 8 patients fidaxomicin, 4 patients methotrexate.</td>
<td>Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within last 90 days.</td>
<td>Bowel purgative: PEG the night before FMT.</td>
<td>At least 90% followed up: Yes.</td>
</tr>
</tbody>
</table>

Overall cure within stated follow-up period: 91.7% (n=11/12). Cure with one infusion alone: 91.7% (n=11/12). Total follow up period: 2-26 months.
declined treatment, then died, four months after initial FMT.
**Rohlke et al, Journal of Clinical Gastroenterology, 2010**

**Case series.**

Number of patients: 19. Female: male: 17: 2. Age (mean): Mean age 49 years. Comorbidities: Not described. CDI features: Recurrent CDI. CDI diagnosis confirmation: Positive *Clostridium difficile* toxin and consistently recurring symptoms over a span of six months. Pre-FMT antibiotics: Not given in detail - all at least three courses of conventional anti-CDI antibiotics, including pulsed and tapered vancomycin.

<table>
<thead>
<tr>
<th>Amount of stool per transplant / administered to patients: 350mls.</th>
<th>Diluent used to prepare: Normal saline.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent used to store if frozen: N/A - fresh.</td>
<td>Preparation methods: Fresh preparation, with manual shaking of stool and saline in large suction canister, followed by filtering.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Not stated.</td>
<td>Time period for storage (frozen): N/A.</td>
</tr>
<tr>
<td>Route administered: Upper GI: nil; lower GI: all given via colonoscopy.</td>
<td>Number of infusions: One routinely, with one patient having a second FMT.</td>
</tr>
<tr>
<td>Bowel purgative: PEG.</td>
<td>Antimotility: Loperamide post-FMT.</td>
</tr>
<tr>
<td>PPI: Not described.</td>
<td>Prokinetics: Not described.</td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: 1-3 days.</td>
<td>Overall cure within stated follow up period: 100% (n=20/20).</td>
</tr>
<tr>
<td>Minor GI adverse events: Nil reported.</td>
<td>Cure with one infusion alone: 95% (n=19/20).</td>
</tr>
<tr>
<td>Minor non-GI adverse events: Nil reported.</td>
<td>Total follow-up period: 6 months to 5 years.</td>
</tr>
<tr>
<td>Serious adverse events: Nil reported.</td>
<td>Deaths: Nil reported.</td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
<td>Consecutively recruited: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: No.</td>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Loss to follow up explained: Yes – variable follow-up.</td>
<td>At least 90% followed up: Yes.</td>
</tr>
</tbody>
</table>
**Rubin et al, Anaerobe, 2013**

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 75.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 75.</td>
<td></td>
</tr>
<tr>
<td>Age (median): Median 63 (range 6-94) years.</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: x10 diabetes mellitus, x8 malignancy, x7 corticosteroids in prior three months.</td>
<td></td>
</tr>
<tr>
<td>CDI features: Not stated.</td>
<td></td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Not described.</td>
<td></td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Oral metronidazole or vancomycin alone or in combination for initial FMT in all cases; not clear exact breakdown/use for recurrences.</td>
<td></td>
</tr>
<tr>
<td>Donors were healthy people from the same household as the patient.</td>
<td></td>
</tr>
<tr>
<td>Donors working in healthcare: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Donor demographics: Not described.</td>
<td></td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: As per Aas et al, Clin Infect Dis, 2003.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A – fresh.</td>
<td></td>
</tr>
<tr>
<td>Route administered: Upper GI: 64 nasogastric, 4 PEG, 7 OGD (75 administrations to 74 patients); lower GI: nil; capsule: nil.</td>
<td></td>
</tr>
<tr>
<td>Number of infusions: One routinely.</td>
<td></td>
</tr>
<tr>
<td>Bowel purgative: Not described.</td>
<td></td>
</tr>
<tr>
<td>PPI: Evening prior to/ morning of procedure - no further details.</td>
<td></td>
</tr>
<tr>
<td>Antimotility: Not described.</td>
<td></td>
</tr>
<tr>
<td>Prokinetics: Not described.</td>
<td></td>
</tr>
</tbody>
</table>

| Amount of stool per transplant/ administered to patients: 30g of stool. | |
| Diluent used to prepare: Saline - As per Aas et al, Clin Infect Dis, 2003. 25ml of stool/ saline mixture per FMT. | |
| Diluent used to store if frozen: N/A - fresh. | |
| Time period for storage (frozen): N/A – fresh. | |
| Overall cure within stated follow up period: 78.7% (n=59/75). | |
| Cure with one infusion alone: 78.7% (n=59/75). | |
| Total follow up period: Up to 60 days. | |
| Minor GI adverse events: Nil. | |
| Minor non-GI adverse events: Nil. | |
| Serious adverse events: Nil. | |
| Deaths: No - up to 60 days. | |
| Selection/ eligibility reported: Yes. | |
| Consecutively recruited: Yes. | |
| Prospectively recruited: No. | |
| Loss to follow up explained: Yes. | |
| At least 90% followed up: Yes. | |
**Additional Appendices**

| Time before CDI treatment was stopped before FMT: Stopped on the day prior to procedure. |   |   |   |
**Case series.**

**Number of patients:** 49.

**Female:** male: 34: 15.

**Age (mean):**
- Fresh: 52 (range 22-81) years; frozen: 61 (range 20-88) years.

**Comorbidities:** Not described in significant details.

**CDI features:**
- Recurrent - mean 4.6 (range 2-12) relapses in fresh; mean 4.9 (range 1-6) relapses in frozen.
- Travel and antibiotic exclusion period: Excluded as donors if had used antibiotics in past six months.

**CDI diagnosis confirmation:** "Positive culture and toxin".

**Pre-FMT antibiotics:** Describes using vancomycin with all, but no specific details.

**Donors were:**
- 15 fresh FMTs with individual donors, 11 fresh FMTs with universal donors; and 23 frozen FMTs with universal donor.
- Donor working in healthcare: Not stated.
- Donor demographics: No clear age or BMI limits.
- Donor screening: Questionnaire - "No antibiotics in past six months and no intestinal symptoms".
- Travel and antibiotic exclusion period: Excluded as donors if had used antibiotics in past six months.
- Donor screening: Questionnaire - "No antibiotics in past six months and no intestinal symptoms".

**Amount of stool per transplant / administered to patients:**
- Fresh - approximately 30g of stool.
- Diluent used to prepare: Fresh - approximately 150ml of tap water.
- Diluent used to store if frozen: Frozen - 30g of stool added to 150ml N/saline and then glycerol.

**Preparation methods:**
- As described.
- Time from preparation to transplant (fresh): Fresh - less than 6 hours between delivery and administration; less than 15 minutes between making FMT and delivery.
- Time period for storage (frozen): Up to 16 weeks; thawed over 4-5 hours at room temp or in 37°C water bath.

**Route administered:**
- Upper GI: nil; lower GI: colonoscopy (49); capsules: nil.

**Number of infusions:** One FMT routinely.

**Bowel purgative:** 4l Colonsteril PEG/ 2l MoviPrep.

**PPI:** Not described.

**Antimotility:** Not described.

**Overall cure within stated follow up period:**
- Fresh: 96% (n=25/26); frozen: 96% (n=22/23).

**Total follow up period:** 12 weeks.

**Minor GI adverse events:** N/A.

**Minor non-GI adverse events:** Mild transient fever in x2 patients with frozen FMT.

**Deaths:**
- x1 fresh faeces patient died within one year of FMT - not related;
- x2 frozen patients had relapse within one year, both treated with further antibiotics – x1 died of recurrent CDI, x1 died of arterial thrombosis.

**Selection/ eligibility reported:** Yes.

**Consecutively recruited:** Yes.

**Prospectively recruited:** No.

**Loss to follow up explained:** Yes.

**At least 90% followed up:** Yes.
Prokinetics: not described.

Time before CDI treatment was stopped before FMT: Stopped at an average of 36 hours prior to administration.

<table>
<thead>
<tr>
<th><strong>Case series.</strong></th>
<th><strong>Amount of stool per transplant / administered to patients:</strong> Stool (unclear how much) mixed with 1l normal saline; approx 250-450cc of FMT administered in total.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients:</strong> 12.</td>
<td><strong>Diluent used to prepare:</strong> Normal saline.</td>
</tr>
<tr>
<td><strong>Female:</strong> male: 9: 3.</td>
<td><strong>Diluent used to store if frozen:</strong> N/A.</td>
</tr>
<tr>
<td><strong>Age (mean)*:</strong> Mean 66 (range 30 - 86) years.</td>
<td><strong>Preparation methods:</strong> Manually shaken then filtered through gauze.</td>
</tr>
<tr>
<td><strong>Comorbidities:</strong> 9 with diverticulosis (with 2 of these having diverticulitis as index infection).</td>
<td><strong>Time from preparation to transplant (fresh):</strong> No details.</td>
</tr>
<tr>
<td><strong>CDI features:</strong> 1 patient with first CDI, 2 with 2nd, 5 with 3rd, 1 with 4th, 1 with 5th, 1 with 6th, 1 with 8th.</td>
<td><strong>Time period for storage (frozen):</strong> N/A.</td>
</tr>
<tr>
<td><strong>CDI diagnosis confirmation:</strong> Toxin testing for either toxin A or B, or assessment of both via EIA.</td>
<td><strong>Route administered:</strong> Upper GI: (N/A) Lower GI: 10-20cc of FMT administered every 5-10cm of withdrawal distance in all 12 patients.</td>
</tr>
<tr>
<td><strong>Pre-FMT antibiotics:</strong> 12 had oral metronidazole, 3 had intravenous metronidazole, 12 had oral vancomycin, 4 x rifaximin, no mention of fidaxomicin.</td>
<td><strong>Number of infusions:</strong> Single.</td>
</tr>
<tr>
<td><strong>Donors were spouses/ partners in 8 patients; for other 4 patients, donors were one son, two daughters, and one granddaughter.</strong></td>
<td><strong>Bowel purgative:</strong> All colonoscopic, but no specific details given.</td>
</tr>
<tr>
<td><strong>Donors working in healthcare:</strong> No.</td>
<td><strong>PPI:</strong> Not described.</td>
</tr>
<tr>
<td><strong>Donor demographics:</strong> No details.</td>
<td><strong>Antimotility:</strong> Not described.</td>
</tr>
<tr>
<td><strong>Donor screening:</strong> Questionnaire - no details.</td>
<td><strong>Prokinetics:</strong> Not described.</td>
</tr>
<tr>
<td><strong>Travel and antibiotic exclusion period:</strong> No details given</td>
<td><strong>Overall cure within stated follow up period:</strong> 100% (n=12/12).</td>
</tr>
<tr>
<td><strong>Screening bloods:</strong> Hepatitis B and C, HIV.</td>
<td><strong>Total follow up period:</strong> 3 weeks to 8 years - no details on relation to individual patients.</td>
</tr>
<tr>
<td><strong>Screening stools:</strong> <em>C difficile</em> toxin, enteric pathogens, ova, cysts and parasites - at treating clinician's discretion.</td>
<td><strong>Minor GI adverse events:</strong> Nil described.</td>
</tr>
<tr>
<td></td>
<td><strong>Minor non-GI adverse events:</strong> Nil described.</td>
</tr>
<tr>
<td></td>
<td><strong>Serious adverse events:</strong> Nil described.</td>
</tr>
<tr>
<td></td>
<td><strong>Deaths:</strong> Nil described.</td>
</tr>
<tr>
<td></td>
<td><strong>Selection/ eligibility reported:</strong> Yes.</td>
</tr>
<tr>
<td></td>
<td><strong>Consecutively recruited:</strong> Yes.</td>
</tr>
<tr>
<td></td>
<td><strong>Prospectively recruited:</strong> No.</td>
</tr>
<tr>
<td></td>
<td><strong>Loss to follow up explained:</strong> No.</td>
</tr>
<tr>
<td></td>
<td><strong>At least 90% followed up:</strong> Yes.</td>
</tr>
</tbody>
</table>
**Additional Appendices**

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<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Time CDI treatment was stopped before FMT: 3 days.</strong></td>
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<tr>
<td>Youngster <em>et al.</em>, JAMA, 2014</td>
<td>Prospective case series.</td>
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<tr>
<td>Number of patients: 20.</td>
<td>Female: male: 9: 11.</td>
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<tr>
<td>Age (median): Median 64.5 (range 11-89) years.</td>
<td>Donors were unrelated adult volunteers.</td>
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<tr>
<td>Comorbidities: Specific comorbidities not described.</td>
<td>Donor working in healthcare: Not stated.</td>
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<tr>
<td>CDI features: Included patients with both recurrent or refractory CDI.</td>
<td>Donor demographics: Age range 18-50 years, BMI 18.5 - 25.</td>
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<tr>
<td>CDI diagnosis confirmation:Toxin and ELISA, PCR if toxin negative but ELISA is positive or indeterminate.</td>
<td>Screening blood tests: Antibodies to hepatitis A, B, and C; HIV; and <em>Treponema pallidum</em> within 2 weeks of donations.</td>
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<tr>
<td>Pre-FMT antibiotics: Failed vancomycin taper and/or fidaxomicin.</td>
<td>Screening stool tests: &quot;Enteric pathogens&quot;.</td>
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<tr>
<td>Amount of stool per transplant / administered to patients: 30 capsules (single treatment) - total 48g of stool.</td>
<td>Diluent used to prepare: saline in 1/10th volume of stool.</td>
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<tr>
<td>Diluent used to store if frozen: 10% glycerol.</td>
<td>Preparation methods: Faecal matter solution was pipetted into size 0 capsules (650 μL), which were closed and then secondarily sealed in size 00 capsules. Capsules were stored frozen at −80°C until use.</td>
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<tr>
<td>Time from preparation to transplant (fresh): N/A.</td>
<td>Time period for storage (frozen): Mean 113 days (30-252 days).</td>
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<tr>
<td>Route administered: All courses were 30 oral capsules.</td>
<td>Number of treatments: 1 course (given as 15 capsules on 2 consecutive days). If failed, retreated at a mean of 7 days.</td>
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<tr>
<td>Overall cure within stated follow up period: 90% (n=18/20).</td>
<td>Number of treatments: 1 course (given as 15 capsules on 2 consecutive days). If failed, retreated at a mean of 7 days.</td>
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<tr>
<td>Cure with one infusion alone: 70% (n=14/20).</td>
<td>Total follow up period: 8 weeks.</td>
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<tr>
<td>Minor GI adverse events: Transient abdominal cramping and bloating in 6 patients (30%) that resolved in 72 hours.</td>
<td>Minor non-GI adverse events: Not described.</td>
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<tr>
<td>Serious adverse events: x1 hospitalised with a documented relapse of severe CDI after taking 15 capsules, but had successful treatment after receiving the remaining 15 capsules. No other severe adverse events (grade 2 or above).</td>
<td>Deaths: none.</td>
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<tr>
<td>Selection/eligibility reported: Yes.</td>
<td>Consecutively recruited: Yes.</td>
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<tr>
<td>Loss to follow up explained: Yes.</td>
<td>At least 90% followed up: Yes.</td>
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</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
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</tbody>
</table>
Prokinetics: Not described.

Time before CDI treatment was stopped before FMT: 48 hours prior to FMT.
**Youngster et al, BMC Medicine, 2016**

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Donors were healthy volunteers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 180.</td>
<td>Donors working in healthcare: Not mentioned.</td>
</tr>
<tr>
<td>Female: male: Not stated.</td>
<td>Donor demographics: 18-50 years of age, on no medications, with a ‘normal body mass index’.</td>
</tr>
<tr>
<td>Age (median): Median 64 (range 7–95) years.</td>
<td>Donor screening: Questionnaire - initial screening using the American Association of Blood Banks donor questionnaire for exposure to infectious agents.</td>
</tr>
<tr>
<td>Comorbidities: Not described.</td>
<td>Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within 6 months.</td>
</tr>
<tr>
<td>CDI features: Three or more mild-to-moderate episodes of CDI or two episodes requiring hospitalisation.</td>
<td>Screening bloods: Blood was screened for antibodies to hepatitis A, B, and C; HIV; and Treponema pallidum within 2 weeks of donations.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Not specifically described.</td>
<td>Screening stool test: Donor faeces were screened for enteric bacterial pathogens including rotavirus, Listeria monocytogenes, Vibrio cholerae, Escherichia coli O157, ova and parasites (including general microscopy, acid-fast staining, and/or antigen testing</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Not described.</td>
<td>Amount of stool per transplant / administered to patients: 30 capsules derived from a mean of 48g of faeces.</td>
</tr>
<tr>
<td></td>
<td>Diluent used to prepare: Normal saline.</td>
</tr>
<tr>
<td></td>
<td>Diluent used to store if frozen: 10% glycerol.</td>
</tr>
<tr>
<td></td>
<td>Preparation methods: Homogenised using a commercial blender then passed through sieves in ambient air.</td>
</tr>
<tr>
<td></td>
<td>Time from preparation to transplant (fresh): N/A.</td>
</tr>
<tr>
<td></td>
<td>Time period for storage (frozen): Study of capsulised FMT. Faecal slurry was double-encapsulated in hypromellose capsules (Capsugel, Cambridge, MA) and stored at −80 °C for up to 6 months pending use.</td>
</tr>
<tr>
<td></td>
<td>Route administered: All received 30 capsules as a ‘dose’.</td>
</tr>
<tr>
<td></td>
<td>Number of infusions: 1 course of capsules in 147 patients, 2 courses in 26 patients and 3 course in 4 patients.</td>
</tr>
<tr>
<td></td>
<td>Bowel purgative: not mentioned.</td>
</tr>
<tr>
<td></td>
<td>PPI: not mentioned.</td>
</tr>
<tr>
<td></td>
<td>Antimotility: not mentioned.</td>
</tr>
<tr>
<td></td>
<td>Overall cure within stated follow up period: 91% (n=164/180)</td>
</tr>
<tr>
<td></td>
<td>Cure with one infusion alone: 82% (n=147/180)</td>
</tr>
<tr>
<td></td>
<td>Total follow up period: 8 weeks for primary response.</td>
</tr>
<tr>
<td></td>
<td>Minor non-GI adverse events: x3 fever, x54 fatigue, malaise, and headache, x12 other complaints.</td>
</tr>
<tr>
<td></td>
<td>Serious adverse events: Related serious (x1 fever, x2 new UC, x6 hospitalisations for CDI/ diarrhoea).</td>
</tr>
<tr>
<td></td>
<td>Unrelated serious adverse events: x26 hospitalisations, x14 deaths.</td>
</tr>
<tr>
<td></td>
<td>Deaths: x14 (unrelated).</td>
</tr>
<tr>
<td>Selection/eligibility reported: Yes.</td>
<td>Consecutively recruited: Yes.</td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
<td></td>
</tr>
<tr>
<td>for Giardia, Cryptosporidium, Isospora, and Microsporidia), C. difficile, and Helicobacter pylori antigen.</td>
<td>Prokinetics: not mentioned. Time before CDI treatment was stopped before FMT: 24–48 hours prior.</td>
</tr>
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</tr>
</tbody>
</table>
### Additional Appendices

**Zainah et al, Digestive Diseases and Sciences, 2014**

<table>
<thead>
<tr>
<th>Case series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 14.</td>
</tr>
<tr>
<td>Female: male: 9:5.</td>
</tr>
<tr>
<td>Age (mean +/- range)*: 73.4 (+/-11.9) years.</td>
</tr>
<tr>
<td>Comorbidities: x4 patients with cancer, x1 OLT patient.</td>
</tr>
<tr>
<td>CDI features: 8 patients had had prev CDI episodes (2-5 episodes prior).</td>
</tr>
<tr>
<td>CDI diagnosis: Diarrhoea (at least 3 unformed stool/d for 2 consecutive days) + positive <em>C difficile</em> EIA and/or PCR. All patients here severe by definition - defined here as age &gt;60 years, albumin &lt;2.5mg/dl, temp at least 38.3°C, WBC &gt; 15 within 48 hour of CDI diagnosis; or at least one of the following: pseudomembranes, treatment in intensive care.</td>
</tr>
<tr>
<td>Donors: 12 patients received FMT from related donor (7 spouse, 5 children); the other two used unrelated donors.</td>
</tr>
<tr>
<td>Donors working in healthcare: Not stated.</td>
</tr>
<tr>
<td>Donor demographics: Not stated.</td>
</tr>
<tr>
<td>Donor screening: Questionnaire - not described.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: No details.</td>
</tr>
<tr>
<td>Screening blood tests: HIV-1/2, hepatitis A IgM, hepatitis B serology, hepatitis C antibody, syphilis (RPR and FTA-ABS).</td>
</tr>
<tr>
<td>Screening stools: <em>C difficile</em> toxin by PCR, stool ova, cysts and parasites.</td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: 30-50g.</td>
</tr>
<tr>
<td>Diluent used to prepare: Warm tap water.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: N/A.</td>
</tr>
<tr>
<td>Preparation methods: Homogenised mixture, then filtered through gauze; 120-180ml of suspension if through nasogastric tube, 300-500ml if through colonoscopy.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): &quot;Same day&quot;.</td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A.</td>
</tr>
<tr>
<td>Route administered: Upper GI: Nasogastric administration in all but one patient (13 patients); lower GI: colonoscopic administration in one patient (1 patient).</td>
</tr>
<tr>
<td>Number of infusions: One routinely; repeated if no response at 48-72hr.</td>
</tr>
<tr>
<td>Bowel purgative: No details.</td>
</tr>
<tr>
<td>PPI: Yes, pre nasogastric administration - no details given.</td>
</tr>
<tr>
<td>Antimotility: Not described.</td>
</tr>
<tr>
<td>Overall cure within stated follow up period: 79% (n=11/14) by seven days.</td>
</tr>
<tr>
<td>Cure with one infusion alone: 71% (n=10/14).</td>
</tr>
<tr>
<td>Total follow up period: Up to 100 days.</td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
</tr>
<tr>
<td>Minor GI adverse events: Not described.</td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not described.</td>
</tr>
<tr>
<td>Serious adverse events: Not described.</td>
</tr>
<tr>
<td>Deaths: x1 within 7 days of FMT - but died of their malignancy.</td>
</tr>
</tbody>
</table>
Additional Appendices

| Pre-FMT antibiotics: 14 patients prior vancomycin, 12 prior metronidazole too. | Prokinetics: Not described. Time before CDI treatment was stopped before FMT: 24 hours. |   |   |   |
C.2. Reviewed randomised studies of FMT for recurrent or refractory CDI
<table>
<thead>
<tr>
<th>Paper</th>
<th>Study and patient characteristics</th>
<th>Donor characteristics</th>
<th>FMT characteristics</th>
<th>Outcomes</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camacho-Ortiz et al, PLoS ONE, 2017</td>
<td>Intervention: FMT (pooled from three donors). Number of patients: 9. Female: male: 3: 4 (data only presented for 7 patients). Age: Mean of 39.7 (+/- 24.8) years. Comparator: Vancomycin (250mg every 6 hours for 10-14 days). Number of patients: 10. Female: Male: 3: 6 (data only presented for 9 patients). Age (mean/median): Mean of 46.7 (+/- 15.8) years. Comorbidities: In FMT arm – x1 abdominal abscess, x1 Child B cirrhotic, x1 pulmonary TB; in vancomycin arm – x2 haemodialysis patients, x1 meningeal TB, x1 ‘abscessed squamous cell carcinoma’.</td>
<td>Donors working in healthcare: Not stated. Donor demographics: &gt;18 years, non-pregnant, BMI 20-25kg/m²</td>
<td>Amount of stool per transplant: 45ml of pooled donor stool (from three donors), at ~0.19g/ml. Diluent used to prepare: 0.9% saline. Diluent used to store if frozen: 15% v/v glycerol. Preparation methods: Stool from donors pooled, mixed, resuspended in saline, filtered to remove particles &gt; 330μm.</td>
<td>Treatment arm: FMT Overall cure rate: 71.4% (n=5/7) (after 2 x FMT) Cure with one infusion alone: 57.1% (n=4/7). Treatment arm: Vancomycin Overall cure rate: 88.9% (n=8/9) (not clear if failed patient received FMT subsequently, as is described in protocol).</td>
<td>Minor GI adverse events: Nil stated. Minor non-GI adverse events: Nil stated. Serious adverse events: Nil stated. Deaths: Nil.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Donor screening: On questionnaire, rejected potential donors who in the past three months had had use of PPI, use of antibiotics, use of immunosuppressives, hospitalisation and/or diarrhoea. Also excluded if high risk sexual behaviour, first degree relative with diabetes mellitus, abdominal surgery, and any GI disease/cancer.</td>
<td>Travel and antibiotic exclusion period: Excluded if antibiotics within the past 3 months. Screening blood tests: Normal full blood count and liver enzymes essential for inclusion. Also screened for HAV, HBV, HCV, HIV, CMV, EBV, <em>Trypanosoma</em>, <em>Brucella</em>, <em>Treponema pallidum</em>.</td>
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<td>Screening stool tests: Included parasites, enteropathogenic bacteria, rotavirus.</td>
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<td>Pre-FMT antibiotics: no antibiotics within FMT arm; patients in vancomycin arm received 250mg</td>
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<td>Number of infusions: routinely 1; patients not resolving after first FMT received 2nd FMT (as did patients not improving with vancomycin). Bowel purgative: Not stated.</td>
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<td>every 6hrs for 10-14 days.</td>
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<tr>
<td>Total follow up period: up to one year.</td>
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<td>Cochrane Collaboration risk of bias assessment: uncertain risk of bias.</td>
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<table>
<thead>
<tr>
<th>PPI: Not stated.</th>
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</thead>
<tbody>
<tr>
<td>Antimotility: Not stated.</td>
</tr>
<tr>
<td>Prokinetics: Not stated.</td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: Nil given.</td>
</tr>
</tbody>
</table>
Cammarota et al, Alimentary Pharmacology and Therapeutics, 2015

<table>
<thead>
<tr>
<th>Intervention: FMT.</th>
<th>Number of patients: 20.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: Male: 12: 8.</td>
<td>Age (mean/median): Mean 71 (range 29-89) years.</td>
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</tbody>
</table>

Comparator: Vancomycin (125mg four times daily for 10 days, followed by a pulse regimen (125-500mg/day every 2-3 days, for at least three weeks). Number of patients: 19. Female: Male: 11: 8. Age (mean/median): Mean 75 (range 49-93) years.

Comorbidities: No significant difference of Charlson comorbidity index between groups.

CDI features: All recurrent. 7/20 in FMT arm with pseudomembranous colitis.

CDI diagnosis confirmation: Diarrhoea and CDT positive within 10 weeks of previous antibiotic treatment.

Pre-FMT antibiotics: All had had vancomycin or metronidazole. 19/20 of FMT arm and 16/20 of vancomycin arm had had previous vancomycin taper.

Total follow up period: 10 weeks.

Donors working in healthcare: no.

Donor demographics: Less than 50 years of age, no antibiotics within past 6 months.

Donor screening: Questionnaire - no antibiotics for last 6/12. Excluded if significant GI disease, metabolic syndrome, chronic illness, immunocompromise, recent travel, high risk lifestyle in last three months.

Time period for storage (frozen): N/A.

Travel and antibiotic exclusion period: 3 month travel exclusion period, 6 month antibiotic exclusion period.

Screening blood tests: Hepatitis A, B, and C, HIV, EBV, syphilis, *Streptococcus*, *Entomoeba histolytica*, FBC, LFTs, creatinine, CRP.

Screening stool tests: *C. difficile* cult and toxin, enteric bacteria, ova, cysts and parasites, VRE, MRSA, Gram negative multi-drug resistant bacteria.

Amount of stool per transplant / administered to patients: Not specified.

Diluent used to prepare: Normal saline 500mls.

Diluent used to store if frozen: N/A – fresh.

Preparation methods: Blended and strained.

Time from preparation to transplant (fresh): 6 hours.

Time period for storage (frozen): N/A.

Route administered: Upper GI; capsule: nil.

Number of infusions: 14 had 1 infusion, 4 had 2 infusions, 1 had 3 infusions and 1 had 4 infusions. Initial protocol was that if non response to first FMT, then second FMT after one week; however, after first two patients, changed to all patients with pseudomembranous colitis receiving repeat FMT every 3 days until resolution of CDI.

Bowel purgative: Macrogol.

PPI: No.

Treatment arm: FMT Overall cure rate: 90% (n=18/20). Cure with one infusion alone: 65% (n=13/20); none of these were patients with pseudomembranous colitis. The 7 patients not cured with first FMT all had pseudomembranous colitis; of these, 5/7 cured with protocol of recurrent FMTs.

Minor GI adverse events: x19 diarrhoea, x12 bloating (all resolved at 12 hours).

Minor non-GI adverse events: None.

Serious adverse events: None.

Deaths: x2 from *C. difficile*-related complications.
Prokinetics: No.  
Time before CDI treatment was stopped before FMT: Between five and two days prior to FMT. |
<table>
<thead>
<tr>
<th>Intervention: Low dose FMT capsules (30 pills once).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 10.</td>
</tr>
<tr>
<td>Female: male: Not stated.</td>
</tr>
<tr>
<td>Age (mean/median): Not stated.</td>
</tr>
<tr>
<td>Comparator: High dose FMT capsules (30 pills daily on two consecutive days).</td>
</tr>
<tr>
<td>Number of patients: 9.</td>
</tr>
<tr>
<td>Female: male: Not stated.</td>
</tr>
<tr>
<td>Age (mean/median): Not stated.</td>
</tr>
<tr>
<td>Comorbidities: Not stated.</td>
</tr>
<tr>
<td>CDI features: Not stated.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Not stated.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Not stated.</td>
</tr>
<tr>
<td>Total follow up period: 8 weeks.</td>
</tr>
<tr>
<td>Cochrane Collaboration risk of bias assessment: uncertain risk of bias.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donors were unrelated donors from universal stool bank (OpenBiome).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donors working in healthcare: No.</td>
</tr>
<tr>
<td>Donor demographics: mean age 26, mean BMI 22.2.</td>
</tr>
<tr>
<td>Donor screening: Questionnaire - as per OpenBiome protocol.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: As per OpenBiome protocol.</td>
</tr>
<tr>
<td>Screening bloods: As per OpenBiome protocol.</td>
</tr>
<tr>
<td>Screening stools: As per OpenBiome protocol.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amount of stool per transplant / administered to patients: 30 pills a day for one day.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent used to prepare: Not stated.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: Stored at -80°C prior to use.</td>
</tr>
<tr>
<td>Preparation methods: Capsules physically stable for 30 days at 25°C using an emulsion-based production protocol.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Not stated.</td>
</tr>
<tr>
<td>Time period for storage (frozen): Not stated.</td>
</tr>
<tr>
<td>Route administered: All capsule – as described above.</td>
</tr>
<tr>
<td>Number of infusions: 30 tablets (over one day).</td>
</tr>
<tr>
<td>Bowel purgative: Not stated.</td>
</tr>
<tr>
<td>PPI: Not stated.</td>
</tr>
<tr>
<td>Antimotility: Not stated.</td>
</tr>
<tr>
<td>Prokinetics: Not stated.</td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: Not stated.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment arm: Low dose FMT capsules (30 pills once).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cure rate: 70% (n=7/10).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment arm: High dose FMT capsules (30 pills daily on two consecutive days).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cure rate: 77.8% (n=7/9).</td>
</tr>
<tr>
<td>Minor GI adverse events: None.</td>
</tr>
<tr>
<td>Minor non-GI adverse events: None.</td>
</tr>
<tr>
<td>Serious adverse events: None.</td>
</tr>
<tr>
<td>Deaths: None.</td>
</tr>
<tr>
<td>Study</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Hota et al, <em>Clinical Infectious Diseases</em>, 2016</td>
</tr>
<tr>
<td></td>
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<tr>
<td>---</td>
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<td></td>
</tr>
</tbody>
</table>
Comparitor: Oral FMT capsules.
Number of patients: 57.
Age (median/standard deviation): 58.7 (+/-18.5) years.
Comparitor: Colonoscopic FMT.
Number of patients: 59.
Female: male: 36: 13.
Age (median/standard deviation): 57.4 (+/-19.1) years.
CDE features: All recurrent.
CDE diagnosis: Recurrence of diarrhea (>3 unformed bowel movements every 24 hours) within 8 weeks of completing a prior course of treatment, with either a positive C. difficile toxin by glutamate dehydrogenase and C difficile toxins A/B (C diff QuikChek Complete; Techlab) or by detection of glutamate dehydrogenase and C difficile cytoxin B gene (Cepheid), plus resolution of diarrhea for the current episode.
Pre-FMT antibiotics: Oral vancomycin (125mg twice daily) up to 24hrs before FMT.
Total follow-up period: 12 weeks.

Donors were unrelated volunteers.
Working in healthcare: Not stated.
Donor demographics: Not stated.
Travel and antibiotic exclusion period: As per Kelly et al, Gastroenterology, 2015.
Screening blood tests: As per Kelly et al, Gastroenterology, 2015.
Screening stool tests: As per Kelly et al, Gastroenterology, 2015.

Amount of stool per transplant / administered to patients: 80-100g.
Diluent used to prepare: Normal saline.
Diluent used to store if frozen: 100% glycerol.
Preparation methods: Mix stool with 200ml of normal saline, and filtered using a Stomacher to homogenise 180ml of faecal slurry.
Time from preparation to transplant (fresh): up to 2 months frozen, collected fresh within 12 hours.
Time period for storage (frozen): up to 2 months.
Route administered: lower GI: 59 (colonoscopy); capsule: 57.
Number of infusions: x1 of colonoscopy, or x40 capsules as one-off.
Bowel purgative: PEG on the night before.
PPI: No.
Antimotility: Not stated.
Prokinetics: Not stated.

Treatment arm: Oral FMT capsules: 96.2% (n=51/53) absence of CDE at 12 weeks.
Cure with one treatment alone: 96.2% (n=51/53).
Treatment arm: FMT via colonoscopy: 96.2% (n=50/52).
Cure with one infusion alone: 96.2% (n=50/52).

Minor GI adverse events: Capsule group: x3 nausea, x2 vomiting, x1 abdominal pain. Colonoscopy group: x1 nausea, x1 vomiting, x1 fever, x5 abdominal pain.

Minor non-GI adverse events: 1 developed confusion in the colonoscopy group between time of screening and delivery of FMT. This was not communicated to team, and despite an uneventful FMT she died three days later from heart failure.

Deaths: x1 in each group from cardiopulmonary disease (see above for colonoscopy). The other patient developed Staphylococcus epidermis bacteraemia 10 weeks after capsule.
Time before CDI treatment was stopped before FMT: 24 hours.
treatment and died from sepsis.
<table>
<thead>
<tr>
<th>Donors working in healthcare:</th>
<th>Not stated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor demographics:</td>
<td>Not stated.</td>
</tr>
<tr>
<td>Donor screening: Questionnaire - potential donors also completed a modified AABB full-length donor history questionnaire, and those with risk factors for infectious agents were excluded.</td>
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</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded as donor if antibiotics within preceeding 90 days.</td>
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</tr>
<tr>
<td>Screening bloods: Testing for HIV-1 and HIV-2 was performed within 2 weeks before donation for FMT. Other serologic testing was performed within 1 month before FMT and included testing for hepatitis A, B, and C viruses; also, testing for Treponema pallidum.</td>
<td></td>
</tr>
<tr>
<td>Screening stool tests: polymerase chain reaction (PCR) testing for detection of C difficile toxin; culture for enteric pathogens (Escherichia coli, Salmonella, Shigella, Yersinia, Campylobacter, Listeria monocytogenes, Vibrio parahaemolyticus, and V cholerae); testing for fecal Giardia and Cryptosporidium antigens; acid-fast stain for detection of Cyclospora and</td>
<td></td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: Mean stool dose of 64 g (standard deviation of 25 g; range, 20 to 100g).</td>
<td></td>
</tr>
<tr>
<td>Diluent used to prepare: 100g of stool in 500mls of normal saline.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to store if frozen: N/A.</td>
<td></td>
</tr>
<tr>
<td>Preparation methods: Not reported.</td>
<td></td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): 6 hours.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A.</td>
<td></td>
</tr>
<tr>
<td>Route administered: Upper GI: nil; lower GI: all patients in both groups (colonoscopy); capsule: nil.</td>
<td></td>
</tr>
<tr>
<td>Number of infusions: 1 infusion only.</td>
<td></td>
</tr>
<tr>
<td>Bowel purgative: polyethylene glycol (PEG).</td>
<td></td>
</tr>
<tr>
<td>PPI: No.</td>
<td></td>
</tr>
<tr>
<td>Antimotility: Not described.</td>
<td></td>
</tr>
<tr>
<td>Prokinetics: No.</td>
<td></td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: continued</td>
<td></td>
</tr>
</tbody>
</table>

<p>| Minor GI adverse events: |
| Low rates of abdominal pain, bloating, nausea, vomiting, diarrhea, flatulence, anorexia, and constipation; these did not differ significantly between groups. |
| Minor non-GI adverse events: |
| None described. |
| Serious adverse events: |
| None described. |
| Deaths: |
| None. |
|   |   | <em>Isospora</em>; ova and parasite testing; and enzyme immunoassay for detection of Rotavirus. | therapy until 2 to 3 days before the procedure. |   |   |
| Intervention: Frozen FMT. Number of patients: 108. Female: male: 72: 36. Age (mean/ standard deviation): Mean age 73.0 (+/16.4) years. Comparator: Fresh FMT. Number of patients: 111. Female: Male: 74: 37. Age (mean/ standard deviation): Mean age 72.5 (+/16.2) years. Comorbidities: Not described. CDI features: All recurrent disease. CDI diagnosis confirmation: Toxin and PCR. Pre-FMT antibiotics: All had prior metronidazole, vancomycin, or both in combination. Almost all patients had prior vancomycin taper. Total follow up period: 13 weeks. Cochrane Collaboration risk of bias assessment: low risk of bias. Donors were unrelated volunteers. Donors working in healthcare: Not specifically described. Donor demographics: Not defined. Donor screening: questionnaire – comparable to blood donor screening questionnaire. Travel and antibiotic exclusion period: Excluded as donor if travel (within the last 6 months) to areas of the world where diarrheal illnesses are endemic or risk of traveler’s diarrhea is high; also excluded if antibiotics within the preceeding 3 months. Screening blood tests: HIV-1 and -2, hepatitis A IgM, HBsAg, anti-HBc (both IgG and IgM), and anti-HBs, hepatitis C antibody, RPR and FTA-ABS. Screening stool tests: <em>Clostridium difficile</em> toxin B by PCR; if unavailable, then evaluation for toxins A and B by EIA; routine bacterial culture for enteric pathogens; faecal <em>Giardia</em> antigen; faecal <em>Cryptosporidium</em> antigen; Acid-fast stain for <em>Cyclospora</em>, Amount of stool per transplant / administered to patients: 100g of stool. Diluent used to prepare: 300mls of water. Diluent used to store if frozen: no solvents used for storage. Preparation methods: 100g of stool homogensied and mixed in 300mls of water. Time from preparation to transplant (fresh): If fresh, administered within 24hrs. Time period for storage (frozen): If frozen, kept for 30 days at -20°C. Route administered: Upper GI: capsule; bowel purgative: PPI. Number of infusions in frozen arm: 57 patients had 1 infusion; 24 patients had 2 infusions; rest had &gt;2 infusions; in fresh arm: 56 patients had 1 infusion; 22 patients had 2 infusion; rest had &gt;2 infusions. Bowel purgative: Not described. PPI: Nil. Treatment arm: Frozen: Overall cure rate: 90.7% (n=98/109). Cure with one infusion alone: 52.8% (n=57/108). Treatment arm: Fresh: Overall cure rate: 85.6% (n=95/111). Cure with one infusion alone: 50.5% (n=56/111). Minor GI adverse events: Transient diarrhoea (70%), abdominal cramps (10%), nausea (5%) in 24 hours post-FMT; constipation (20%) and flatulence (25%) in follow-up period. No difference between the two groups. Minor non-GI adverse events: None described. Serious adverse events: x12 patients required hospitalization because of illnesses unrelated to FMT. Deaths: x6 deaths in frozen and x13 deaths in fresh arm (all unrelated to FMT). |</p>
<table>
<thead>
<tr>
<th>Isospora and, if antigen testing unavailable, Cryptosporidium; ova, cysts and parasites.</th>
<th>Antimotility: Not described. Prokinetics: Not described. Time before CDI treatment was stopped before FMT: Discontinued 24 - 48 hours prior to FMT.</th>
<th></th>
</tr>
</thead>
</table>
van Nood et al, New England Journal of Medicine, 2013

Intervention: FMT + bowel lavage.
Number of patients: 16.
Female: male: 8: 8.
Age (mean/ standard deviation): 73 (+/- 13) years.

Comparator: Vancomycin (500mg orally four times daily for 14 days).
Number of patients: 13.
Age (mean/ standard deviation): 66 (+/-14) years.

Comorbidities: No significant difference in median Charlson comorbidity index between groups.
CDI features: All recurrent.
CDI diagnosis confirmation: Toxin and PCR.
Pre-FMT antibiotics: At least one course of adequate antibiotic therapy (≥10 days of vancomycin at a dose of ≥125mg four times a day or ≥10 days of metronidazole.

Donors were healthy volunteers.
Donors working in healthcare: No.
Donor demographics: <60 years of age.
Donor screening: questionnaire: questionnaire addressed risk factors for potentially transmissible diseases.
Travel and antibiotic exclusion period: Excluded as donor if travel to tropical area within past 3 months, or antibiotic use within the past two months.
Screening blood tests: Blood was screened for HIV; human T-cell lymphotropic virus types 1 and 2; hepatitis A, B, and C; cytomegalovirus; Epstein-Barr virus; Treponema pallidum; Strongyloides stercoralis; and Entamoeba histolytica.
Screening stool tests: Donor feces were screened for parasites, including Blastocystis hominis and Dientamoeba fragilis; C

Amount of stool per transplant / administered to patients: A mean (+/-standard deviation) of 141+/71g of faeces was infused.
Diluent used to prepare: Faeces were diluted with 500mls of sterile saline, 0.9%.
Diluent used to store if frozen: N/A.

Preparation methods: The solution was stirred, and the supernatant strained and poured in a sterile bottle.
Time from preparation to transplant (fresh): Mean time from defecation to infusion was 3.1+/1.9 hours.
Time period for storage (frozen): N/A.
Route administered: Upper GI: 16 (via nasoduodenal tube); lower GI: nil; capsule: nil.
Number of infusions: 16 patients had 1 infusion; 3 who did not respond in this group had 2nd infusion.
Bowel purgative: 4 litres of macrogol solution (Klean-Prep) on the last day of antibiotic treatment.
PPI: Not stated.

Treatment arm: FMT + bowel lavage
Overall cure rate: 94% (n=15/16).
Cure with one infusion alone: 81% (n=13/16).

Treatment arm: Vancomycin
Overall cure rate: 315 (n=4/13) patients at 10 weeks.

Minor GI adverse events: 94% immediate diarrhoea, 31% abdominal pain with cramping, 19% belching - resolved within 3 hours. During follow-up, x3 patients had constipation (19%).
Minor non-GI adverse events: Nil.

Serious adverse events: Nil described.
Deaths: None.
<p>| at a dose of 500mg three times per day). |
| Total follow up period: After first infusion at 10 weeks; follow-up was extended to 10 weeks after the second infusion. |
| Cochrane Collaboration risk of bias assessment: low risk of bias. |
| <strong>difficile</strong>, and enteropathogenic bacteria. |
| Antimotility: Not stated. |
| Prokinetics: Not stated. |
| Time before CDI treatment was stopped before FMT: 24 hours. |</p>
<table>
<thead>
<tr>
<th>Youngster et al, <em>Clinical infectious diseases</em>, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donors were healthy volunteer non-pregnant adults. Donors working in healthcare: No. Donor demographics: 18-50 years of age, on no medications, with a normal body mass index. Donor screening: questionnaire - initial screening using the American Association of Blood Banks donor questionnaire for exposure to infectious agents. Travel and antibiotic exclusion period: Excluded if antibiotic use within 6 months. Screening blood tests: Blood was screened for antibodies to hepatitis A, B, and C; HIV; and <em>Treponema pallidum</em> within 2 weeks of donations. Screening stool tests: Donor faeces were screened for enteric bacterial pathogens including rotavirus, <em>Listeria monocytogenes</em>, <em>Vibrio</em></td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: 90mls of thawed FMT (41g). Diluent used to prepare: Normal saline. Diluent used to store if frozen: 10% glycerol. Preparation methods: Homogenised using a commercial blender then passed through sieves. Time from preparation to transplant (fresh): N/A. Time period for storage (frozen): Inocula were stored frozen for up to 156 days, range, 29-156 days. Route administered: Upper GI (nasogastric) 10; lower GI (colonoscopy): 10; capsule: nil. Number of infusions: Colonoscopy: 8 patients - 1 infusion, 2 patients – 2 infusions; NG: 7 patients - 1 infusion; 3 patients – 2 infusions. Bowel purgative: For colonic route - 4 liters of PEG solution. PPI: 20mg of omeprazole orally for 48 hours prior to FMT.</td>
</tr>
<tr>
<td>Treatment arm: Colonoscopy: Overall cure rate: 100% (n=10/10). Cure with one infusion alone: 80% (n=8/10). Treatment arm: Nasogastric: Overall cure rate: 80% (n=8/10). Cure with one infusion alone: 60% (n=6/10).</td>
</tr>
<tr>
<td>Minor GI adverse events: Mild abdominal discomfort and bloating in x4 patients (20%). X1 child treated colonoscopically had a transient fever of 38.8°C on day 2 that resolved spontaneously. Minor non-GI adverse events: Nil described. Serious adverse events: x1 new diagnosis of malignancy, x1 hospitalisation for Fournier gangrene (unrelated to FMT). Deaths: x2 deaths (unrelated to FMT).</td>
</tr>
<tr>
<td>Cochrane Collaboration risk of bias assessment: uncertain risk of bias.</td>
</tr>
</tbody>
</table>
C.3. Reviewed randomised studies of FMT for non-CDI indications
<table>
<thead>
<tr>
<th>Paper</th>
<th>Study and patient characteristics</th>
<th>Donor characteristics</th>
<th>FMT characteristics</th>
<th>Outcomes</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moayyedi et al, <em>Gastroenterology</em>, 2015</td>
<td>Intervention: FMT. Number of patients: 38. Female: male 20: 18. Age (mean +/-range)<em>: 42.2+/-15.0 years. Comparator: Water enema. Number of patients: 37. Female: male: 11: 26. Age (mean +/-range)</em>: 35.8+/-12.1 years. Primary outcome: Remission at week 7, defined as full Mayo score &lt; 3 and complete healing of mucosa at flexible sigmoidoscopy (endoscopic Mayo score: 0). Secondary outcome: Clinical response (at least 3 point reduction in Mayo score), change in Mayo, IBDQ Questionnaire scores, EQ-5D scores. Inclusion criteria: &gt;18 years with UC - Mayo at least 4 with endoscopic subscore at least 1 (included patients with severe disease). Exclusions - antibiotics/ probiotics in past 30 days, concomitant <em>C difficile</em>/ other enteric pathogens, disease severity requiring hospitalisation, pregnancy, unable to take stool or enema. Donors were unrelated volunteers - six donors used. Plus - one patient in active treatment arm had spouse as donor (treatment failure). Working in healthcare: Not specifically stated. Donor demographics: 18-60 years. Donor screening: Questionnaire – yes. Travel and antibiotic exclusion period: Retesting of stool whenever donor travelled outside North America. Excluded as donor if antibiotics within past 3 months. Screening repeated regardless every 6 months. Screening blood tests: HIV, hepatitis A lgM, HBsAg, hepatitis C antibody, syphilis, HTLV-1/-2. Screening stool tests: MC&amp;S, ova, cysts and parasites, <em>C difficile</em> toxin, VRE, MRSA. Amount of stool per transplant / administered to patients: 8.3g of stool per enema. Diluent used to prepare: 50g of stool mixed with 300ml of commercial bottled drinking water, then 50ml of mixture administered as enema. Diluent used to store if frozen: No glycerol. FMT administered either fresh, or stored at -20 degrees. 21 received frozen, 15 received fresh, 1 mixture of fresh and frozen. Preparation methods: Not anaerobic. Single donor per FMT. Time from preparation to transplant (fresh): Processing within 5hr of collection. Time period for storage (frozen): Not stated.</td>
<td>Remission rates: 24% (n=9/38). Clinical response rates: 40% (n=15/38) had reduction in full Mayo score of at least 3 points. Quality of Life Assessment: Yes - IBDQ and EQ-5D not significantly different between groups.</td>
<td>FMT arm: Minor GI adverse events: Two patients developed patchy inflam in the colon and also rectal abscess formation - resolved with antibiotics. Minor non-GI adverse events: None. Water enema arm: Remission rates: 5% (n=2/37) (p=0.03) Clinical response rates: 24% (n=9/37) had reduction in full Mayo score of at least 3 points (p=0.16). Water enema arm: Minor GI adverse events: x1 patient developed patchy inflammation in the colon and also rectal abscess formation - resolved with antibiotics. Minor non-GI adverse events: None.</td>
<td>Minor GI adverse events: x1 patient changed diagnosis from UC to Crohn's colitis; x1 serious adverse events: None.</td>
<td></td>
</tr>
</tbody>
</table>
to give informed consent.

Concomitant medications: Stable dose thiopurines, mesalamine, corticosteroids, and anti-TNF allowed as long as stable dose for at least 12 weeks (4 weeks for steroids).

Total follow-up period: Up to 12 months.

Cochrane Collaboration risk of bias assessment: low risk of bias.

Prokinetics: Not described.

Admitted with hospital with active severe colitis and required colectomy.

Deaths: None.
<table>
<thead>
<tr>
<th>Rossen et al, Gastroenterology, 2015</th>
</tr>
</thead>
</table>
| **Intervention:** Donor faeces. Number of patients: 23. Female: male: 12: 11. Age (median, range): 40 (33-56) years. Comparator: Autologous faeces. Number of patients: 25. Female: male: 14:11. Age (median, range): 41 (30 – 48) years. **Primary outcome:** Clinical remission (defined as a SCCAI score ≤2) in combination with 1-point improvement on the combined Mayo endoscopic score of the sigmoid and rectum, as compared with baseline sigmoidoscopy, 12 weeks after the first treatment. Secondary outcome: Endpoints at 6 and 12 weeks were clinical response (defined as a reduction of 1.5 points on the Simple Clinical Colitis Activity Index (SCCAI), a validated disease activity index tool in ulcerative colitis), clinical remission (defined as a SCCAI of ≤2), endoscopic response, change in median [Inflammatory Bowel Disease Questionnaire (IBDQ)] score from baseline to shortly after treatment (week 6), and adverse events. Inclusion criteria: enteric infection, use of biologics within 8 weeks or **Donors were healthy partners, relatives, or volunteers.** Working in healthcare: Not stated Donor demographics: ≥18 yrs Donor screening: Questionnaire - Dutch Red Cross Questionnaire addressing risk factors for potential transmissible diseases used for screening of blood donors in The Netherlands. Travel and antibiotic exclusion period: Excluded as donor if antibiotics within 8 weeks. Screening blood tests: CMV (IgG + IgM), EBV (IgG + IgM), hepatitis A (total antibody), hepatitis B (HBsAg), hepatitis C (hepatitis C virus antibody), HIV (1+2 antibodies/antigen), HTLV (I + II antibody), Entamoeba (antibodies against Entamoeba histolytica), Strongyloides (Strongyloides ELISA). Screening stools: Multiplex PCR containing probes against enteral viruses (rotavirus, norovirus, enterovirus pareochovirus, sapovirus, adenovirus 40/41/S2, astrovirus), FT + TFT II: PCR op Giardia, SSYC, Clostridium toxin | Amount of stool per transplant / administered to patients: 120g Diluent used to prepare: Normal saline Diluent used to store if frozen: not stated Preparation methods: Not anaerobic Time from preparation to transplant (fresh): not stated Time period for storage (frozen): not stated Route administered and frequency: Upper GI: Nasoduodenal route. 2 infusions three weeks apart. Nil lower GI or capsule Bowel purgative: Macrogol before both infusions PPI: Not described Antimotility: Not described Prokinetics: Not described | Donor faeces arm: Remission rates: 30% (n=7/23) Clinical response rates: 47.8% (n=11/23) at 12 weeks. **Quality of Life Assessment:** IBDQ only calculated based on responders vs nonresponders. Autologous faeces arm: Remission rates: 20% (n=5/23), (p=0.51). Clinical response rates: 52% (n=13/25) at 12 weeks. Minor GI adverse events: 78.3% (n=18/23) of donor stool and 64% (n=16/25) of autologous stool experienced side effects post FMT: transient borborygms, diarrhoea, vomiting, fever. Minor non-GI adverse events: None. Serious adverse events: x4 overall (small bowel perforation – secondary to Crohn’s), CMV infection, abdominal pain, cervical carcinoma. Deaths: Nil.
methotrexate within 4 weeks

Concomitant medications: stable doses of thiopurines, mesalamine, or corticosteroids 10 mg/day for the 8 weeks before inclusion.

Total follow-up period: 12 weeks.

Cochrane Collaboration risk of bias assessment: low risk of bias.
Intervention: FMT. 
Number of patients: 41. Female: male 19: 22. Age (median, (range)): 35.6 (27.8-48.9) years.

Comparator: Placebo-isotonic saline with added colourant odourant and glycerol cryoprotectant (concentration 10%).
Number of patients: 40. Female: male: 15: 25. Age (median, (range)): 35.4 (27.7-45.6) years.

Primary outcome: Composite of steroid-free clinical remission and endoscopic remission or response at week 8, defined as a total Mayo score of 2 or less, with all Mayo subscores of 1 or less, and at least a 1 point reduction from baseline in the endoscopy subscore.

Secondary outcomes were: steroid-free clinical remission (defined as combined Mayo subscores of 1 or less for rectal bleeding plus stool frequency); steroid-free clinical response (defined as either a decrease of 3 points or more on the Mayo score, a 50% or greater reduction from baseline in combined rectal bleeding plus stool frequency Mayo subscores, or both); steroid-free endoscopic remission or response (defined as either a 1 point reduction from baseline in endoscopy subscore).

Donors were between 3-7 unrelated donors.
Working in healthcare: No.
Donor demographics: Not described.
Donor screening: Questionnaire asked regarding:
- Known HIV, hepatitis B or hepatitis C infection
- Known exposure to HIV or viral hepatitis within the previous 12 months
- High risk sexual behavior (e.g. sexual contact with anyone with HIV/AIDS or viral hepatitis, men who have sex with men, sex for drugs or money)
- Use of illicit drugs
- Tattoo or body piercing within the preceding 6 months
- Incarceration or history of incarceration
- Known current communicable disease (e.g. upper respiratory tract infection)
- Risk factors for variant Creutzfeldt-Jakob disease
- Travel within last 2 weeks to areas of the world where diarrhoeal illnesses are endemic or risk of traveler’s diarrhea is high
- History of or current inflammatory bowel disease (IBD)
- History of or current irritable bowel disease
- History of or current infectious enterocolitis

Amount of stool per transplant / administered to patients: 37.5g of blended stool to isotonic saline; volume of each infusion was 150mL.

Diluent used to prepare: isotonic saline with 10% glycerol cryoprotectant.
Diluent used to store if frozen: -80°C with glycerol cryoprotectant (concentration 10%).

Preparation methods: Donors had to provide faeces within 4 hours of a bowel movement, which was inspected visually for suitability (formed stool, no blood or mucus). Donor stool homogenised for a given batch on each day in a biosafety cabinet in isotonic saline then filtered. Placebo infusions comprised isotonic saline; brown food colourant, odourant, and glycerol cryoprotectant (concentration 10%) was added to all study infusions (investigational and placebo). The volume of each infusion was 150 mL. Infusions were stored at −80°C until dispensed to patients at fortnightly study visits for home freezer storage at −20°C before daily administration.

Time from preparation to transplant (fresh): Not described.

Primary outcome: Composite of steroid-free clinical remission and endoscopic remission or response at week 8, defined as a total Mayo score of 2 or less, with all Mayo subscores of 1 or less, and at least a 1 point reduction from baseline in the endoscopy subscore.

Secondary outcome: Secondary outcomes were: steroid-free clinical remission (defined as combined Mayo subscores of 1 or less for rectal bleeding plus stool frequency); steroid-free clinical response (defined as either a decrease of 3 points or more on the Mayo score, a 50% or greater reduction from baseline in combined rectal bleeding plus stool frequency Mayo subscores, or both); steroid-free endoscopic remission or response (defined as either a 1 point reduction from baseline in endoscopy subscore).

Donors were between 3-7 unrelated donors.
Working in healthcare: No.
Donor demographics: Not described.
Donor screening: Questionnaire asked regarding:
- Known HIV, hepatitis B or hepatitis C infection
- Known exposure to HIV or viral hepatitis within the previous 12 months
- High risk sexual behavior (e.g. sexual contact with anyone with HIV/AIDS or viral hepatitis, men who have sex with men, sex for drugs or money)
- Use of illicit drugs
- Tattoo or body piercing within the preceding 6 months
- Incarceration or history of incarceration
- Known current communicable disease (e.g. upper respiratory tract infection)
- Risk factors for variant Creutzfeldt-Jakob disease
- Travel within last 2 weeks to areas of the world where diarrhoeal illnesses are endemic or risk of traveler’s diarrhea is high
- History of or current inflammatory bowel disease (IBD)
- History of or current irritable bowel disease
- History of or current infectious enterocolitis

Amount of stool per transplant / administered to patients: 37.5g of blended stool to isotonic saline; volume of each infusion was 150mL.

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Preparation methods: Donors had to provide faeces within 4 hours of a bowel movement, which was inspected visually for suitability (formed stool, no blood or mucus). Donor stool homogenised for a given batch on each day in a biosafety cabinet in isotonic saline then filtered. Placebo infusions comprised isotonic saline; brown food colourant, odourant, and glycerol cryoprotectant (concentration 10%) was added to all study infusions (investigational and placebo). The volume of each infusion was 150 mL. Infusions were stored at −80°C until dispensed to patients at fortnightly study visits for home freezer storage at −20°C before daily administration.

Time from preparation to transplant (fresh): Not described.
response (defined as a Mayo endoscopy subscore of 1 or less, with a reduction of at least 1 point from baseline); steroid-free endoscopic remission (defined as a Mayo endoscopy subscore of 0); quality of life (assessed with the IBDQ); and safety (assessed by adverse events).

Inclusion criteria:
1. 18-75 years;
2. UC for >3 months;
3. UC of any extent except isolated proctitis <5cm;
4. currently active mild-moderate UC as measured by a Mayo score of 4-10, endoscopy score must be greater or equal to 1 and a physician global assessment score of less than or equal to 2;
5. Written consent.

Concomitant medications:
Drugs permitted as long as the dose was stable preceding enrolment: oral 5-aminosalicylates (stable dose for 4 weeks); thiopurines and methotrexate (on medication for ≥90 days and dose stable for 4 weeks); and oral prednisolone (dose ≤20mg daily and stable for 2 weeks). During the study, patients remained on the same dose of 5-aminosalicylate, thiopurine, and methotrexate. For oral prednisolone, patients received a mandatory taper of up to 2.5 mg per week so that patients would be steroid-free by week 8.

bowel syndrome (IBS), chronic constipation, chronic diarrhea or other intrinsic gastrointestinal illness / condition
- History of or current gastrointestinal malignancy or known polyposis or strong family history of colorectal cancer
- History of major gastrointestinal surgery (e.g. gastric bypass, partial colectomy)
- Antimicrobials (antibiotics, antivirals, antifungals), probiotics or proton pump inhibitors (PPIs) within the preceding 3 months
- Major immunosuppressive medications (e.g. calcineurin inhibitors, biological agents, exogenous glucocorticoids)
- Systemic anti-neoplastic agents
- Household members with active GI infection Systemic autoimmunity (e.g. multiple sclerosis, connective tissue disease)
- Atopic disease (e.g. moderate -severe asthma, eosinophilic disorders of the gastrointestinal tract)
- Metabolic syndrome, obesity (BMI >30) or moderate to severe undernutrition / malnutrition
- Chronic pain syndromes (e.g. chronic fatigue syndrome, fibromyalgia) or neurologic / neurodevelopmental disorders
- History of malignant illness or ongoing oncologic therapy

Time period for storage (frozen): Not described.
Route administered and frequency:
Upper GI: 0; lower GI: 5 enemas per week following colonoscopic delivery - 5 days on, two days off for 8 weeks (40 enemas per patient); capsule: 0.
Bowel purgative: Yes, but no details
PPI: Not described
Antimotility: Not described
Prokinetics: Not described

Minor non-GI adverse events: None.
Serious adverse events: x1 (3%) - admitted to hospital (no details why).
Deaths: Nil.
Cochrane Collaboration risk of bias assessment: low risk of bias.

Travel and antibiotic exclusion period: Excluded if travel within last 2 weeks to areas where diarrheal illnesses are endemic or risk of travelers diarrhea is high.

Screening blood tests: Complete blood count, electrolytes, urea and creatinine, LFTS, ESR, CRP, HIV-1 and -2, hepatitis A IgM, hepatitis B SAg, hepatitis B core antibody (IgM and IgG) and surface antibody, hepatitis C antibody, rapid plasma reagin and/or fluorescent treponemal antibody-absorbed, HTLV-1 and HTLV-2.

Screening stools: *C difficile* PCR, faecal MC&S with routine bacterial culture for enteric pathogens, *Giardia* antigen, *Cryptosporidium* antigen, faecal ova/cysts/parasites including *Blastocystis hominis* and *Dientamoeba fragilis*, and Norovirus.
| Intervention: Donor FMT.  
Number of patients: 38.  
Female: male: Not stated.  
Age (mean/median): Not stated. | Donor FMT arm:  
Remission rates: 32% ($n=12/38$) in steroid-free remission at week 8.  
Clinical response rates: 55% ($n=21/38$).  
Quality of Life Assessment: Not described. | Costello et al, *Journal of Crohn's and Colitis* (abstract), 2017 |
| Comparator: Control - autologous FMT in saline.  
Number of patients: 35.  
Female: male: Not stated.  
Age (mean/median): Not stated. | Donor FMT arm:  
Minor GI adverse events: Nil.  
Minor non-GI adverse events: Nil.  
Serious adverse events: Worsening colitis in x2 patients.  
Deaths: Nil. |
| Primary outcome: Steroid-free remission of UC, as defined by total Mayo of 2 or less with an endoscopic Mayo score of 1 or less at week 8.  
Secondary outcome: Clinical response (at least 3 point reduction in Mayo score), clinical remission (i.e. SCCAI of 2 or less), endoscopic remission (Mayo 1 or less), and safety. | Control - autologous FMT in saline arm.  
Minor GI adverse events: Nil.  
Minor non-GI adverse events: None.  
Serious adverse events: Worsening colitis in x2 placebo patients. x1 patient requiring colectomy, x1 pneumonia.  
Deaths: Nil. |
| Inclusion criteria: UC - Mayo 3-10 with endoscopic subscore at least 2.  
Concomitant medications: Stable dose of immunomodulator, 5-ASA, biological, tapering prednisolone.  
Cochrane Collaboration risk of bias assessment: uncertain risk of bias. | Donor FMT arm:  
Remission rates: 9% ($n=3/35$) in steroid-free remission at week 8 ($p<0.01$).  
Clinical response rates: 20% ($n=7/35$) ($p<0.01$).  
Quality of Life Assessment: Not described. |
| Donors were healthy volunteers.  
Working in healthcare: Not clear.  
Donor demographics: Not described.  
Donor screening: Questionnaire – yes but no details described.  
Screening blood tests: Yes but not described.  
Screening stool tests: Yes but not described. | Donors were healthy volunteers.  
Working in healthcare: Not clear.  
Donor demographics: Not described.  
Donor screening: Questionnaire – yes but no details described.  
Screening blood tests: Yes but not described.  
Screening stool tests: Yes but not described. |
| Amount of stool per transplant / administered to patients: 50g of stool for first FMT, 25g of stool in subsequent enemas.  
Diluent used to prepare: 65% saline.  
Diluent used to store if frozen: Yes - frozen with 10% glycerol.  
Preparation methods: Anaerobic prep, donor stool pooled from 3-4 donors.  
Time from preparation to transplant (fresh): N/A.  
Time period for storage (frozen): Not stated.  
Route administered and frequency: Upper GI: nil; lower GI: FMT via colonoscopy on day 0, followed by 2 enemas on day 7 (38); capsule: nil  
Bowel purgative: PEG before colonoscopy but not enema  
PPI: Not described  
Antimotility: Not described  
Prokinetics: Not described | Donors were healthy volunteers.  
Working in healthcare: Not clear.  
Donor demographics: Not described.  
Donor screening: Questionnaire – yes but no details described.  
Screening blood tests: Yes but not described.  
Screening stool tests: Yes but not described. |
| Minor GI adverse events: Nil.  
Minor non-GI adverse events: Nil.  
Serious adverse events: Worsening colitis in x2 patients.  
Deaths: Nil. | Minor GI adverse events: Nil.  
Minor non-GI adverse events: None.  
Serious adverse events: Worsening colitis in x2 placebo patients. x1 patient requiring colectomy, x1 pneumonia.  
Deaths: Nil. |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Intervention:</strong> Donor FMT.</td>
</tr>
<tr>
<td>Number of patients: 55.</td>
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<tr>
<td>Female: male: 36: 19.</td>
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<tr>
<td>Age (median, range): 44 (33-54) years.</td>
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<tr>
<td><strong>Comparator:</strong> Control - autologous FMT.</td>
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<tr>
<td>Number of patients: 28.</td>
</tr>
<tr>
<td>Age (median, range): 45 (34-57) years.</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> 18-75 yrs of age, IBS with diarrhoea or mixed IBS according to Rome III criteria.</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> participants with severe cardiac disease, pulmonary disease, or kidney failure, non-IBS type abdominal pain, immunodeficiency or on immunomodulating agents.</td>
</tr>
<tr>
<td><strong>Cochrane Collaboration risk of bias assessment:</strong> low risk of bias</td>
</tr>
<tr>
<td>Donors were two volunteers screened at start and at 7 months post donation.</td>
</tr>
<tr>
<td><strong>Working in healthcare:</strong> Not stated.</td>
</tr>
<tr>
<td><strong>Donor demographics:</strong> Not described.</td>
</tr>
<tr>
<td><strong>Donor screening:</strong> Questionnaire - new tattoos or piercings in the past 3 months; high-risk sexual behaviour; former imprisonment; or history of any of the following conditions: chronic diarrhoea, constipation, inflammatory bowel disease, IBS, colorectal polyps or cancer, immunosuppression, obesity, metabolic syndrome, atopic skin disease, or chronic fatigue.</td>
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<tr>
<td><strong>Travel and antibiotic exclusion period:</strong> Excluded if antibiotics within past three months.</td>
</tr>
<tr>
<td><strong>Screening blood tests:</strong> Glycated haemoglobin; and serology for HIV, <em>Treponema pallidum</em>, and hepatitis A, B, and C.</td>
</tr>
<tr>
<td><strong>Screening stool tests:</strong> <em>Salmonella</em> spp, <em>Shigella</em> spp, <em>Campylobacter</em> spp, <em>Yersinia</em> spp, and toxin-producing <em>C difficile</em>; faecal tests for <em>Helicobacter pylori</em> antigen.</td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: 50 to 80g of stool in 50mls.</td>
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<tr>
<td><strong>Diluent used to prepare:</strong> 200ml isotonic saline and 50mls of 85% glycerol.</td>
</tr>
<tr>
<td><strong>Diluent used to store if frozen:</strong> glycerol, only for autologous transplants.</td>
</tr>
<tr>
<td><strong>Preparation methods:</strong> Aerobic, stool from both donors was mixed together.</td>
</tr>
<tr>
<td><strong>Time from preparation to transplant (fresh):</strong> 7 hours.</td>
</tr>
<tr>
<td><strong>Time period for storage (frozen):</strong> 2-4 weeks.</td>
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<tr>
<td><strong>Route administered and frequency:</strong> upper GI: none; lower GI: single infusion of FMT via colonscopy; nil capsule.</td>
</tr>
<tr>
<td><strong>Bowel purgative:</strong> Picoprep.</td>
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<tr>
<td><strong>PPI:</strong> Not described.</td>
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<tr>
<td>Donor FMT arm: Remission rates: 66% (n=36/55) .</td>
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<tr>
<td>Quality of Life Assessment: Not described.</td>
</tr>
<tr>
<td>Autologous FMT arm: Remission rates: 43% (n=12/28) (p=0.49).</td>
</tr>
<tr>
<td>Quality of Life Assessment: Not described.</td>
</tr>
<tr>
<td><strong>Minor GI adverse events:</strong> Tile limiting intermittent abdominal pain x1, self limiting nausea and vertigo x1.</td>
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<tr>
<td><strong>Minor non-GI adverse events:</strong> Nil.</td>
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<tr>
<td><strong>Serious adverse events:</strong> Nil.</td>
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<tr>
<td><strong>Deaths:</strong> Nil.</td>
</tr>
<tr>
<td><strong>Placebo arm:</strong> Minor GI adverse events: self limiting intermittent abdominal pain x2.</td>
</tr>
<tr>
<td><strong>Minor non-GI adverse events:</strong> Nil.</td>
</tr>
<tr>
<td><strong>Serious adverse events:</strong> Nil.</td>
</tr>
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<td><strong>Deaths:</strong> Nil.</td>
</tr>
</tbody>
</table>
viruses (norovirus, rotavirus, Sapovirus, adenovirus), and faecal calprotectin.
**Intervention:** Donor FMT.
Number of patients: 10.
Female: male: 0: 10.
Age (mean+/standard deviation): 64.5 +/- 5.1 years.

**Comparator:** Standard of care (lactulose/ rifaximin).
Number of patients: 10.
Female: male: 0: 10.
Age (mean+/standard deviation): 62.9 +/- 9.8 years.
Aetiology (HCV / alcohol / HCV+alcohol / NAFLD / others): 1/5/2/1/1.

**Primary outcome:** Proportion of participants with FMT-related serious adverse events (SAEs) at day 150, a composite endpoint of death, hospitalisations, emergency room visits or transmissible infections, as defined by the FDA.

**Secondary outcomes:** Changes in cognitive function at day 20, cirrhosis severity (MELD score, albumin), changes in liver function and white blood cell (WBC) count, development of all adverse events (AEs), and changes in microbiota composition and function in the FMT arm compared to standard of care arm.

**Screening and testing:**
- Stool tests: *Clostridium difficile* Toxin B and PCR, *Cryptosporidium* and *Isospora* Examination, ova, cysts and parasites with *Giardia* Antigen EIA, *Salmonella/ Shigellosa Campylobacter* Culture, *Shiga* Toxin EIA with Reflex to *E. coli* O157 Culture and *Vibrio* Culture, *Cryptosporidium* Antigen EIA, *Helicobacter pylori* Antigen EIA, *Helicobacter pylori* Antigen EIA.

**Screening and testing:**
- Amount of stool per transplant / administered to patients: 37.5g of stool.
- Diluent used to prepare: 90mls glycerol saline buffer in total.
- Diluent used to store if frozen: glycerol.
- Preparation methods: Aerobic.
- Time from preparation to transplant (fresh): N/A - frozen.
- Time period for storage (frozen): not stated.
- Route administered and frequency: Upper GI: non; lower GI: Single infusion of FMT via enema.
- PPI: Not described.
- Antimotility: Loperamide 8mg 2 hrs before.
- Prokinetics: None.

**FMT arm:**
- Patients with SAEs at day 150: 20% (n =2/10) (p=0.02).
- Total SAEs at day 150: 20% (n =2/10) (p=0.01).
- Patients with altered mental status by day 150: 0% (n =0/10) (p=0.03).
- Total HE episodes at day 150: 0% (n =0/10) (p=0.03).
- Stroop OffTime+OnTime change (day 0 and day 20); positive indicates improvement: 29.1 +/- 27.9 (p=0.04) (N.B. Stroop OffTime+OnTime is a validated tool for objectively assessing for hepatic encephalopathy using a smartphone app).
- PHES score change (day 0 and day 20); negative indicates improvement - 3.1+/-2.1 (p=0.01).

**Deaths:** Nil.

**Standard of care arm:**
- Serious adverse events: x1 hospitalisation for acute kidney injury, and 1 was due to chest pain (all within 5 months post FMT).
- Patients with SAEs at day 150: 20% (n=8/10).

**Deaths:** Nil.

**Note:**
- The data is from Bajaj et al., *Hepatology*, 2017.
Inclusion criteria: >18 yrs outpatients with cirrhosis and recurrent hepatic encephalopathy (HE) defined as at least two documented overt HE episodes requiring therapy.

Exclusion criteria: MELD score >17, on oral or intravenous antimicrobial agents besides nonabsorbable rifaximin, allergies to pretreatment antibiotics, immunosuppressive medications, positive C. difficile test, pregnancy, active infection, those with active alcohol abuse, and unable to provide informed consent.

Cochrane Collaboration risk of bias assessment: low risk of bias.

Stool Norovirus EIA, Stool Rotavirus Antigen Detection, Adenovirus Antigen Detection, Gastroenteritis EIA, Vancomycin-resistant Enterococcus Culture, Microsporidia Exam.

500 mg orally three times daily. All antibiotics were discontinued at least 12 hours before FMT. This regime was not used in patients randomised to standard of care arm.

Total SAEs at day 150: 11.

Patients with altered mental status day 150: 50% (n = 5/10).

Total HE eps day 150: 6
Stroop OffTime+OnTime change (day 0 and day 20): -43.5 +/- 95.7.

PHES score change (day 0 and day 20): 0.0 +/- 3.1.

MELD score change (day 0 and day 35): 0.2 +/- 2.7.

N.B. no significant difference in serum albumin, AST, ALT, WBC or haemoglobin counts between the two groups.
<table>
<thead>
<tr>
<th>Intervention: Donor FMT (one for six days in a row).</th>
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<tbody>
<tr>
<td>Number of patients: 30.</td>
</tr>
<tr>
<td>Female: male 19: 11.</td>
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<tr>
<td>Age (mean+/-SD): 53.1 +/- 10.2 years.</td>
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<tr>
<td>Comparator: Standard of care</td>
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<tr>
<td>(education, behavioural strategies, oral laxaives;</td>
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<tr>
<td>expressively told to avoid antibiotics). Macrogol</td>
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<td>permitted if no bowel movement for three days, and</td>
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<tr>
<td>enema permitted if even this failed. Number of</td>
</tr>
<tr>
<td>patients: 30.</td>
</tr>
<tr>
<td>Female: male 21: 9.</td>
</tr>
<tr>
<td>Age (mean+/-SD)*: 55.4 +/- 12.1 years.</td>
</tr>
<tr>
<td>Primary outcome: At least three complete spontaneous</td>
</tr>
<tr>
<td>bowel movements (CSBMs) per week during the 12 week</td>
</tr>
<tr>
<td>follow-up.</td>
</tr>
<tr>
<td>Secondary outcomes: 1) Proportion</td>
</tr>
<tr>
<td>of patients with average increase of at least 1</td>
</tr>
<tr>
<td>CSBM per week; 2) Number of CSBMs per week; 3)</td>
</tr>
<tr>
<td>Colonic transit time (assessed via abdominal x-ray/</td>
</tr>
<tr>
<td>radiopaque markers); 4) subjective stool</td>
</tr>
<tr>
<td>consistency; 5) Wexner</td>
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<tr>
<td>constipation scale.</td>
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<tr>
<td>Inclusion criteria: ≥18 yrs outpatients with</td>
</tr>
<tr>
<td>cirrhosis and recurrent hepatic encephalopathy</td>
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<tr>
<td>(HE) defined as at last two</td>
</tr>
</tbody>
</table>

| One universal donor used throughout (24 year old    |
| healthy university student).                         |
| Working in healthcare: No.                           |
| Donor demographics: As above.                       |
| Donor screening: Similar to FDA blood screening.    |
| Screening blood tests: Full blood count, chemistry  |
| and iron profile, hepatitis A, B and C, HIV-1 and-2,|
| CMV, EBV, HSV, VZV, and Treponema pallidum.         |
| Screening stool tests: Yersinia spp, Salmonella spp,|
| Shigella spp, Campylobacter jejuni, C difficile     |
| toxin, helminths, ova, parasites, and Helicobacter  |
| pylori.                                             |

| Amount of stool per transplant / administered to     |
| patients: 100g of stool.                             |
| Diluent used to prepare: Either 500mLs normal saline,|
| or normal saline amended with glycerol to final     |
| concentration of 10%.                                |
| Diluent used to store if frozen: Glycerol.           |
| Preparation methods: Not stated.                    |
| Time from preparation to transplant (fresh): 2 hours.|
| Time period for storage (fresh): 1-4 weeks.         |
| Route administered and frequency: Upper GI: all via  |
| nasojejunal tube (originally placed endoscopically);|
| lower GI: nil.                                       |
| Bowel purgative: Not described.                     |
| PPI: Not described.                                 |
| Antimotility: Not described.                        |
| Prokinetics: None.                                  |

| Donor FMT arm                                       |
| Meeting primary outcome: 37% (n=11/30) (p=0.04).    |
| Meeting second outcomes: At least one more CSBM per |
| week: 53% (n=16/30) (p=0.009).                      |
| Number of CSBMs per week: 3.2 +/- 1.4.              |
| Stool consistency score: 3.9 +/- 1.3.                |
| Colonic transit time (hours): 58.5 +/- 9.8.         |
| Wexner constipation score: 8.6 +/- 1.5.             |

| FMT arm: 50 in total (1 x sedation contraindications,|
| x 22 endoscopy-related respiratory difficulty, x 12  |
| nausea, x 5 abdominal pain, x 4 diarrhoea, x 4       |
| flatulence, x 2 transient fever).                    |
| Placebo arm: x 4 in total (x 0 sedation             |
| contraindications, x 0 endoscopy-related            |
| respiratory difficulty, x 0 nausea, x 3 abdominal    |
| pain, x 0 diarrhoea, x 1 flatulence, x 0 transient   |
| fever).                                             |

**Tian et al, PLoS ONE, 2017**
documented overt HE episodes requiring therapy.

Exclusion criteria: At least 18 years, BMI of 18-25 kg/m², and slow transit constipation defined as colonic transit time of >48 hr, and symptoms unresponsive to dietary modification, enemas or biofeedback in the previous six months.

Cochrane Collaboration risk of bias assessment: low risk of bias.

Colonic transit time (hours): 73.6+/8.7.

Wexner constipation score: 12.7+/2.5.

Quality of Life Assessment: Not described.
<table>
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<tbody>
<tr>
<td><strong>Intervention:</strong> Donor FMT</td>
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<tr>
<td><strong>Number of patients:</strong> 9.</td>
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<tr>
<td>Female: male 0: 9.</td>
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<tr>
<td>Age (mean+/− SD): 47 +/- 4 years.</td>
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<tr>
<td><strong>Comparator:</strong> Autologous FMT.</td>
</tr>
<tr>
<td><strong>Number of patients:</strong> 9.</td>
</tr>
<tr>
<td>Female: male 0: 9.</td>
</tr>
<tr>
<td>Age (mean+/− SD): 53 +/- 3 years.</td>
</tr>
<tr>
<td><strong>Primary outcome:</strong> Effect of lean donor gut microbiota infusion on insulin sensitivity after 6 weeks.</td>
</tr>
<tr>
<td><strong>Secondary outcomes:</strong> Change in specific small- and large-gut microbiota as well as produced fecal short chain fatty acids.</td>
</tr>
</tbody>
</table>

| Inclusion criteria: Male Caucasian obese subjects with characteristics of the metabolic syndrome, specifically with a body mass index > 30 kg/m^2, or waist circumference > 102 cm, and a fasting plasma glucose level > 5.6 mmol/L. |
| Exclusion criteria: History of cholecystectomy were excluded, as well as subjects who used any medication, probiotics, and/or antibiotics in the past 3 months. |
| Cochrane Collaboration risk of bias assessment: low risk of bias. |

| Lean healthy Caucasian males (body mass index < 23 kg/m^2). |
| Working in healthcare: Not stated. |
| Donor demographics: As above. |
| Donor screening: Questionnaires regarding diet and bowel habits, travel history, comorbidity including (family history of) diabetes mellitus, and lack of medication use. |
| Screening blood tests: Human immunodeficiency virus; human T-lymphotropic virus; hepatitis A, B, and C; cytomegalovirus; Epstein–Barr virus; *Strongyloides*; and amoebiasis. |
| Screening stool tests: Presence of parasites (eg, *Blastocystis hominis* or *Dientamoeba fragilis*), *Clostridium difficile*, or other pathogenic bacteria (*Shigella*, *Campylobacter*, *Yersinia*, *Salmonella*) |

| Amount of stool per transplant / administered to patients: Not stated. |
| Diluent used to prepare: 500mls of normal saline. |
| Diluent used to store if frozen: N/A. |
| Preparation methods: Faeces was covered with sterile saline (500 ml 0.9% NaCl) to reduce exposure to oxygen, transferred to a blender, and mixed for 10 minutes. The homogenized solution then was filtered twice through a clean metal sieve. |
| Time from preparation to transplant (fresh): Same day. |
| Time period for storage (frozen): N/A. |
| Route administered and frequency: Upper GI: all via nasoduodenal tube (originally placed endoscopically); lower GI: nil. |
| Bowel purgative: PEG solution. |
| PPI: Not described. |
| Antimotility: Not described. |
| Prokinetics: None. |

| Donor FMT arm: |
| Median rate of glucose disappearance, Rd: from 26.2 to 45.3 μmol/kg/min; p<0.05. |
| Autologous FMT arm: |
| Median rate of glucose disappearance, Rd: from 18.9 to 19.5 μmol/kg/min. |
| Quality of Life Assessment: Not described. |

| Secondary outcomes: No change in the total numbers of fecal bacteria (allogenic, from 10.8 +/- 0.2 to 11.0 +/- 0.4 vs autologous, from 11.6 +/- 0.6 to 11.3 +/- 0.4 log_{10} bacteria/g faeces, non significant [NS]). Fecal short-chain fatty acids decreased after allogenic gut microbiota infusion (median acetate from 49.5 to 37.6; p <0.05; butyrate, from 14.1 to 8.9; p < 0.05; and propionate, from 18.2 to 16.3 mmol/kg feces; NS). |

<p>| No adverse events |</p>
<table>
<thead>
<tr>
<th>Kootte et al, Cell Metabolism, 2017</th>
<th>Intervention: Donor FMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 26. Female: male 0: 26. Age (mean): 54 years.</td>
<td>Lean healthy Caucasian males (body mass index &lt; 25 kg/m²).</td>
</tr>
<tr>
<td>Primary outcome: Change in intestinal microbiota composition upon FMT in relation to insulin sensitivity.</td>
<td>Donor demographics: As above.</td>
</tr>
<tr>
<td>Secondary outcomes: Post-prandial lipid, glucose excursions and plasma metabolites.</td>
<td>Donor screening: Questionnaires regarding diet and bowel habits, travel history, comorbidity including (family history of) diabetes mellitus, and lack of medication use.</td>
</tr>
<tr>
<td>Inclusion criteria: All adult (age 21-69 years) Caucasian males, who had obesity (body mass index (BMI) &gt; 30 kg/m²), fulfilled the National Cholesterol Education Program (NCEP)-criteria for metabolic syndrome, were treatment-naïve and who where otherwise healthy.</td>
<td>Screening blood tests: Human immunodeficiency virus; human T-lymphotropic virus; hepatitis A, B, and C; cytomegalovirus; Epstein–Barr virus; Strongyloides; lues and amoebiasis.</td>
</tr>
<tr>
<td>Exclusion criteria: History of recent weight loss, cardiovascular event, cholecystectomy and the use of any medication known to influence gut microbial composition in the last three months (including proton pump inhibitors, antibiotics and pre-/pro-/synbiotics) or treatments targeting metabolic diseases.</td>
<td>Screening stool tests: Pathogenic parasites (e.g., Blastocystis hominis, dientamoeba fragilis, giardia lamblia), bacteria (Shigella, Campylobacter, Yersinia, Salmonella, enteropathogenic E. coli and Clostridium difficile) or viruses (noro-, rota-, astro-, adenovirus (40/41/52), entero-, parecho- and sapovirus).</td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: Not stated.</td>
<td>Diluent used to prepare: 500mls of normal saline.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: N/A.</td>
<td>Preparation methods: Faeces was covered with sterile saline (500 ml 0.9% NaCl) to reduce exposure to oxygen, transferred to a blender, and mixed for 10 minutes. The homogenized solution then was filtered twice through a clean metal sieve.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Same day.</td>
<td>Time period for storage (frozen): N/A.</td>
</tr>
<tr>
<td>Route administered and frequency: Upper GI: Single infusion all via nasoduodenal tube (originally placed endoscopically). A subgroup of patients receiving donor FMT had a second infusion; lower GI: nil.</td>
<td>Bowel purgative: PEG solution.</td>
</tr>
<tr>
<td>PPI: Not described.</td>
<td>Antimotility: Not described.</td>
</tr>
<tr>
<td>Prokinetics: None.</td>
<td>No adverse events</td>
</tr>
</tbody>
</table>

Donor FMT arm: improved peripheral insulin sensitivity at week 6 (from 25.8 to 28.8 µmol/kg/min, , \( p < 0.05 \). This change was no longer significant at week 18 (including those that had a second infusion).

Autologous FMT arm: FMT had no effect at week 6 (from 22.5 to 20.8 µmol/kg/min, NS) 

Quality of Life Assessment: Not described.

Secondary outcomes: No significant changes in fecal butyrate levels (butyrate from 13 to 20 mmol/g faeces, \( p = 0.096 \)). Fecal acetate levels, however, were significantly increased from 62 to 85] mmol/g feces \( p < 0.05 \) after allogenic FMT, whereas fecal propionate was borderline significantly altered (from 23 to 28 mmol/g faeces, \( p = 0.062 \).
| Cochrane Collaboration risk of bias assessment: low risk of bias. |   |   |   |
Appendix D. Excluded clinical studies

D.1. *Clostridium difficile* infection:

D.1.1. Studies excluded at Sift 2 by working group:

<table>
<thead>
<tr>
<th>Paper:</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Type of Study</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Tvede M, Tinggaard M, Helms M. Rectal bacteriotherapy for recurrent <em>Clostridium difficile</em>-associated diarrhoea: results from a case series of 55</td>
<td>Case series of ‘FMT’ for CDI, but bacteriotherapy rather than true FMT.</td>
</tr>
</tbody>
</table>
D.1.2. Abstracts not fulfilling selection criteria:


D.N. S, Seril DN, Shen B. Clostridium difficile infection in patients with ileal pouches. Am J Gastroenterol. B. Shen, Department of Gastroenterology/Hepatology-A31, Digestive Disease Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States. E-mail: shenb@ccf.org: Nature Publishing Group (Houndmills, Basingstoke, Hampshire RG21 6XS, United Kingdom); 2014;109(7):941–7.


Roediger R, Grinspan A. Safety and efficacy of fecal microbiota transplantation for clostridium difficile in a cohort of patients with a severe infection and/or IBD. Am J Gastroenterol. 2016;111(PG-S446):S446.


D.1.3. Case series not fulfilling selection criteria


Dimitry J, Keshteli A, Kao D. Independent predictors of failure of fecal microbiota transplantation (FMT) for recurrent or refractory clostridium difficile infection. Can J Gastroenterol Hepatol Conf. 2016;(pagination PG-).


D.1.4. Case reports


Alang N, Kelly CR. Weight gain after fecal microbiota transplantation. Open Forum Infect Dis. 2015;2 (1) (no pagination)(ofv004 PG-).


Berro ZZ, Hamdan RH, Dandache IH, Saab MN, Karnib HH, Younes MH. Fecal microbiota transplantation for severe clostridium difficile infection after left ventricular assist device implantation: A case control study and concise review on the local and regional therapies. BMC Infect Dis. 2016;16 (1) (no pagination)(234 PG-).


Navalkele BD, Lerner SA. Intravenous tigecycline facilitates cure of severe Clostridium difficile infection (CDI) after failure of standard therapy: A case report and literature review of tigecycline use in CDI. Open Forum Infect Dis. 2016;3(2) (no pagination)(ofw094 PG-).


D.1.5. Non-English language:


*Czech* Polak P, Freibergerova M, Husa P, Jurankova J, Svacinka R, Mikesova L, et al. Fecal bacteriotherapy for the treatment of recurrent Clostridium difficile colitis used in the Clinic of Infectious Diseases of the


French Seksik P. Clostridium difficile associated colitis. [French]. Hepato-Gastro Oncol Dig. 2016;23(8 PG-775-784):775–84.


D.1.6. Basic sciences:


Moelling K, Broecker F. Fecal microbiota transplantation to fight Clostridium difficile infections and other intestinal diseases. Bacteriophage. 2016;18(PG-).


Shanahan F. Separating the microbiome from the hyperbolome. Genome Med. 2015;7(1):17(17 PG-).


D.1.7. Narrative reviews


Anonymous. Donor faeces for recurrent Clostridium difficile diarrhoea? BMJ. 2013;346 (no pagination)(f376 PG-).


Anonymous. Probiotics are beneficial in Clostridium difficile infection: Healthy microbiota by probiotics or fecal transplantation prevent diarrhea. [Dutch]. Pharm Weekbl Wet Platf. 2014;149(10:PG-).


Anonymous. Therapy: FMT effective in patients with severe and/or complicated CDI. Nat Rev Gastroenterol Hepatol. 2015;21(PG-).

Anonymous. Therapy: FMT effective in patients with severe and/or complicated CDI. Nat Rev Gastroenterol Hepatol. 2015;21(PG-).


Antonopoulos DA, Chang EB. Transplanting a microbial organ: The good, the bad, and the unknown. MBio. 2016;7(3) (no pagination)(e00572-16:PG-).


Clostridium difficile Infection in Older Adults: Systematic Review of Efforts to Reduce Occurrence and Improve Outcomes


Colonoscopic fecal bacteriotherapy in the treatment of recurrent Clostridium difficile infection—results and follow-up

Colonoscopic versus nasogastric fecal transplantation for the treatment of Clostridium difficile infection: A review and pooled analysis. Consensus report: faecal microbiota transfer - clinical applications and procedures

Consultant Pharmacist Jan 01 2017;32(1):24-41


Drekonja, D.; Reich, J.; Gezahegn, S.; Greer, N.; Shaukat, A.; MacDonald, R.; Rutks, I.; Wilt, T. J. Fecal microbiota transplantation for clostridium difficile infection a systematic review Annals of Internal Medicine 05 May 2015;162(9):630-638


Rossen NG, MacDonald JK, de Vries EM, et al. Fecal microbiota transplantation as novel therapy in gastroenterology: a systematic review

Fecal microbiota transplantation via nasogastric tube for recurrent clostridium difficile infection in pediatric patients


Fuentes S, De Vos WM. How to manipulate the microbiota: Fecal microbiota transplantation. E-mail: barbara.b.bertram@gsk.com: Springer New York LLC; 2016;(902 PG-143-153):143–53.


Hashash JG, Binion DG. Managing Clostridium difficile in Inflammatory Bowel Disease (IBD). Curr Gastroenterol Rep. 2014;16 (7) (no pagination)(393 PG-).


I, Y. T.; Cai, H. F.; Wang, Z. H.; Xu, J.; Fang, J. Y.


Infection December 2012;40(6):643-648
Infection February 2014;42(1):43-59


Journal of Digestive Diseases September 2016;17():43
Journal of Gastroenterology and Hepatology (Australia) November 2016;31():155
Journal of Pediatric Gastroenterology and Nutrition 13 Jan 2015;60(1):23-26


Korman TM. Diagnosis and Management of Clostridium difficile Infection. Semin Respir Crit Care Med. 2015;36(1 PG-31-43):31–43.


Marra F, Ng K. Controversies Around Epidemiology, Diagnosis and Treatment of Clostridium difficile Infection. Drugs. 2015;75(10 PG-1095-1118):1095–118.


Mullish BH, Williams HR. Obstacles to establishing an NHS faecal transplant programme. BMJ. 2015;351(PG-h6043):h6043.

Mullish BH, Williams HRT. Obstacles to establishing an NHS faecal transplant programme. BMJ. 2015;351 (no pagination)(3496 PG-).


Too early to determine whether fecal microbiota transplant has therapeutic promise for ulcerative colitis? Journal of Pediatric Gastroenterology and Nutrition. G.H. Russell, Division of Gastroenterology and Nutrition, Boston Children’s Hospital, 300 Longwood Ave, Boston, MA 02115, United States: Lippincott Williams and Wilkins; 2015. p. 3.


van Nood E, Speelman P, Kuijper EJ, Keller JJ. Struggling with recurrent Clostridium difficile infections: is donor faeces the solution? Euro Surveill. 2009;14(34 PG-).


Woodworth MH, Carpentieri C, Sitchenko KL, Kraft CS. Challenges in fecal donor selection and screening for


D.1.8. Commentary/editorials/opinion:


Heuer AH. Fecal transplantation with side effect: Bearer of hope for Clostridium difficile patients is still insufficiently researched. Dtsch Apotheker Zeitung. 2016;156(46 PG-).


Mayor S. Donor faecal transplantation is highly curative in recurrent C difficile infection, trial finds. BMJ. 2016;354 (no pagination)(i4638 PG-).


**D.1.9. Letters**


Mawer DP, Wilcox MH. Clarifying the management of Clostridium difficile infection. BMJ. 2015;351(PG-h6130):h6130.


Spector T, Knight R. Authors’ reply to Mawer and Wilcox and Mullish and Williams. BMJ. 2015;351(PG-h6132):h6132.

Spector T, Knight R. Faecal transplants. BMJ. 2015;351 (no pagination)(h5149 PG-).


D.1.10. Not relevant, miscellaneous

A.M. B, C.P. K, Berg AM, Kelly CP, Farraye FA. Clostridium difficile infection in the inflammatory bowel disease patient. Inflamm Bowel Dis. A.M. Berg, Section of Gastroenterology, Boston Medical Center, 85 East Concord St., Suite 7720, Boston, MA 02118-2338, United States. E-mail: adam.berg@bmc.org; Lippincott Williams and Wilkins (530 Walnut Street, P O Box 327, Philadelphia PA 19106-3621, United States); 2013;19(1):194−204.


American Journal of Gastroenterology Lecture: Intestinal microbiota and the role of fecal microbiota transplant (FMT) in treatment of C. difficile infection. American Journal of Gastroenterology. L.J. Brandt, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467, United States. E-mail: lbrandt@montefiore.org; Nature Publishing Group (Houndmills, Basingstoke, Hampshire RG21 6XS, United Kingdom); 2013. p. 177–85.


Broecker F, Klumpp J, Moelling K. Long-term microbiota and virome in a Zurich patient after fecal transplantation against Clostridium difficile infection. E-mail: subscrip@blackwellpub.com: Blackwell Publishing Inc.; 2016;(1372 1 PG-29-41):29–41.


Colitis. Netherlands: Brace, Chantalle. Dept. Medicine, GI Diseases Research Unit, Queen’s University, Kingston, ON, Canada. Electronic address: chantalle.brace@queensu.ca.; 2014;8(9):1133–7.


Carlet J. The gut is the epicentre of antibiotic resistance. Antimicrob Resist Infect Control. 2012;1 (no pagination)(39 PG-).


Claassen E. Healthy microbiota by probiotics or fecal transplantation prevent diarrhea: Probiotics are beneficial in case of Clostridium difficile infection. [Dutch]. Pharm Weekbl. 2014;149(10 PG-16-17):16–7.


Donnelly SC. Elements: In this month’s issue. Qjm. 2015;108(5 PG-351-351):351.


Gianotti RJ, Moss AC. Fecal microbiota transplantation: From clostridium difficile to inflammatory bowel...


Shen NT, Gold SL, Schneider Y, Cohen-Mekelburg SA, Maw AM, Crawford CV. Probiotic sepsis in patients with


Staley C, Kelly CR, Brandt LJ, Khoruts A, Sadowsky MJ. Complete microbiota engraftment is not essential for recovery from recurrent Clostridium difficile infection following fecal microbiota transplantation. MBio. 2016;7(6) (no pagination)(e01965-16 PG-).


Taylor KN, McHale MT, Saenz CC, Plaxe SC. Diagnosis and treatment of Clostridium difficile (C. diff) colitis: Review of the literature and a perspective in gynecologic oncology. Gynecol Oncol. 2016;23(PG-).


D.2. Non-CDI indications:

D.2.1. Abstracts not fulfilling selection criteria:


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D.2.2. Case series not fulfilling selection criteria:


D.2.3. Narrative reviews:


D.2.4. Miscellaneous, not relevant:

Aarbiou J, Leeming DJ, Cruwys S, Gudmann NS, Brockbank S, Young A, et al. A comparison of compounds...


Cao Z, Li Z, Liu Y, Mo R, Ren P, Chen L, et al. The role of bacterial infection (BI) in decompensated cirrhosis...


Davis SC, Yadav JS, Barrow SD, Robertson BK. Gut microbiome diversity influenced more by the Westernized dietary regime than the body mass index as assessed using effect size statistic. MicrobiologyOpen. 2017;6 (4) (no pagination)(e00476).


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Venereology. 2017;31:16.


Duman N, Utkutan S, Ozkan H, Ozdogan S. Are the stool characteristics of preterm infants affected by infant formulas? The Turkish journal of pediatrics. 2000;42(2):138-44.


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Hadengue A, Spahr L. From bench to bedside: Is the road trickier in alcoholic liver disease? Alcoholism: Clinical and Experimental Research. 2010;34:53A.


Journois D, Safran D, Castelain MH, Chanu D, Drevillon C, Barrier G. [Comparison of the antithrombotic


Kallarackal GU, Ansari EA, Amos N, Martin JC, Lane C, Camilleri JP. A comparative study to assess the clinical use of Fluorescein Meniscus Time (FMT) with Tear Break up Time (TBUT) and Schirmer's tests (ST) in the diagnosis of dry eyes. Eye. 2002;16(5):594-600.


 Orr DW, Myint H, Murphy R. Probiotic supplementation after Very Low Calorie Diet does not aid improvement of the metabolic syndrome or maintenance of weight loss post Liver Transplant. A randomised double-blind placebo controlled trial. Hepatology. 2016;64 (1 Supplement 1):113A-4A.


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Sabharwal S, Abraham JM, Grand R, Mascarenhas M. "Ins and outs" of constipation and DIOS. Pediatric Pulmonology. 2016;51:147.


Shukla A. Those spots on his penis: It is bannayan riley ruvalcaba syndrome!! Pediatric Dermatology. 2017;34:S141-S2.


Sunshine A, Mulhern SA, Olson N, Elkind A, Almas M, Sikes C. Comparative sensitivity of stopwatch


Yao Q, Huang Q, Cao Y, Qian P, Chen H. Porcine interferon-gamma protects swine from foot-and-mouth


Appendix E. Peer review

Healthcare Infection Society

Consultation – The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

Closing date: 5pm on 18 January 2018

<table>
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<tr>
<th>Organisation</th>
<th>Royal College of General Practitioners</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title (e.g. Dr, Mr, Ms, Prof)</td>
<td>Drs</td>
</tr>
<tr>
<td>Name</td>
<td>Clinical Adviser: Kevin Barrett</td>
</tr>
<tr>
<td>Medical Director</td>
<td>Matthew Hoghton</td>
</tr>
<tr>
<td>Job title or role</td>
<td>As above</td>
</tr>
<tr>
<td>Address and post code</td>
<td>30 Euston square, London, Nw1 2FB</td>
</tr>
<tr>
<td>Telephone number</td>
<td>0203 188 7688</td>
</tr>
<tr>
<td>Email address</td>
<td><a href="mailto:clinicaladvisers@rcgp.org.uk">clinicaladvisers@rcgp.org.uk</a></td>
</tr>
</tbody>
</table>

Please note: comments will only be accepted electronically on this proforma.

Please provide comments on the draft guideline on the form below, putting each new comment in a new row. When feeding back, please note the section you are commenting on (for example, section 1 Introduction and line number). If your comment relates to the guideline as a whole then please put ‘general’. Add extra rows if required.
<table>
<thead>
<tr>
<th>Section</th>
<th>Comments</th>
<th>Working group response</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>This is an important consultation of an important treatment for recurrent or refractory CDI. The recommendations are sensible and will help produce a universal service to patients across the UK.</td>
<td>Thank you for your comment.</td>
</tr>
<tr>
<td>B</td>
<td>Hudson et al doi: 10.1128/CMR.00049-16Clin. Microbiol. Rev. January 2017 vol. 30 no. 1 1191-2311 January 2017 review suggests that faecal microbiota transplant in the United States is used not only in refractory or recurrent Clostridium Difficile (CDI) but also in initial CDI and Ulcerative colitis</td>
<td>We cannot find mention of FMT use as treatment for initial CDI in this review. Updated searches have identified a small RCT evaluating the use of FMT as treatment for first CDI (Camacho-Ortiz et al, 2017), and this is now evaluated by the working group within the guideline (Section 8.1.1.3). All published RCTs evaluating the use of the FMT as treatment for ulcerative colitis have been reviewed by the working group within the guideline (Section 8.6.2).</td>
</tr>
<tr>
<td>C</td>
<td>There is a lack of GP representation on the working group (5.6) and this is reflected in the consultation with a lack of a suggested referral pathway for community based patients</td>
<td>We agree that the implications of this guideline for primary care were not well-described, and we have strengthened this within the guideline. In particular, we have more strongly highlighted the responsibility of microbiology staff in clinical laboratories to liaise proactively with primary care teams regarding the possibility of FMT when recurrent positive stool samples are received from the community on a particular patient (Section 8.7.1).</td>
</tr>
<tr>
<td>D</td>
<td>There has also been a reported case of the development of obesity following FMT from an overweight donor but this has not been substantiated in other studies. The BMI restriction on donors (8.3.2) may restrict donors.</td>
<td>The recruitment of suitable donors is relatively restrictive by necessity since FMT is an unlicensed and poorly-studied medicinal product. There is a growing literature base demonstrating an association between a high or low BMI and perturbation of the structure and/or function of the gut microbiota and subclinical chronic inflammation. The implications of this for the safety and efficacy of FMT are not well-defined. The suggested BMI range does not make it prohibitively difficult to find suitable donors. As such, the working group believes that their existing recommendation is reasonable.</td>
</tr>
</tbody>
</table>
Section | Comments | Working group response
--- | --- | ---
E | It would be useful to have a standard UK pre and post questionnaire for patients to standardise recording (8.1.2.3) | We agree that the introduction of standardised questionnaires would have clear potential advantages for clinical care and/ or research. We now discuss this further in Section 10, ‘further research’.

F | It may useful to consider measuring the microbiol strains of donors to monitor the impact of combinations of specific microbial strains to understand the undefined nature of faecal preparations | We agree of the importance of this, and this is now discussed in more detail in Section 10, ‘further research’.

G | The lack of universal definitions of cures (8.1.2.4) is likely to hamper future studies | We agree with this comment. Section 10, ‘further research’ has been amended accordingly. Furthermore, we expect that the attention generated by this guideline will highlight this inadequacy.

H | With the introduction of the clinical term SNOMECT across primary care in 2018 and secondary care in 2020 it is important to record faecal microbiota transplant so that long term sequelae can be measured and patients can be potentially contacted in the future. | We agree that there should be specific procedure codes for FMT (according to route of administration), so that this can be accurately recorded in the patient’s medical record. This would also lay the foundation for a future HRG code and tariff for the procedure which is not currently funded by CCGs. Members of the working group are in discussion with NHS England about this.

Closing date: Please forward this electronically by 5pm on January 2018 at the very latest to consultations@his.org.uk

Healthcare Infection Society

Consultation – The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.
Closing date: 5pm on January 2018

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<tbody>
<tr>
<td>Title (e.g. Dr, Mr, Ms, Prof)</td>
<td>Dr</td>
</tr>
<tr>
<td>Name</td>
<td>Alex Cochrane</td>
</tr>
<tr>
<td>Job title or role</td>
<td>Consultant Microbiology and Infectious Diseases</td>
</tr>
<tr>
<td>Address and post code</td>
<td>Raigmore Hospital, Perth Road, Inverness IV2 3UJ</td>
</tr>
<tr>
<td>Telephone number</td>
<td>01463 704000</td>
</tr>
<tr>
<td>Email address</td>
<td><a href="mailto:Alexandra.cochrane@nhs.net">Alexandra.cochrane@nhs.net</a></td>
</tr>
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<tbody>
<tr>
<td>8.1.1.1</td>
<td>I don't think you should limit FMT for first recurrence to those with specific risk factors. If clinicians wish to use FMT rather than fidaxomicin for the first recurrence on cost effectiveness grounds then that is reasonable. Suggest that you recommend FMT may be offered for the first or second or subsequent recurrences.</td>
<td>As FMT is currently an unlicensed medicinal product with poorly-studied long term sequelae, the working group considered that it should generally be reserved for patients who have had more than three episodes of infection. There are no studies directly comparing its effectiveness with some of the newer agents such as fidaxomicin or bezlotoxumab, hence this recommendation is made on the basis of safety. However, the working group felt that it may be reasonable in certain patient groups (with ongoing risk factors for further infections) to consider FMT for the first recurrence if cost effectiveness is a concern.</td>
</tr>
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249
<table>
<thead>
<tr>
<th>Section</th>
<th>Comments</th>
<th>Working group response</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1.1.3 (ii)</td>
<td>I disagree that patients should have previously been treated with extended/pulsed vancomycin or fidaxomicin before being offered FMT. You don’t present any evidence to show that these antibiotic treatment is superior to FMT. Where FMT is the preferred treatment for the first recurrence it is quite likely that the patient will not have had a prolonged or tapered course, and this should not be a barrier to giving FMT which as you say is highly efficacious.</td>
<td>As above, there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT (Hota et al, 2017). The safety profile of these medications is well-established from large randomised controlled trials, whilst randomised studies involving FMT have tended to be smaller, and have more variable patient follow-up. As such, on the balance of safety, the working group agreed that antimicrobial/antitoxin therapy associated with reduced CDI recurrence should be considered prior to FMT. Reflecting the uncertainties in this area within the reviewed literature, the relevant recommendation is ‘conditional’ rather than ‘strong’.</td>
</tr>
<tr>
<td>8.1.1.3 (iii)</td>
<td>You don’t cite any evidence that fidaxomicin or bezlotoxumab have better cure rates than FMT. My practice has been not to use fidaxomicin in life threatening C. difficile due to lack of evidence of efficacy in this setting, though I may be out of date with this.</td>
<td>Pre-planned subgroup analysis of patients with severe CDI in a randomised trial demonstrated a significantly lower recurrence rate when treated with fidaxomicin (13.0%, n=12/92) than when treated with vancomycin (26.6%, n=29/209) (Louie et al, 2011); this finding was replicated in another randomised controlled trial, with 8.3% (n=4/48) and 32.6% (n=14/43) experiencing a recurrence respectively (Cornely et al, 2012). In a further randomised trial, bezlotoxumab (together with standard of care antibiotics) was shown to reduce recurrence of severe CDI compared to standard of care antibiotics alone (10.9% (n=6/55) vs 20% (n=13/65) respectively) (Wilcox et al, 2017). The working group noted that there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT (Hota et al, 2017). The working group agreed that in the absence of this evidence, on</td>
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the balance of safety and potential risks, consideration should be given to using antimicrobial/antitoxin therapy associated with reduced CDI recurrence prior to considering the use of FMT.

8.5.1.1 (iii)  Is there adequate published material or experience to ensure the safety of loperamide? It is usually avoided in C. difficile disease due to increased risk of complications.

We agree that loperamide should not be used expressly for the treatment of CDI diarrhoea. However, a number of studies (references within the guideline) have used a single dose of loperamide after lower GI FMT to retention, and no potential safety issues associated with this use have been identified.

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<tr>
<td>Title (e.g. Dr, Mr, Ms, Prof)</td>
<td>Dr</td>
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<tr>
<td>Name</td>
<td>Ewan Olson</td>
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Please provide comments on the draft guideline on the form below, putting each new comment in a new row. When feeding back, please note the section you are commenting on (for example, section 1 Introduction and line number). If your comment relates to the guideline as a whole then please put ‘general’. Add extra rows if required.

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<td>8.3.4.</td>
<td>Laboratory Screening of donors</td>
<td>Whilst vancomycin-resistant <em>Enterococci</em> (VRE) carriage is relatively common in the community (probably related to food consumption) (Endtz <em>et al</em>, 1997), community strains of VRE are genetically distinct from (and generally of much lower pathogenicity than) those found nosocomially (Willems <em>et al</em>, 2005); as such, the working group felt that routine screening was not justified. However, the working group acknowledged that the potential infection risk from VRE (and MRSA) would vary regionally dependent upon local prevalence and pathogenicity, and as such recommended that a risk assessment was performed to assess whether screening for these organisms should be considered.</td>
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<td></td>
<td>“Whilst vancomycin-resistant <em>Enterococci</em> (VRE) carriage is relatively common in the community, they are of low pathogenicity, and screening for them was not felt to be justified.”</td>
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<td>VRE can cause life threatening infections that are difficult to treat. Any patient who is VRE positive requires isolation in a sideroom with ensuite facilities.</td>
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<td>I would suggest that donors should be screened for VRE before accepting stool for donation. If there is a shortage of donor patients</td>
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 | should be offered VRE positive donations only with informed consent. |  

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**Consultation** – The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

**Organisation**
On behalf of European Study Group for *C. difficile* (ESGCD), and the National Donor Feces Bank at Leiden University Medical Center (drs. E. Terveer, drs. E. Boeije-Koppenol, prof. Hein Verspaget, dr. Y van Beurden, drs. R Ooijevaar, dr. Josbert Keller) and Department of Infectious Diseases, University of Koln (dr. Maria Vehreschild).

**Title (e.g. Dr, Mr, Ms, Prof)**
Prof. Dr.

**Name**
Ed Kuijper

**Job title or role**
Head of Experimental Bacteriology

**Address and post code**
LUMC, Albinusdreef2, 2333 ZA, Leiden

**Telephone number**
31-71-5263574

**Email address**
e.j.kuijper@lumc.nl

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<td>general</td>
<td>The literature was searched until April 2017, but please use the recently published document of E.M Terveer et al. entitled &quot;How to: Establish and run a stool bank&quot; and published in Clin Microbiol Infect. 2017 Dec;23(12):924-930. This document has considerable overlap with the proposed guideline, but also shows some important unresolved issues.</td>
<td>This reference has been added. Literature searches have been updated, to January 2018.</td>
</tr>
<tr>
<td>Lay summary, line 3</td>
<td>Capsules may also be prepared by use of non-freeze dried microbiota. Also, the possibility of using frozen products in general may be mentioned in this sentence.</td>
<td>We agree that these changes are important, and these amendments have been accordingly.</td>
</tr>
<tr>
<td>8.1.1.1</td>
<td>The authors are correct that CDI due to Type 07 responds less to FMT compared with CDI due to other PCR ribotypes. We register all infections by PCR ribotype to obtain more insights in successes and failures associated with strain characteristics and think that this is relevant for future recommendations, such as repeated FMT treatments for specific PCR ribotypes.</td>
<td>We presume that this refers to ribotype 027, and agree that this is important, and further reference has been made to this in Section 10, further research.</td>
</tr>
<tr>
<td>recommendation</td>
<td>“FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe CDI (strong).” Please elucidate how this risk assessment can be performed.</td>
<td>The working party noted that these risk factors are well-described in previous studies, and do not require further elucidation within the manuscript.</td>
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<td>8.1.1.2</td>
<td>Refractory CDI is also considered as an indication for FMT. Can the authors please provide a recommendation on the number of FMTs that should be used? Are patients on Intensive Care Units with refractory CDI also eligible? in 8.2.1 IC admission can be considered as a contraindication, but there are sufficient publications supporting to apply it for patients with severe CDI at ICU.</td>
<td>In Section 8.2.1, the working group reviewed the literature on contraindications to receiving FMT, and noted that certain studies have made ‘admission to Intensive Care’ such a contraindication. However, the working group have not themselves at any point stated that this is a contraindication to receiving FMT. As stated in Section 8.1.1.2, there are a relatively small number of cases reported in the reviewed literature of refractory CDI. As such, the working group are unable to give recommendations that patients with refractory CDI receiving FMT should be managed in any particular way differently to those with recurrent CDI.</td>
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<tr>
<td>8.1.1.3</td>
<td>Antibiotic treatment of rCDI. Though the literature search was until April 2017, please mention the recent trials of tapered doses of vancomycin and fidaxomicin (PMID 29273269, PMID: 28591789; PMID 29255732).</td>
<td>We agree that these trials are all relevant, and have updated the guideline accordingly.</td>
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<td></td>
<td>Recommendation II is less clear. How have the authors interpreted the literature that a tapered dosage of vancomycin before FMT increases the success rate of FMT? Are these studies also available for fidaxomicin?</td>
<td>There are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT (Hota et al, 2017). The safety profile of these medications is well-established from large randomised controlled trials, whilst randomised studies involving FMT have tended to be smaller, and have more variable patient follow-up. Furthermore, FMT remains (in the UK) an unlicensed medicine. As such, on the balance of safety, the working group agreed that antimicrobial/ antitoxin therapy associated with reduced CDI recurrence should be considered prior to FMT. Reflecting the uncertainties in this area within the reviewed literature, the relevant recommendation is ‘conditional’ rather than ‘strong’.</td>
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<td></td>
<td>Recommendation iii is difficult to understand; do the authors recommend to treat severe and complicated CDI not with vancomycin, but with fidaxomicin or vanco+bezlo? If a recurrence occurs, then followed by a FMT?</td>
<td>The wording of this recommendation has been amended, along with expansion of the explanatory text of Section 8.1.1.4.</td>
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<td></td>
<td>A recommendation for FMT treatment in severe (refractory), complicated CDI is missing (e.g. multiple sequential FMTs); should this also be accompanied with anti-CDI antibiotics? See review v. Beurden, Ther Advances in Gast, 2017 and Fischer, Ali Pharm Ther 2015</td>
<td>As stated in Section 8.1.1.2, there are a relatively small number of cases reported in the reviewed literature of refractory CDI. As such, the working group are unable to give recommendations that patients with refractory CDI receiving FMT should be managed in any particular way differently to those with recurrent CDI.</td>
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<tr>
<td>8.1.2.1</td>
<td>We suggest to differentiate between &quot;non-responding&quot; and &quot;late failure&quot;. The latter can be defined as a relapse of CDI after an initial response to FMT. For instance, use of antibiotics in the first month after FMT may provoke a new episode of CDI. This new episode doesn’t need a FMT and can be treated with conventional anti-CDI treatment, preferably microbiota sparing such as fidaxomicin.</td>
<td>We agree that this distinction is useful, and have amended the guideline accordingly.</td>
</tr>
<tr>
<td>8.1.2.2</td>
<td>Should a psychological questionnaire routinely be taken from recipients (before and after FMT) and from donors (regularly)? A ten-week follow-up is too short to recognize long term side-effects of FMT.</td>
<td>The working group did not consider that this was a priority.</td>
</tr>
<tr>
<td>8.1.2.3</td>
<td>We consider swallowing disorders a contraindication for upper GI delivery; death of a patient due to aspiration pneumonia with upper GI delivery has been described (PMID: 29026601); this patient had a swallowing disorder following oropharyngeal radiation after surgical removal of a maxillary carcinoma.</td>
<td>We note that this patient received a very large volume (500ml) of nasoduodenal FMT. This guideline recommends a much lower maximum volume with the specific aim of minimising this problem. Nevertheless, we agree that this is an important consideration, and have amended Section 8.1.2.3 and Section 8.5.2.2 accordingly.</td>
</tr>
<tr>
<td>8.2.1</td>
<td>What is the advice of the committee for coeliac patients with recurrent CDI?</td>
<td>The working group did not have any specific advice regarding patients with coeliac disease.</td>
</tr>
<tr>
<td>8.2.2</td>
<td>FMT in immunocompromised patients: we think that the presence of neutropenia (&lt;0.5 × 10⁹/L) can be considered as a contraindication for FMT, especially if hematological patients are treated with</td>
<td>The working group have recommended that FMT is offered ‘with caution’ to immunosuppressed patients, reflecting the careful individualised assessment required for each patient.</td>
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<td>8.2.3</td>
<td>The effect of FMT on the IBD status for IBD patients with rCDI is under discussion. Is it possible that FMT will result in cure of CDI but an exacerbation of IBD. Should we differentiate UC from CD? Ref 71 suggests that IBD can worsen. The recommendation &quot;strong&quot; is debatable. Is the IBD group not a better candidate for vancomycin tapering, fidaxomicin (tapering) or bezlotoxumab before FMT is given?</td>
<td>We agree with the comment regarding matching donors and immunosuppressed recipients for EBV and CMV status, and have updated Section 8.2.2 and Section 8.3.4 accordingly. We agree that there is evidence that FMT to treat CDI in patients with IBD may be associated with a flare of IBD activity (Qazi et al, 2017); we have updated the recommendation accordingly.</td>
</tr>
<tr>
<td>8.3.2</td>
<td>Age and BMI of the donor. We agree with the BMI of the donor but have some difficulties with the age. We consider an age above 50 as a contraindication, based on the risks to develop colon carcinoma and metabolic (diabetes) diseases. Additionally, older people seems to have a less stable gut microbiota.</td>
<td>We note from a recent paper that Bacteroides: Firmicutes ratio and microbial diversity were similar in donors &gt; 60 years compared to younger donors, and donations from older donors had similar efficacy and no higher rate of adverse outcomes (Anand et al, 2017). As such, the working group agreed to uphold their prior recommendation.</td>
</tr>
<tr>
<td>8.3.3</td>
<td>Donor screening history. Donors should also undergo a long term follow-up to recognize microbiota related diseases, including colon malignancies, autoimmune diseases, metabolic diseases and psychiatric illnesses.</td>
<td>We agree with the principle of this statement, and allude to this in Section 8.7.7.</td>
</tr>
<tr>
<td>8.3.4</td>
<td>Screening of the donor. Table 4. The Dutch guideline advises screening donors for multi-drug resistant bacteria (MDR), including VRE, MRSA, CPE and ESBL-producing Gram-negatives, and quinolone/aminoglycoside resistant Enterobacteriaceae. Most of the patients with rCDI have much comorbidity and are frequently hospitalized or encounter nosocomially acquired infections, such as</td>
<td>We agree with the suggestion, and have amended Section 8.3.3 accordingly. The working group reviewed their recommendation regarding screening for multi-drug resistant bacteria, and Section 8.3.4 has been updated accordingly.</td>
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We agree with the principle of a ‘window period’/ quarantine prior to repeat donor screening in centres using frozen FMT;
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<td>UTI. Infections with MDR are more difficult to treat, mostly with intravenously administered antibiotics. If these patients become colonized with MDR they should be nursed with specific infection control precautions. We also apply a &quot;window period&quot;; donors stools samples are stored in quarantine for 2 months and only become available after a negative second screening. We additionally screen for: <em>Yersinia enterocolitica</em>, <em>Yersinia pseudotuberculosis</em>, <em>Plesiomonas shigelloides</em>, shiga toxin producing <em>E. coli</em> (not only 0157 E.coli), Astrovirus, Sapovirus, Adenovirus, Enterovirus, Parechovirus, Hepatitis E, <em>Entamoeba histolytica</em>, <em>Microsporidium</em> species, <em>Blastocystis hominis</em>, <em>Dientamoeba fragilis</em>, and Strongyloides (if a travel history to Middle and South America, Africa, or Asia is present). We advise to include carriersonship of <em>E. histolytica</em> and Strongyloides to the mandatory screening, because of the serious infections that occur in immunocompromised patients. We have detected unexpectedly a donor carrying <em>E. histolytica</em> (Terveer, CMI, 2017).</td>
<td>Section 8.3.5 has been updated accordingly, and a new flow chart to illustrate the process (Figure 1) added. The working group agreed that recommendations should be made to test for Shiga toxin-producing <em>Escherichia coli</em>, hepatitis E IgM, <em>Entamoeba histolytica</em> serology and <em>Strongyloides stercoralis</em> IgG (Table 3). However, the working group consensus was that screening with the other tests suggested is not justified.</td>
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<tr>
<td>8.4.1</td>
<td>Recommendation i. Please elucidate how donors should deliver their stools. We favour the use of specific device systems to prevent contamination with environmental microorganisms. Recommendation ii. Processing within 6 hours is proven effective, consider changing ‘conditional’ to ‘strong’ recommendation Recommendation iii. A meta-analysis concludes that less than 50 gram of feces is related to a 4-fold increase in recurrence rates. The recommendation status should be changed to ‘strong’.</td>
<td>i. We think that the text as it stands gives sufficient information about best practice in this area. ii. We agree with this suggestion, and have amended Section 8.4.1 accordingly. iii. We agree with this suggestion, and have amended Section 8.4.1 accordingly.</td>
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<tr>
<td>8.4.2</td>
<td>An important advantage of frozen FMT is the possibility to use a “window period” of, for example, two months. When donors are screened after this window period, the results determine if the stored FMTs can be used. We have cross-referenced Section 8.4.2 to Section 8.3.5, where the concept of a window period/quarantine is discussed in more detail.</td>
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<td>8.4.3</td>
<td>We think that there is not enough evidence to state that feces suspensions can only be used up to six months from preparation. There is no sufficient data that show a decreased efficacy with feces suspensions stored over 6 months. Additionally, multiple stool banks set the expiration date at 1 year after storage. A trend towards decrease in the viability of certain gut bacterial groups was noted when faecal aliquots were frozen in 10% glycerol for six months (Costello et al, Alimentary Pharm &amp; Ther, 2015), and as such, the working group agreed that six months was the acceptable limit for freezing of an FMT in glycerol. This rationale is now within the text.</td>
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<td>Good practice point: Thawing overnight in a 4C refrigerator is also a good and much used alternative. None of the working group had sufficient experience with this means of thawing FMT, and as such were unable to make this good practice point.</td>
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<td>8.5.1.1</td>
<td>It is not clear, why the administration of a bowel lavage in upper GI administration, of PPI, of loperamide and of metoclopramide are recommended. There is no evidence to support their use, and all of them are drugs with known side effects. The only reason why they are used is that the first RCT used them. However, the RCT did not assess their importance, and there are many case series showing that FMT has a high success rate even without their use. All of these interventions have a clear biological or practical rationale for their use. Significant side effects in association with a single dose of these medications are generally rare, and their use has not been associated with adverse outcomes in FMT studies. Our recommendations for their use are only conditional. As such, the working group uphold their recommendations.</td>
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<tr>
<td>8.5.2.1</td>
<td>Not all capsules necessarily contain lyophilized microbiota, frozen preparations have also been shown to be effective. We agree with this comment, and have updated the guideline accordingly.</td>
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<tr>
<td>8.5.2.2</td>
<td>Are there studies indicating that 50 ml for upper gastrointestinal have comparable efficacy as 250 ml? If not, this should be more pronounced mentioned, also in the research session. We use at least 50 gram suspended in 200 ml and a slow infusion of 10cc/min. As described in the text, the working group considered that mass of stool was a more important consideration than volume of diluent. They also noted that as low as 25ml of FMT has been demonstrated to be effective as upper GI FMT (Aas et al, Clin Infect Dis, 2003). However, the working group revised their decision, and now recommend 100ml as the threshold volume for upper GI FMT administration.</td>
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<td>8.5.2.4.</td>
<td>The recommendation not to use capsules seems rather strong. It is unlikely that concerning transmission of infection, the risk would differ in any way from other ways of administration. Also, no safety concerns based on endoscopic complications can possibly arise. We would therefore not pronounce a recommendation against use.</td>
<td>We agree with this statement. Of note, whilst the Kao et al, 2017 study (RCT of capsulised vs colonoscopic FMT) was not published at the time of initial searches, it has been identified by updated searches and has now been reviewed by the working group. As such, the guideline has been updated accordingly.</td>
</tr>
<tr>
<td>8.6</td>
<td>Consider to add that specific donor microbiota may have better outcomes (e.g. donor B in Moayyedi, gastroenterology, 2015) FMT for other conditions than rCDI. Why have the authors not included the role of FMT to eradicate MDR from the intestinal tract?</td>
<td>Reference to Donor B in this paper has been added to Section 8.6.2.2.</td>
</tr>
<tr>
<td>8.6.3.</td>
<td>Consider adding: characterisation of specific CU patient population that would potentially benefit from FMT. “However, recommendations for clinical use for this indication cannot be made until there is clearer evidence of the most appropriate CU patient characteristics, methodology for its preparation, route of delivery, and intensity of administration of FMT”</td>
<td>We agree with this comment, and have updated the guideline accordingly.</td>
</tr>
<tr>
<td>8.7.2 and 8.7.4</td>
<td>FMT is considered as a medicinal product under supervision of MHRA and licensing should follow the GMP guidelines. The activities should be performed in a dedicated containment level 2 laboratory with personal protective equipment and a quality assessment system. Does this indicate that FMTs should be prepared under GMP conditions at the Pharmacy Department and not within the Medical Microbiology? Or is this statement too strong?</td>
<td>No. MHRA guidance does not specify where the manufacture should take place. This could be pharmacy, the microbiology laboratory, or another place.</td>
</tr>
<tr>
<td>8.7.6</td>
<td>Please consider to add that aliquots of donor FMT materials (and original feces samples) used for patients treatment should be stored,</td>
<td>We agree, and we have updated Sections 6.3 and 8.7.6 accordingly.</td>
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<td>enabling to use these samples when adverse effects after FMT developed. This should also been included in 6.3 (auditing).</td>
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<tr>
<td>Table 4</td>
<td>PCRs are more sensitive than conventional microscopy and antigen tests for parasites. Second, can the authors please specify the parasites? There is some debate on the significance of Blastocystis spp. and Dientamoeba spp. Why is only E. coli 157 excluded and not other STEC pathogens?</td>
<td>Table 4 has been updated to specify Shiga toxin-producing <em>Escherichia coli</em> screening by PCR. The working group did not consider that specific screening for <em>Blastocystis spp</em> or <em>Dientamoeba spp</em> was justified.</td>
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<tr>
<td>Propose to add: Eligibility of patients for FMT</td>
<td>At the NDFB, all requests by the treating physician are evaluated by at least two clinical members of our feces bank board to determine the eligibility of the patient. It is required that patients have a laboratory documented episode of recurrent CDI following at least one course of adequate CDI antibiotic therapy. Recurrent CDI is defined as the re-appearance of diarrhoea (≥ 3 unformed stools per 24 hours for two consecutive days; or ≥ 8 unformed stools per 48 hours) within eight weeks after cessation of antibiotic therapy in combination with a positive diagnostic test for <em>C. difficile</em>. We strongly recommend a two-stage testing algorithm, as recently advised by the <em>C. difficile</em> working group/ESCMID (ESGCD). Using this algorithm, we reject approximately 20% of all requests for FMT. We would like to add our experience that of 79 candidate patients for FMT, only 75% were considered as suitable candidates for FMT treatment; most rejected requests were patients with underlying IBD who concomitantly carried <em>C. difficile</em>.</td>
<td>Thank you for this comment. Definitions of recurrent CDI are outside of the remit of this working group. Testing is discussed in Section 8.1.1., where we refer to current ESCMID guidance.</td>
</tr>
<tr>
<td>Need for antimicrobial stewardship after FMT (also for 8.5.1.3)</td>
<td>After FMT, we advise that an infectious disease specialist or medical microbiologists should be involved for antibiotic treatment (or prophylaxis) of the patient during the first month after FMT, since 50% of our registered failures were patients who received antibiotics within one month after FMT. Interestingly, all patients responded to conventional anti-CDI treatment and did not need a second FMT. It can be considered to use microbiota sparing fidaxomicin after FMT.</td>
<td>We agree with this comment, and have updated Section 8.5.1.3 accordingly.</td>
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<td>Title (e.g. Dr, Mr, Ms, Prof)</td>
<td>Dr</td>
</tr>
<tr>
<td>Name</td>
<td>Majdi Osman</td>
</tr>
<tr>
<td>Job title or role</td>
<td>Clinical Program Director, OpenBiome; Visiting Assistant Professor, Harvard Medical School</td>
</tr>
<tr>
<td>Address and post code</td>
<td>200 Inner Belt Road, Somerville, MA 02143</td>
</tr>
<tr>
<td>Telephone number</td>
<td>+1 (617) 575-2201</td>
</tr>
<tr>
<td>Email address</td>
<td><a href="mailto:majdi@openbiome.org">majdi@openbiome.org</a></td>
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Please provide comments on the draft guideline on the form below, putting each new comment in a new row. When feeding back, please note the section you are commenting on (for example, section 1 Introduction and line number). If your comment relates to the guideline as a whole then please put ‘general’. Add extra rows if required.
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<tr>
<td>8.1.1.1. Recurrent <em>Clostridium difficile</em> infection</td>
<td>“FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe CDI (strong).” We agree however for full clarity we would recommend re-wording to: “FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe-complicated CDI (strong).”</td>
<td>We agree with this statement, and have updated the guideline accordingly.</td>
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<td>8.1.1.2. Refractory <em>Clostridium difficile</em> infection:</td>
<td>“FMT should be considered in cases of refractory CDI (conditional).” We agree.</td>
<td>Thank you for this comment.</td>
</tr>
<tr>
<td>8.1.1.3. Antimicrobial therapy prior to considering FMT for patients with CDI:</td>
<td>i. FMT for recurrent CDI should only be considered after failure of antimicrobial anti-<em>C. difficile</em> therapy which has been administered for a minimum of 10 days (conditional). ii. Recipients of FMT as treatment for recurrent CDI should have previously been treated with extended/ pulsed vancomycin and/or fidaxomicin (conditional). iii. For those with severe or complicated CDI, which appears to be associated with reduced cure rates, consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin and bezlotoxumab), before offering FMT (conditional).</td>
<td>Pre-planned subgroup analysis of patients with severe CDI in a randomised trial demonstrated a significantly lower recurrence rate when treated with fidaxomicin (13.0%, n=12/92) than when treated with vancomycin (26.6%, n=29/209) (Louie <em>et al</em>, 2011); this finding was replicated in another randomised controlled trial, with 8.3% (n=4/48) and 32.6% (n=14/43) experiencing a recurrence respectively (Cornely <em>et al</em>, 2012). In a further randomised trial, bezlotoxumab (together with standard of care antibiotics) was shown to reduce recurrence of severe CDI compared to standard of care antibiotics alone (10.9% (n=6/55) vs 20% (n=13/65) respectively) (Wilcox <em>et al</em>, 2017). The working group noted that there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study...</td>
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complicated CDI before FMT. There is little evidence on the role of bezlotoxumab and fidaxomicin in severe or severe-complicated CDI. Although the evidence base is similarly lacking for FMT in severe or severe-complicated disease, there is a growing body of evidence from trials, multiple case series and reports indicating the potential for FMT in this population.

Bezlotuxumab: The performance of bezlotoxumab has not been evaluated in a severe or severe-complicated population. Results from MODIFY I and II suggest a modest 10% improvement in rates of sustained cure with bezlotoxumab. Importantly, only 15.6% were severe CDI. Based on the modest gains in efficacy and the few severe/severe-complicated patients in the MODIFY trials, we feel that further evidence is required before proposing bezlotuxumab be offered ahead of FMT in this patient population.

In comparison, across similar patient populations FMT has demonstrated in several randomized controlled trials reduced risk of recurrence. Based on the available evidence we therefore feel that the statement that bezlotoximab is “associated with reduced risk of recurrence” compared to FMT is not supported by the evidence.

Fidaxomicin: Similarly, there is a dearth of evidence on the role of fidaxomicin in the severe CDI population. We agree that it has demonstrated superior efficacy compared to vancomycin in the general CDI population. In an RCT comparing extended-pulsed fidaxomicin versus vancomycin for CDI, Guery et al (2017) observed increased recurrence in severe CDI compared to non-severe CDI with an odds ratio 0.57 (95% CI 0.36–0.91) p=0.019. We therefore recommend that fidaxomixin should be offered to patients with severe CDI. However, there is no evidence to suggest that the comparing a vancomycin taper to FMT (Hota et al, 2017). The working group agreed that in the absence of this evidence, on the balance of safety and potential risks, consideration should be given to using antimicrobial/antitoxin therapy associated with reduced CDI recurrence prior to considering the use of FMT.
performance of fidaxomicin would be better than FMT. We acknowledge that access to fidaxomicin is likely to be more timely in settings where FMT is not readily available.

**The role of FMT in severe CDI:** In their recent review, Van Beurden et al (2017) reviewed the literature on FMT in severe CDI and found 23 reports (12 case reports; 11 case series) about FMT as treatment for severe or complicated CDI. The patients described (n=200) all had severe or complicated CDI, did not respond to conventional CDI antibiotic treatment and received FMT as last resort treatment. In all studies, patients were treated with (sequential) FMT, whether or not followed by additional antibiotic treatment for CDI. FMT, with or without additional antibiotic CDI treatment, appears to be a promising curative treatment option in patients with severe and complicated CDI who do not respond sufficiently to conventional antibiotic treatment. FMT has been proposed by Fischer et al (2015) as an option utilizing an endoscopic response-guided approach, which may be particularly useful in non-surgical candidates. In an open-label cohort study (n = 17), FMT was delivered by colonoscopy. If pseudomembranes were identified, patients reinitiated oral vancomycin 24 hour after FMT and continued for 5 days. A repeat FMT by colonoscopy was given on day 7. If pseudomembranes persisted, vancomycin was restarted the following day for a 5 days course and a third FMT was offered on day 13. If pseudomembranes were absent during any colonoscopy, no further therapy was initiated. The results were promising with a combined clinical cure rate of 88%.

In conclusion, we agree that there is a lack of evidence available to make a strong recommendation on the role of FMT in severe CDI. However, there is insufficient evidence to suggest that fidaxomicin
or bezlotuximab would be superior to FMT in this population. On the contrary, the growing pool of experience in using FMT in severe and severe-complicated CDI patients demonstrates that it appears to be generally safe and effective (quality of evidence: 3).

We would therefore suggest re-wording point iii to:

**iii. For those with severe or complicated CDI, which appears to be associated with reduced cure rates, consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin or bezlotuxumab), or offering FMT (conditional).**


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<td>8.1.2.1. Management of FMT failure:</td>
<td><strong>Further FMT should be offered after initial FMT failure (strong).</strong> We agree.</td>
<td>Thank you for this comment.</td>
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<td>8.1.2.2. General approach to follow-up post-FMT:</td>
<td><strong>All FMT recipients should routinely receive follow-up. Given the relative novelty of FMT and the potential for unexpected sequelae, clinicians should follow-up FMT recipients for long enough to fully</strong></td>
<td>Thank you for this comment. In light of other comments from the working group and stakeholders, this follow-up period has been adjusted to ‘at least eight weeks in total’.</td>
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| 8.1.2.3. Management of the FMT recipient: | *establish efficacy/ adverse events, and at least ten weeks in total (strong).*  
   
   We agree.  
   
   **i.** Immediate management after endoscopic administration of FMT should be as per endoscopy unit protocol *(strong).*  
   
   **ii.** Patients should be warned about short term adverse events, in particular the possibility of self-limiting GI symptoms. They should be advised that serious adverse events are rare *(strong).*  
   
   **iii.** After enteral tube administration, patients may have the tube removed and oral water given from 30 minutes post-administration *(strong).*  
   
   We agree.  
   
   Thank you for this comment. |
| 8.1.2.4. Definition of cure post-FMT for CDI: | *A decision regarding cure/remission from CDI should be recorded during follow-up. However, this has no uniformly-agreed definition, and should be decided on a case-by-case basis (strong).*  
   
   We agree.  
   
   Thank you for this comment. |
| 8.1.2.5. Definition of treatment failure post-FMT for CDI: | *Treatment failure/recurrence should be defined on a case-by-case basis. Routine testing for C. difficile toxin after FMT is not recommended, but is appropriate to consider in the case of persistent CDI symptoms/suspected relapse (strong).*  
   
   When testing is to be performed, we would recommend clinicians follow the 2016 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for CDI testing, which state that no single commercial test can be used as a stand-alone test for diagnosing CDI, and recommend a 2-step approach (highly sensitive with reflex to highly specific test). These guidelines recommend performing an initial test with a high negative predictive value;  
   
   We agree on the use of ESCMID guidelines in CDI testing, and refer to these clearly in Section 8.1.1.1. However, Section 8.1.2.5 specifically refers to diagnosing failure post-FMT for CDI rather than initial diagnosis of CDI, and no good uniform definition exists for this. We think that the guidance given, to define treatment failure on a case-by-case basis, is the most fair summary of the current literature on this topic.  
   
   We agree. |
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<td>therefore, if negative, no further testing needs to be done. Specifically, they suggest glutamate dehydrogenase (GDH) EIA or NAAT/PCR testing. Our recommendation is GDH EIA as it is less expensive and has a slightly superior NPV at higher CDI prevalence compared with NAAT/PCR (98 vs 96 at hypothetical CDI prevalence of 50%), and an NPV of 100% at lower CDI prevalence. The second test should be a test with a high positive predictive value, such as EIA for toxin A/B. Obtaining CDI testing at each suspected CDI recurrence and working with institutional laboratories to use an appropriate testing algorithm is a key component to ensuring appropriate patient selection for FMT. As currently worded, the recommendations risk encouraging over testing in a context where patients may develop post-infectious IBS. This concept is highlighted by evidence suggesting that up to 25% of patients referred to an FMT center for “C difficile infection” were found to have an alternative diagnosis, with younger patients being more likely to have a non-CDI diagnosis (Jackson 2016). Jackson M, Olefson S, Machan JT, Kelly CR. A high rate of alternative diagnoses in patients referred for presumed clostridium difficile infection. J Clin Gastroenterol. 2016 Oct;50(9):742-6.</td>
<td>The working group thought it important to emphasise the ‘good practice point’ that in patients with true anaphylaxis, the risks of FMT administration were likely to outweigh the benefits. As such, this suggestion has not been incorporated.</td>
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<td>8.2.1. General approach to co-morbidities and FMT:</td>
<td><strong>FMT should be offered with caution in patients with decompensated chronic liver disease and should be avoided in those with anaphylactic food allergy (strong).</strong> The authors may want to consider the approach recommended by Allegretti et al (2017). In patients with a severe food allergy, a potential option for FMT could be from a patient identified donor living with the patient (e.g. spouse) who avoids the same allergens.</td>
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<td>8.2.2.</td>
<td>FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (strong).</td>
<td>Thank you for this comment.</td>
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| 8.2.3. | **Recommendation:**  
i. FMT should be offered to those with recurrent CDI and inflammatory bowel disease (strong).  
ii. FMT should be considered for appropriate patients with recurrent CDI regardless of other comorbidities (conditional). | Thank you for this comment. |
| 8.3.1. | Related or unrelated donors should both be considered acceptable. However, where possible, FMT is best sourced from a centralised stool bank, from a healthy unrelated donor (conditional). | Thank you for this comment. |
| 8.3.2. | People should only be considered as potential FMT donors if they are ≥18 and ≤60 years old, and have a BMI of <30 kg/m² (conditional). | Thank you for this comment. |
| 8.3.3. | A donor-screening history/ questionnaire is mandatory (Table 2) (strong).  
1. Receipt of antimicrobials within the past three months. | |
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<td>2.</td>
<td>Known prior exposure to HIV and/or viral hepatitis, and known previous or latent tuberculosis.</td>
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<td>3.</td>
<td>Risk factors for blood-borne viruses - including high risk sexual behaviours, use of illicit drugs, any tattoo/body piercing/needlestick injury/blood transfusion/acupuncture, all within previous six months.</td>
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<td>4.</td>
<td>Receipt of a live attenuated virus within the past six months.</td>
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<td>5.</td>
<td>Underlying gastrointestinal conditions (e.g. history of IBD, IBS, chronic diarrhoea, chronic constipation, coeliac disease, bowel resection or bariatric surgery).</td>
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<td>6.</td>
<td>Family history of any significant gastrointestinal conditions (e.g. family history of IBD, or colorectal cancer).</td>
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<td>7.</td>
<td>History of atopy (e.g. asthma, eosinophilic disorders).</td>
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<td>8.</td>
<td>Any systemic autoimmune conditions.</td>
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<td>9.</td>
<td>Any metabolic conditions, including diabetes and obesity.</td>
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<td>10.</td>
<td>Any neurological or psychiatric conditions, or known risk of prion disease.</td>
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<td>11.</td>
<td>History of chronic pain syndromes, including chronic fatigue syndrome and fibromyalgia.</td>
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<td>12.</td>
<td>History of any malignancy.</td>
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<td>13.</td>
<td>Taking particular regular medications, or such medications within the past three months, i.e. antimicrobials, proton pump inhibitors, immunosuppression, chemotherapy</td>
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<td>14.</td>
<td>History of receiving growth hormone, insulin from cows, or clotting factor concentrates.</td>
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<td>15.</td>
<td>History of receiving an experimental medicine or vaccine within the past six months.</td>
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8.3.4. Laboratory screening of potential donors:

Blood and stool screening of donors is mandatory (Tables 2 and 3) (strong).

Table 3: Recommended blood screening for stool donors:

Pathogen screening:
- Hepatitis A IgM
- Hepatitis B (HBsAg and HbcAb)
- Hepatitis C antibody
- Hepatitis E IgM
- HIV -1 and -2 antibodies
- HTLV-1 and -2 antibodies
- Treponema pallidum antibodies (TPHA, VDRL)
- Epstein-Barr virus IgM
- Cytomegalovirus IgM
- Strongyloides stercoralis IgG
- Entamoeba histolytica serology

General/ metabolic screening:
- Full blood count with differential.
- Creatinine and electrolytes
- Liver enzymes (including albumin, bilirubin, aminotransferases, gamma-glutamyltransferase and alkaline phosphatase).
- C-reactive protein

Table 4: Recommended stool screening for stool donors:
- Clostridium difficile PCR
- Campylobacter, Salmonella, and Shigella by standard stool culture and/or PCR
- Escherichia coli 0157 H7 by culture and/or PCR

We agree with the comment regarding matching donors and immunosuppressed recipients for EBV and CMV status, and have updated Section 8.2.2 and Section 8.3.4 accordingly.

The working group did not think that screening for adenovirus was justified.

Whilst vancomycin-resistant Enterococci (VRE) carriage is relatively common in the community (probably related to food consumption) (Endtz et al, 1997), the form of VRE in the community is genetically distinct from that found nosocomially, with much lower pathogenicity in community forms (Willems et al, 2005). As such, the working group strongly opined that routine screening was not justified. However, it was acknowledged that the potential infection risk from VRE (and MRSA) would vary regionally depending on local prevalence and pathogenicity, and as such a local risk assessment has been recommended to decide whether screening for these organisms should be considered.
We recommend:

**CMV and EBV**: Given the high rates of carriage for both EBV and CMV in a healthy, adult population, excluding EBV or CMV positive donors would make it prohibitively difficult to identify suitable donors to provide access to care (Bate et al). Moreover, excluding EBV or CMV positive candidates is not expected to provide a significant benefit to the majority of the patients that would be served by a centralized stool bank, who are not severely immunocompromised.

Given the need to ensure a reliable supply of material for the vast majority of rCDI patients while protecting severely immunocompromised patients, until now OpenBiome has chosen not to test for EBV and CMV. Instead, we treat material as presumptively CMV and EBV positive and discourage use in severely immunocompromised patients who are seronegative for CMV or EBV.

We are sensitive to the fact that this leaves clinicians with an additional challenge for managing these already difficult cases (severely immunocompromised rCDI patients). Should FMT be indicated then we would suggest that in the immunocompromised
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<td>patient at risk of CMV or EBV infection either: 1) CMV and EBV testing of the recipient to confirm positive serology, in which case FMT may be considered after extensive discussion of the risks, benefits, and alternatives in the informed consent process; or 2) the use of a directed donor with matching serology.</td>
<td>Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988-2004. Clin Infect Dis. 2010;50:1439–1447.</td>
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<td>Adenovirus: We recommend including adenovirus on stool in addition to norovirus and rotavirus.</td>
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<td>Vancomycin resistant enterococcus (VRE): VRE should be specifically mentioned in “Multi-drug resistant bacteria”. VRE is a leading cause for donor exclusion despite prospective donors having no known risk factors for colonization.</td>
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<td>Further final screening should take place prior to collection of a stool sample for processing into FMT (strong).</td>
<td>Thank you for this comment. In light of this and other comments, the recommendation on repeat screening has been strengthened.</td>
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| Recommendation:  
  i. Donor stool collection should follow a standard protocol (strong).  
  ii. Donor stool should be processed within 6 hours of defecation (conditional).  
  iii. Both aerobically and anaerobically prepared FMT treatments should be considered suitable when preparing FMT for the treatment of recurrent CDI (strong). | Thank you for this comment. |
### Section 8.4.2. Fresh vs frozen FMT:

**The use of banked frozen FMT material should be considered preferable to fresh preparations for CDI (strong).**

We agree.

Thank you for this comment.

### Section 8.4.3. Use of frozen FMT:

**Recommendation:**

- FMT material stored frozen at -80°C should be regarded as having a maximum shelf life of six months from preparation (strong).

**Good practice point:**

- Consider thawing frozen FMT should at ambient temperature and using within six hours of thawing (conditional).

We agree.

Thank you for this comment.

### Section 8.5.1. Use of specific medications in the period around FMT administration:

**Recommendation:**

- Bowel lavage should be administered prior to FMT via the lower GI route, and bowel lavage should be considered prior to FMT via the upper GI route; polyethylene glycol preparation is preferred (conditional).

We agree.

Thank you for this comment.
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| 8.5.1.1. General principles of FMT administration: | *ii.* For upper GI FMT administration, a proton pump inhibitor should be considered, e.g. the evening before and morning of delivery (conditional).  
  
  *iii.* Loperamide (or other anti-motility drugs) should be considered following lower GI FMT delivery (conditional).  
  
  **Good practice point:**  
  *i.* Prokinetics (such as metoclopramide) should be considered prior to FMT via the upper GI route (conditional).  
  
  *ii.* Best practice for prevention of further transmission of CDI should be applied throughout when administering FMT to patients with CDI (nursing with enteric precautions, sporicidal treatment of endoscope, etc).  
  
  We agree. | |
| 8.5.1.2. Additional antibiotics pre-FMT: | Consider further antimicrobial treatment for CDI for at least 72 hours prior to FMT (conditional).  
  
  We agree. | Thank you for this comment. |
| 8.5.1.3. Washout period between antibiotic use and FMT: | To minimise any deleterious effect of antimicrobials on the FMT material, there should be a minimum washout period of 24 hours between the last dose of antibiotic and treatment with FMT (strong).  
  
  We agree. | Thank you for this comment. |
| 8.5.2.2. Upper gastrointestinal tract administration of FMT: | **Recommendation:**  
  
  *i.* Upper GI administration of FMT as treatment for recurrent or refractory CDI should be used where clinically appropriate (strong).  
  
  *ii.* Where upper GI administration is considered most appropriate, FMT administration should be via nasogastric, | Thank you for this comment. In light of further discussion by the working group, the maximum volume of FMT recommended by upper GI administration is now 100ml. |
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<td>nasoduodenal, or nasojejunal tube, or alternatively via upper GI endoscopy. Administration via a permanent feeding tube is also appropriate (strong).</td>
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<td>Good practice point: It is recommended that no more than 50ml of FMT is administered to the upper GI tract (conditional).</td>
<td>We agree.</td>
<td>We agree with this suggestion, and have updated the guideline accordingly.</td>
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| 8.5.2.3. Lower gastrointestinal tract administration of FMT: | **Recommendation:** i. Colonoscopic administration of FMT as treatment for recurrent or refractory CDI should be used where appropriate (strong).  
ii. Where colonoscopic administration is employed, consider preferential delivery to the caecum or terminal ileum, as this appears to give the highest efficacy rate (conditional).  
iii. FMT via enema should be used as a lower GI option when colonoscopic delivery is not possible (strong). | |
| We recommend rewording point iii. Although there is limited data, flexible sigmoidoscopy may be the preferred route of delivery where colonoscopic delivery is not possible. Several experts have advised less invasive modalities such sigmoidoscopy in high risk patients (Brandt 2013; Kelly 2014). This may provide a more effective method for delivering material as proximally as possible and improving retention. We therefore recommend re-wording point iii to:  
FMT via enema should be used as a lower GI option when colonoscopic or flexible sigmoidoscopy delivery is not possible (strong). | | |
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<td><strong>8.5.2.4. Capsulised FMT:</strong></td>
<td><strong>Capsulised FMT holds promise as a treatment option for recurrent CDI, but further evidence regarding its safety and efficacy is awaited, and it should not be considered for use at present (conditional).</strong></td>
<td>We largely agree with this comment. Whilst the Kao et al, 2017 study was not published at the time of initial searches, it has been identified by updated searches and has now been reviewed by the working group. The guideline has been updated accordingly.</td>
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<td>There is a growing body of evidence on encapsulated FMT and the delivery modality presents a potential option in circumstances where it may be inappropriate, contraindicated, or contrary to patient preferences to deliver material via traditional routes of administration for CDI.</td>
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<td>In terms of patient perceptions, Zipursky and colleagues report that more aesthetically appealing FMT formulations, such as capsules, would both eliminate potential barriers to treatment and reduce the necessity for healthcare resources and procedure time for clinicians. Capsules appear well tolerated. For example, the mean time of 30 capsule administration is approximately 20 minutes (range 10-30 minute) (Allegretti, unpublished data).</td>
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<td>Although the optimal dose is still under investigation (as with other FMT delivery modalities), there have been several studies that have shown equivalent efficacy rates. Youngster and colleagues reported their experience with a capsule formulation that averaged 1.6 grams</td>
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<td>of stool per capsule in which they dosed 15 capsules on 2 consecutive days. They reported a 70% cure rate after an initial dose in a cohort of 140 patients. Those that failed to achieve cure were re-treated, bringing the cumulative cure rate up to 90%.</td>
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<td>Similarly, Hirsch and colleagues demonstrated a clinical cure rate of 68% in the 19 participants, using capsules containing purified, concentrated, and cryopreserved fecal bacteria and this increased to 89% with retreatment.</td>
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<td>Allegretti and colleagues conducted the first dose-finding study for FMT capsules (0.75 grams of stool per capsule with upper GI release) assessing 30 capsules once (low dose) versus 30 capsules on 2 consecutive days (high dose). Efficacy rates between the groups were similar on initial dose (70%) and there were no adverse events reported.</td>
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<td>Lastly the largest randomized control trial to date of FMT used encapsulated FMT with good safety and efficacy outcomes equivalent to colonoscopy FMT. In Kao et al’s non-inferiority randomized clinical trial (cited in the guidelines) that included 116 adults with rCDI, the proportion without recurrence over 12 weeks was 96.2% after a single treatment in a group treated with oral capsules and in a group treated via colonoscopy. Given this 1+ level of evidence, in addition to multiple smaller studies of encapsulated FMT, we feel that there is a good body of evidence to support the short-term safety of encapsulated FMT. We agree that further evidence is needed on optimal dosing and formulation, however this applies to all delivery modalities.</td>
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<td>We agree that capsule availability is very limited in the UK at present however this shouldn’t preclude guidelines recommending this as a potential FMT delivery option.</td>
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<td>We therefore recommend rewording the 8.5.2.4 to:</td>
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<td>25</td>
<td><strong>Capsulised FMT holds promise as a treatment option for recurrent CDI and should be offered to patients as a potential treatment modality. Capsule preparations should follow a standard protocol. Further evidence regarding its optimal dosing and formulation is needed (conditional).</strong></td>
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<td>Zipursky JS, Sidorsky TI, Freedman CA, Sidorsky MN, Kirkland KB. Patient attitudes toward the use of fecal microbiota transplantation</td>
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| 8.6. What is the clinical effectiveness of faecal microbiota transplant in treating conditions other than Clostridium difficile infection? | *FMT is not currently recommended as treatment for inflammatory bowel disease. There is insufficient evidence to recommend FMT for any other gastrointestinal or non-gastrointestinal disease (strong).*  
We agree. | Thank you for this comment. |
| 8.7. Basic requirements for implementing a FMT service | *The development of FMT centres should be encouraged (strong).*  
We agree. | Thank you for this comment. |
| 8.7.5. FMT manufacturing: | *Ensure traceability of supply (strong).*  
We agree. | Thank you for this comment. |
| FMT in patients with IBD | We recommend emphasizing the importance of counselling patients with IBD on the risk of flare or worsening IBD activity post-FMT. | We agree with this comment, and have updated Section 8.2.3. accordingly. |
| FMT in paediatric populations | A recommendation on paediatric FMT should be include. The evidence base is limited but safety and efficacy appears comparable to adult FMT. Patients and caregivers should be counselled on the unknown long-term risks of FMT.  
Recommen| FMT in the paediatric setting is outside of the remit of this working group. We have updated Section 5.4 to clarify this. |

**Closing date:** Please forward this electronically by 5pm on January 2018 at the very latest to consultations@his.org.uk
The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

Benjamin H Mullish*,1,2, Mohammed Nabil Quraishi*,3, Jonathan P Segal*,1,4, Victoria L McCune*,6, Melissa Baxter7, Gemma L Marsden8, David Moore9, Alaric Colville7, Neeraj Bhala3,9,10, Tariq H Iqbal3,10, Christopher Settle11, Graziella Kontkowski12, Ailsa L Hart4, Christopher M Hawkey6, Horace RT Williams1,2, Simon D Goldenberg13,14.

1. Division of Integrative Systems Medicine and Digestive Disease, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK.
2. Departments of Gastroenterology and Hepatology, St Mary’s Hospital, Imperial College Healthcare NHS Trust, Paddington, London, UK.
3. Department of Gastroenterology, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.
4. Inflammatory Bowel Disease Unit, St Mark’s Hospital, Harrow, London, UK.
6. Institute of Microbiology and Infection, University of Birmingham, Birmingham, UK.
7. Department of Microbiology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK.
9. Institute of Applied Health Research, University of Birmingham, Birmingham, UK.
10. Institute of Translational Medicine, University of Birmingham, Edgbaston, Birmingham, UK.
11. Department of Microbiology, City Hospitals Sunderland NHS Foundation Trust, Sunderland, UK.
12. CDiff Support, UK.
13. Centre for Clinical Infection and Diagnostics Research, King’s College London, London, UK.
14. Department of Microbiology, Guy’s and St Thomas’ NHS Foundation Trust, London UK.

*Joint first authors.

○ Joint senior authors.

□ Corresponding author.
“NICE has accredited the process used by the Healthcare Infection Society to produce ‘The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines’. The NICE accreditation of HIS methodology is valid for 5 years from March 2015. More information on accreditation can be viewed at http://www.nice.org.uk/about/what-we-do/accreditation”

Versions of this Guideline are published simultaneously in The Journal of Hospital Infection and Gut. http://dx.doi.xxxxx. The Editors of the Journals have agreed that joint publication of the article is justified to ensure dissemination of the guidance to all relevant healthcare professionals.

1. **Executive summary:**

Interest in the therapeutic potential of faecal microbiota transplant (FMT) has been increasing globally in recent years, particularly as a result of randomised studies in which it has been used as an intervention. The main focus of these studies has been the treatment of recurrent or refractory Clostridium difficile infection (CDI), but there is also an emerging evidence base regarding potential applications in non-CDI settings. The key clinical stakeholders for the provision and governance of FMT services in the United Kingdom (UK) have tended to be in two major specialty areas: gastroenterology and microbiology/infectious diseases. While the National Institute for Health and Care Excellence (NICE) guidance (2014) for use of FMT for recurrent or refractory CDI has become accepted in the UK, clear evidence-based UK guidelines for FMT have been lacking. This resulted in
discussions between the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS), and a joint BSG/HIS FMT working group was established. This guideline document is the culmination of that joint dialogue.

2. Lay summary:
Faecal microbiota transplant (FMT) involves the transfer of a sample of faeces from a healthy donor to a recipient. There are several different ways to administer the transplant, including via endoscopy, rectally as an enema, via nasogastric/nasoenteral tube (tube passed through the nose into the stomach/upper part of the small intestine), or via oral ingestion of capsules that contain faecal material. The transplant may either be administered fresh (i.e. immediately after preparation), or may be prepared in advance, stored in a freezer and thawed when required. FMT is an accepted and effective treatment for recurrent infection by Clostridium difficile, a bacterium which can cause severe illness with diarrhoea, most commonly in frail elderly populations as a complication of antibiotic use. Despite adequate treatment, Clostridium difficile infection recurs in about 25% of patients, and some may suffer multiple recurrences.

This guideline reviews the evidence for FMT as a treatment for Clostridium difficile infection (CDI) and other conditions. Recommendations are made for: which patients are most likely to benefit, how donors should be selected and screened, how FMT should be prepared and administered, how patients should be followed up, and how FMT services should be configured.

3. Introduction:
The aim of the British Society of Gastroenterology (BSG)/Healthcare Infection Society (HIS) faecal microbiota transplant (FMT) working group was to establish a guideline that defined best practice in all aspects of a FMT service, by providing evidence-based recommendations wherever possible, and consensus multi-disciplinary expert opinion where specific published evidence is currently lacking.
This included the evaluation of the use of FMT in the treatment of Clostridium difficile infection (CDI; also referred to as Clostridioides difficile [1]), and also in potential non-CDI indications. Relevant guidance published to date includes the interventional procedure guidance from the National Institute for Health and Care Excellence (NICE) [2], UK, European and US microbiological guidelines on the treatment of Clostridium difficile infection (CDI) [3–5], and recent expert consensus documents on FMT in clinical practice [6,7]. Furthermore, there have also been national
recommendations regarding FMT produced by working groups in several different countries [8–10]. Principally as a result of randomised studies that have been published in recent years [11–18], FMT has become an accepted treatment for recurrent/refractory CDI.

The unique remit and objectives of this guideline when commissioned by the BSG and HIS were:

i. To review the rapidly-growing body of randomised trial evidence for the efficacy of FMT in the treatment of adults (≥18 years), both in CDI and in other clinical conditions, much of which has been published after the publication of current CDI treatment algorithms [3,4].

ii. To provide specific guidance about best practice for an FMT service within the context of the regulatory framework for the intervention as it currently exists in the UK [19,20].

The elucidation of the mechanisms underlying the efficacy of FMT in treating CDI remains an active area of global research, with the aim of rationalising FMT from its current crude form to a more targeted, refined therapeutic modality [21]. Previous research has demonstrated that commensal bacteria cultured from the stool of healthy donors [22], sterile faecal filtrate [23], and/or spores of Firmicutes derived from ethanol-treated stool from healthy donors [24] may have similar efficacy to conventional FMT in treating CDI, although results of the latter approach produced disappointing outcome data when extended to a Phase II clinical trial [25]. For the purposes of this guideline, the BSG/HIS working group considered only studies that used the administration of manipulated whole stool (including encapsulated faeces). They deemed studies using cultured microorganisms (or their proteins, metabolites or other components), or microbiota suspensions, to be in the pre-clinical research stage, without firm evidence.

FMT has been shown to be very acceptable to patients, both in the setting of CDI [11,26] and in non-CDI settings, e.g. ulcerative colitis [27]. However, the absence of appropriate protocols [28–31] specifically taking into account UK clinical practice and regulation of FMT has been perceived as a barrier to the use of FMT in the UK and Ireland: these guidelines seek to rectify this problem.

4. Guideline Development Team

4.1. Acknowledgements
The authors would like to acknowledge the support of the Gut Microbiota for Health Expert Panel of the British Society of Gastroenterology, along with that of the Healthcare Infection Society. They would also like to thank Ian Rees from the MHRA for contributions regarding the legal aspects and clinical governance of FMT within the UK and beyond.

4.2. Source of funding

There was no external funding for this work. BHM is the recipient of a Medical Research Council Clinical Research Training Fellowship (grant reference: MR/R000875/1). BHM and HRTW receive support from the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre (BRC) based at Imperial College Healthcare NHS Trust and Imperial College London.

4.3. Disclosure of potential conflict of interest

- THI: Acted as consultant, advisor or speaker for Pharmacosmos and Shield Therapeutics.
- ALH: Acted as consultant, advisory board member or speaker for AbbVie, Atlantic, Bristol-Myers Squibb, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. ALH also serves on the Global Steering Committee for Genentech.
- SDG: Received consultancy fees, speaker fees and research grant support from Astellas between 2015-2017; received consultancy fees and speaker fees from MSD between 2015-2017; and received consultancy fees in 2017 from Pfizer.
- All other authors declared no conflict of interest.

4.4. Relationship of authors with sponsor

BSG and HIS commissioned the authors to undertake the Working Party Report. The authors represent the membership of both societies.

4.5. Responsibility for guidelines

The views expressed in this publication are those of the authors, and have been endorsed by BSG and HIS following consultation.

5. Working Party Report
5.1. **What is the Working Party Report?**

The report is a set of recommendations covering key aspects of safe and efficacious delivery of a FMT service for recurrent/ refractory *Clostridium difficile* infection (CDI). The guidelines also review the evidence for the use of FMT for non-CDI indications.

The diagnosis and management of *Clostridium difficile* infection in general are outside the remit of these guidelines.

The working group recommendations have been developed systematically through multi-disciplinary discussions based on published evidence. They should be used in the development of local protocols for all relevant healthcare settings.

5.2. **Why do we need a Working Party Report for this topic?**

There is widespread and growing interest in the use of FMT as a treatment for recurrent CDI. The previous absence of randomised trials and lack of evidence-based guidelines describing best practice related to its use has led to uncertainty as to how to establish an FMT service. Existing services may be providing suboptimal clinical care. There is now a developing portfolio of randomised study evidence (including randomised controlled trial data) regarding the use of FMT in CDI and non-CDI indications, providing the opportunity to develop an evidence-based guideline for its use. There have also been recent changes to the UK regulatory framework for FMT (see Section 9.7), which are not well-understood by clinicians.

5.3. **What is the purpose of the Working Party Report’s recommendations?**

The main purpose is to inform clinicians about the use of FMT (and about the establishment of an FMT service) for the treatment of recurrent and refractory CDI, and other possible future indications. The recommendations provide an evidence-based approach to a high quality clinical service, with appropriate governance structures. This document also serves to illustrate areas in which there are current gaps in knowledge, which will help to direct future areas of research.

5.4. **What is the scope of the guidelines?**
The main scope of the guidelines is to provide guidance for the optimal provision of an effective and safe FMT service, principally for recurrent or refractory CDI, but non-CDI indications are also considered. These guidelines only apply to adult patients (≥18 years); the working party did not consider the role of FMT in the treatment of either CDI or non-CDI indications in children or young people. The guidelines were written with a focus on UK practice, but also with consideration of more global practice as it applied.

5.5. What is the evidence for these guidelines?
Questions for review were derived from the Working Party Group, which included patient representatives in accordance with the PICO process [32]. To prepare these recommendations, the working group collectively reviewed relevant peer-reviewed research. Methods are described fully below; they were in accordance with SIGN 50 [33] and the Cochrane Collaboration [34].

5.6. Who developed these guidelines?
The working group included gastroenterologists, infectious diseases/microbiology clinicians, a clinical scientist, a systematic reviewer, and patient representatives.

5.7. Who are these guidelines for?
Any healthcare practitioner may use these guidelines and adapt them for their use. It is anticipated that users will include clinical staff, as well as healthcare infection prevention and control teams. It is expected that these guidelines will raise awareness of FMT amongst clinicians who care for patients with recurrent or refractory CDI, but who may be unaware that it is a feasible and accessible treatment option. The guidelines are also designed to be read by patients with CDI, helping them to understand whether FMT may be an appropriate treatment option for them.

5.8. How are the guidelines structured?
Each section comprises an introduction, a summary of the evidence base with levels, and a recommendation graded according to the available evidence.

5.9. How frequently are the guidelines reviewed and updated?
The guidelines will be reviewed at least every four years and updated if change(s) in the evidence are sufficient to require a change in practice.

5.10. Aim
The primary aim of this report was to assess the current evidence for all aspects relating to provision of an FMT service as treatment for recurrent or refractory CDI. A secondary aim was to review the current evidence for the efficacy of FMT in treating non-CDI conditions.

6. Summary of guidelines:
6.1. Which patients with *Clostridium difficile* infection should be considered for faecal microbiota transplant, and how should they be followed up after treatment?

6.1.1. Prior to faecal microbiota transplant. Patient selection:
6.1.1.1. Recurrent *Clostridium difficile* infection:
Recommendation:
FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe-complicated CDI (strong).

6.1.1.2. Refractory *Clostridium difficile* infection:
Recommendation:
FMT should be considered in cases of refractory CDI (conditional).

6.1.1.3. FMT as initial therapy for *Clostridium difficile* infection:
Recommendation:
FMT should not be administered as initial treatment for CDI (strong).

6.1.1.4. Antimicrobial/ antitoxin therapy prior to considering FMT for patients with CDI:
Recommendations:

i. FMT for recurrent CDI should only be considered after recurrence of symptoms following resolution of an episode of CDI that was treated with appropriate antimicrobials for at least 10 days (conditional).

ii. Consider treatment with extended/ pulsed vancomycin and/or fidaxomicin before considering FMT as treatment for recurrent CDI (conditional).

iii. For those with severe or complicated CDI, which appears to be associated with reduced cure rates, consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin and bezlotoxumab), before offering FMT (conditional).

6.1.2. Post-FMT follow-up, outcomes and adverse events:

6.1.2.1. Management of FMT failure:

Recommendation:

Further FMT should be offered after initial FMT failure (strong).

6.1.2.2. General approach to follow-up post-FMT:

Recommendation:

All FMT recipients should routinely receive follow-up. Clinicians should follow-up FMT recipients for long enough to fully establish efficacy/adverse events, and for at least eight weeks in total (strong).

6.1.2.3. Management of the FMT recipient:

Recommendations:

i. Immediate management after endoscopic administration of FMT should be as per the endoscopy unit protocol (strong).

ii. Patients should be warned about short term adverse events, in particular the possibility of self-limiting GI symptoms. They should be advised that serious adverse events are rare (strong).
After enteral tube administration, patients may have the tube removed and oral water given from 30 minutes post-administration (strong).

6.1.2.4. Definition of cure post-FMT for CDI:

Good practice point:

A decision regarding cure/remission from CDI should be recorded during follow-up. However, this has no uniformly-agreed definition, and should be decided on a case-by-case basis (strong).

6.1.2.5. Definition of treatment failure post-FMT for CDI:

Good practice point:

Treatment failure/recurrence should be defined on a case-by-case basis. Routine testing for C. difficile toxin after FMT is not recommended, but it is appropriate to consider in the case of persistent CDI symptoms/suspected relapse (strong).

6.2. What recipient factors influence the outcome of faecal microbiota transplant when treating people with Clostridium difficile infection?

6.2.1. General approach to co-morbidities and FMT:

Good practice points:

i. FMT should be avoided in those with anaphylactic food allergy (strong).

ii. FMT should be offered with caution to patients with CDI and decompensated chronic liver disease (conditional).

6.2.2. Immunosuppression and FMT:

Recommendation:

FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (strong).

Good practice point:
Immunocompromised FMT recipients at risk of severe infection if exposed to EBV or CMV should only receive FMT from donors negative for EBV and CMV (strong).

6.2.3. Other comorbidities and FMT:
Recommendations:

i. FMT should be offered to those with recurrent CDI and inflammatory bowel disease, but patients should be counselled about a small but recognised risk of exacerbation of IBD (strong).

ii. FMT should be considered for appropriate patients with recurrent CDI regardless of other comorbidities (conditional).

6.3. What donor factors influence the outcome of faecal microbiota transplant when treating people with Clostridium difficile infection?

6.3.1. General approach to donor selection:
Recommendation:

Related or unrelated donors should both be considered acceptable. However, where possible, FMT is best sourced from a centralised stool bank, from a healthy unrelated donor (conditional).

6.3.2. Age and BMI restrictions for potential donors:
Recommendation:

People should only be considered as potential FMT donors if they are ≥18 and ≤60 years old, and have a BMI of ≥18 and ≤30 kg/m² (conditional).

6.3.3. General approach to the donor screening assessment:
Recommendation:
It is mandatory to screen potential donors by questionnaire and personal interview, to establish risk factors for transmissible diseases and factors influencing the gut microbiota (Table 1) (strong).

6.3.4. Laboratory screening of potential donors:

Recommendation:

Blood and stool screening of donors is mandatory (Tables 2 and 3) (strong).

6.3.5. Repeat donor checks, and donation pathway:

Recommendations:

i. In centres using frozen FMT, before FMT may be used clinically, donors should have successfully completed a donor health questionnaire and laboratory screening assays both before and after the period of stool donation. This is the preferred means of donor screening (strong).

ii. In centres using fresh FMT, a repeat health questionnaire should be assessed at the time of each stool donation. To ensure ongoing suitability for inclusion as a donor, the donor health questionnaire and laboratory screening should be repeated regularly (strong).

6.4. What factors related to the preparation of the transplant influence the outcome of faecal microbiota transplant when treating people with Clostridium difficile infection?

6.4.1. General principles of FMT preparation:

Recommendations:

i. Donor stool collection should follow a standard protocol (strong).

ii. Donor stool should be processed within 6 hours of defaecation (strong).

iii. Both aerobically and anaerobically prepared FMT treatments should be considered suitable when preparing FMT for the treatment of recurrent CDI (strong).
iv. Sterile 0.9% saline should be considered as an appropriate diluent for FMT production, and cryoprotectant such as glycerol should be added for frozen FMT (strong).

v. Use ≥50g of stool in each FMT preparation (strong).

Good practice points:

i. Stool should be mixed 1:5 with diluent to make the initial faecal emulsion (conditional).

ii. Homogenisation and filtration of FMT should be undertaken in a closed disposable system (conditional).

6.4.2. Fresh vs frozen FMT:

Recommendation:

The use of banked frozen FMT material should be considered preferable to fresh preparations for CDI (strong).

6.4.3. Use of frozen FMT:

Recommendation:

FMT material stored frozen at -80°C should be regarded as having a maximum shelf life of six months from preparation (strong).

Good practice points:

i. Consider thawing frozen FMT at ambient temperature, and use within six hours of thawing (conditional).

ii. Do not thaw FMT in warm water baths, due to the risks of cross contamination with *Pseudomonas* (and other contaminants) and reduced bacterial viability (strong).
6.5. **What factors related to administration of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?**

6.5.1. **Use of specific medications in the period around FMT administration:**

6.5.1.1. **General principles of FMT administration:**

Recommendations:

i. Bowel lavage should be administered prior to FMT via the lower GI route, and bowel lavage should be considered prior to FMT via the upper GI route; polyethylene glycol preparation is preferred (conditional).

ii. For upper GI FMT administration, a proton pump inhibitor should be considered, e.g. the evening before and morning of delivery (conditional).

iii. A single dose of loperamide (or other anti-motility drugs) should be considered following lower GI FMT delivery (conditional).

Good practice points:

i. Prokinetics (such as metoclopramide) should be considered prior to FMT via the upper GI route (conditional).

ii. Best practice for prevention of further transmission of CDI should be applied throughout when administering FMT to patients with CDI (nursing with enteric precautions, sporicidal treatment of endoscope, etc).

6.5.1.2. **Additional antibiotics pre-FMT:**

Recommendation:

Administer further antimicrobial treatment for CDI for at least 72 hours prior to FMT (strong).

6.5.1.3. **Washout period between antibiotic use and FMT:**

Recommendation:
To minimise any deleterious effect of antimicrobials on the FMT material, there should be a minimum washout period of 24 hours between the last dose of antibiotic and treatment with FMT (strong).

Good practice point:

Consider consultation with infectious disease specialists or medical microbiologists for advice whenever FMT recipients also have an indication for long-term antibiotics, or have an indication for non-CDI antibiotics within eight weeks of FMT (conditional).

6.5.2. Route of FMT delivery:

6.5.2.1. Upper gastrointestinal tract administration of FMT:

Recommendations:

i. Upper GI administration of FMT as treatment for recurrent or refractory CDI should be used where clinically appropriate (strong).

ii. Where upper GI administration is considered most appropriate, FMT administration should be via nasogastric, nasoduodenal, or nasojejunal tube, or alternatively via upper GI endoscopy. Administration via a permanent feeding tube is also appropriate (strong).

Good practice points:

i. It is recommended that no more than 100ml of FMT is administered to the upper GI tract (conditional).

ii. Upper GI administration of FMT should be used with caution in those with swallowing disorders (strong).

6.5.2.2. Lower gastrointestinal tract administration of FMT:

Recommendations:
i. Colonoscopic administration of FMT as treatment for recurrent or refractory CDI should be used where appropriate (strong).

ii. Where colonoscopic administration is used, consider preferential delivery to the caecum or terminal ileum, as this appears to give the highest efficacy rate (conditional).

iii. FMT via enema should be used as a lower GI option when delivery using colonoscopy or flexible sigmoidoscopy is not possible (strong).

6.5.2.3. Capsulised FMT:

Recommendation:

Capsulised FMT holds promise as a treatment option for recurrent CDI and should be offered to patients as a potential treatment modality where available. Capsule preparations should follow a standard protocol. Further evidence regarding optimal dosing and formulation is required (conditional).

6.6. What is the clinical effectiveness of FMT in treating conditions other than *Clostridium difficile* infection?

Recommendation:

FMT is not currently recommended as treatment for inflammatory bowel disease. Apart from CDI, there is insufficient evidence to recommend FMT for any other gastrointestinal or non-gastrointestinal disease (strong).

6.7. Basic requirements for implementing a FMT service

6.7.1. General considerations:

Good practice points:

i. The development of FMT centres should be encouraged (strong).

ii. FMT centres should work to raise awareness about FMT as a treatment option amongst clinicians caring for patients with CDI, and provide training to relevant
healthcare professionals on the practicalities of delivering an FMT service (conditional).

6.7.2. Legal aspects and clinical governance:

Good practice point:
In the UK, FMT must be manufactured in accordance with MHRA guidance for human medicines regulation. When FMT is supplied on a named patient basis, within a single organisation, a pharmacy exemption may be used, subject to ensuring proper governance and traceability. All centres that are processing and distributing FMT should seek guidance from the MHRA and where necessary obtain appropriate licenses prior to establishing an FMT service. This is a legal requirement. In countries other than the UK, FMT should only be manufactured following appropriate approval from the national authority of that country (strong).

6.7.3. Multidisciplinary teams:

Good practice point:
A multidisciplinary team should be formed to deliver FMT services (strong).

6.7.4. Infrastructure:

Good practice point:
Utilise suitable laboratory facilities and infrastructure for FMT production (strong).

6.7.5. FMT manufacturing:

Good practice point:
Ensure traceability of supply (strong).

6.7.6. FMT production quality control:

Good practice point:
Monitor, notify and investigate all adverse events and reactions related to FMT (strong).

6.7.7. **Donor screening governance:**

Good practice point:

Ensure the clinical governance of donor screening (strong).

7. **Implementation of these guidelines:**

7.1. **How can these guidelines be used to improve clinical effectiveness?**

Primarily, these guidelines will inform the development of local FMT services and appropriate local operational protocols, and will guide clinical decision-making. They also provide a framework for clinical audit, a tool for improving clinical effectiveness. In addition, the future research priorities identified by the working group will allow researchers to refine applications to funding bodies.

7.2. **How much will it cost to implement these guidelines?**

Where FMT is being provided under a MHRA license according to Good Manufacturing Practice (GMP) standards, there are significant costs associated with initial setup and maintenance of the service. These include the cost of obtaining the relevant license, laboratory design and equipment to enable quality assurance, storage facilities for samples, etc. However, there is counterbalance to this, as the expectation of the working group is that the publication of this guideline may encourage provision of FMT as treatment for recurrent or refractory CDI. This has consistently been shown to be cost effective in comparison with anti-*C. difficile* antimicrobial therapy [35–38], so overall costs associated with treating the condition may actually decrease. Furthermore, there may be changes to the practice of clinicians already offering the service. For example, encouraging the use of healthy unrelated donors (who can provide multiple stool donations after one screening) reduces the cost of screening when compared to the use of an FMT recipient’s relative as donor, who is likely to provide one donation only.

7.3. **Summary of audit measures**
• All donors to have completed initial screening questionnaires and blood and stool screening results, as well as final health check prior to each stool donation processed to FMT. Results from each subsequent serial round of screening also to be documented.

• All FMT recipients to have clear documentation of details of their disease course and preparation prior to FMT, including whether recurrent or refractory disease, previous antimicrobial courses, and use of bowel purgatives/other preparatory medications pre-FMT.

• All FMT recipients to have sufficient documentation to allow clear traceability of the exact FMT aliquot transfused. Records should include identification of the donor, in addition to a frozen FMT aliquot (and original faecal sample) - as well as serum - from that donor.

• All FMT recipients for recurrent or refractory CDI to have documentation during follow-up of treatment success or failure (and subsequent treatment plan if failure), together with clear documentation of any adverse events that may be attributable to FMT.

7.4. E-learning tools:
Continuing Professional Development questions and their answers are provided for self-assessment in Appendix 4 of this document.

8. Methodology:

8.1. Evidence appraisal
Questions for review were derived from the Working Party Group, which included patient representatives in accordance with the PICO process [32]. Methods were in accordance with SIGN 50 [33] and the Cochrane Collaboration [34].

8.2. Data sources and search strategy
A systematic literature search was undertaken using MEDLINE and EMBASE databases, and the Cochrane Library, for relevant articles published from 1st January 1980 to 1st January 2018. The MEDLINE and EMBASE strategy is shown in Appendix 2ii of this document. Free text and MESH/index terms for faecal microbial transplant and Clostridium difficile or other diseases of interest were combined. In addition, conference proceedings from microbiology, infectious disease and gastroenterology conferences were also searched to identify additional studies.
8.3. Study eligibility and selection criteria

The members of the guideline group determined criteria for study inclusion. Two reviewers (BHM, MNQ) screened the titles and abstracts of each article for relevance independently; any disagreements were resolved by discussion with a third reviewer (JPS). Copies of relevant articles were obtained and assessed for inclusion as evidence in the guideline by all three reviewers. The reason for not selecting studies was recorded. Only articles published in English and human clinical studies were included. For evidence on FMT for CDI, both randomised studies (including randomised controlled trials (RCTs)) and case series with at least 10 patients were selected. Only randomised trials were included as evidence for FMT for non-CDI indications. Conference abstracts were only included for CDI and non-CDI indications if they reported a randomised trial; where abstracts were available reporting data from a randomised trial that was subsequently published, only the published paper was reviewed.

8.4. Data extraction and quality assessment

The initial search identified 2658 publications, and of these, 802 duplicates were excluded. From here, 1856 studies were subsequently screened, from which 78 studies were assessed by reviewing the full text for eligibility (see Appendix 2iii of this document and Additional Appendix D). Of these 78 studies, 58 studies were included as the basis of evidence for writing this guideline. In total, 39 were case studies in CDI including at least 10 patients (see Additional Appendix C.1), and ten were randomised studies in CDI (see Additional Appendix C.2). Nine were randomised trials for non-CDI indications (see Additional Appendix C.3). Data were extracted for patient demographics, disease characteristics, donor screening characteristics, stool preparation and administration, clinical outcomes and adverse events. The quality of randomised studies was assessed with the Cochrane Collaboration’s risk of bias tool. Case series were assessed using the Centre for Reviews and Dissemination guidance.

8.5. Rating of evidence and recommendations

Evidence tables were presented and discussed by the working group, and guidelines were prepared according to the nature and applicability of the evidence regarding efficacy and patient preference and acceptability. For the HIS version of this guideline, the strength of evidence was defined by SIGN [33] (Table 4A), and the strength of recommendation was adopted from GRADE (Grades of Recommendation Assessment, Development and Evaluation) [39] (Table 4B). In addition, where there was no clear evidence or a paucity of evidence, good practice recommendations were made by
expert experience and consensus. The section entitled ‘Basic requirements for implementing an FMT service’ was based on expert opinion, since this was a key area of the working party’s remit but not one amenable to evaluation by the PICO process. Face-to-face meetings and group teleconferences were held to agree on recommendations. Any disagreements on recommendations or the strength of recommendation were resolved by discussion and, where necessary, voting by the members of the working group, with consensus achieved when >80% were in agreement.

8.6. Consultation process

Feedback on draft guidelines was received from the Scientific Development Committee (SDC) of HIS, and changes made. These guidelines were then opened to consultation with relevant stakeholders (see Appendix 3 of this document). The draft report was available on the HIS website for one month. Views were invited on format, content, local applicability, patient acceptability, and recommendations. The working group reviewed stakeholder comments, and collectively agreed revisions. Final changes were made after repeat reviews from HIS (chair of the SDC and HIS Council) and BSG (BSG CSSC and BSG Council), and after further external peer review.

9. Rationale for recommendations:

9.1. Which patients with Clostridium difficile infection should be considered for faecal microbiota transplant, and how should they be followed up after treatment?

9.1.1. Prior to faecal microbiota transplant. Patient selection:  

9.1.1.1. Recurrent Clostridium difficile infection:

As already described, there is widespread consensus that FMT is an efficacious treatment for recurrent CDI. In defining recurrent CDI, some studies have relied on a minimum threshold of return of clinical symptoms (e.g. at least three unformed bowel movements within 24 hours, for at least two consecutive days) [12,18] following previous successful CDI treatment; most studies have also included a requirement for a positive microbiological test [12,14,18,40–50]. Other studies explicitly state that a positive test was not required [51]. Recommendations for CDI testing are beyond the scope of this guideline, and there are already well-established evidence-based guidelines [52]. These recommend testing with either a nucleic acid amplification test (NAAT) or glutamate dehydrogenase (GDH) assay, followed by detection of free toxin (either by toxin A/B enzyme immunoassay (EIA) or cytotoxin neutralisation assay), which allows differentiation of patients with active disease as well as those who are likely colonised [52]. However, the working group discussed
the importance of the accurate diagnosis of true recurrent CDI prior to consideration of FMT; in particular, they noted a study which observed that of 117 patients with presumed recurrent CDI referred for work-up for FMT, 25% (n=29/117) were determined to have a non-CDI diagnosis, with irritable bowel syndrome (n=18) and inflammatory bowel disease (n=3) being the most common alternative diagnoses, and younger patients more likely to be misdiagnosed [53].

All of the reviewed studies have included patients with recurrent CDI but some studies offered FMT to patients at the first recurrence (second episode) [12,15,16,18,40,42,47,48,51,54], whereas others offered FMT after the second recurrence (third episode) [13,14,44,46,49,50,55,56]. Some protocols offered FMT after three or more recurrences [57], while others did not define the point at which it was administered [45,58].

The severity of infection has been used as a parameter to decide at which stage FMT is offered. Youngster et al. offered FMT to patients with at least three episodes of mild to moderate CDI, or at least two episodes of severe CDI resulting in hospitalisation and associated with significant morbidity [17]. Another study selected patients for FMT using four categories of severity, which also accounted for prior anti-CDI therapy and requirement for hospitalisation [59].

None of the studies directly compared the efficacy of FMT according to the stage at which it was offered (i.e. first recurrence vs. ≥ two recurrences). A small number of studies [60–62] included patients with severe CDI (defined as hypoalbuminaemia with increased peripheral white cell count and/or abdominal tenderness) or complicated CDI (defined as admission to Intensive Care, altered mental status, hypotension, fever, ileus, white blood cell count > 30 x 10⁹/l, lactate > 2.2mmol/l, or evidence of end organ damage). A single study described an apparent lower rate of treatment success when FMT was used to treat patients with recurrent CDI with disease caused by ribotype 027 [48], but this is the case for all anti-CDI treatment modalities for this ribotype in comparison with others. The working group agreed that there was insufficient evidence to suggest that C. difficile ribotype should influence whether or not FMT is offered.

A lower primary cure rate was reported for complicated CDI (66%) compared with recurrent CDI (82%) and severe CDI (91%) in one study [60]; in a case series of 17 patients who all had severe and/or complicated CDI, a primary cure rate of 88% was described [62]. A cohort of 328 patients was analysed to determine which factors were associated with failure of FMT [63]. Higher early (one month) failure rates were found in patients with severe (72%, n=19/25) or severe-complicated CDI
(52.9%, n=9/17) than for recurrent CDI (11.9%, n=34/286). This study also identified that patients who were treated with FMT as an inpatient were nearly four times more likely to fail as those who had FMT as an outpatient; however, the working group noted that the authors of this study themselves identified that in-patient status is likely a proxy of severity of CDI and/or co-morbidities.

A further similar study, including 64 patients treated with FMT as treatment for recurrent CDI, also identified severe CDI as the strongest independent risk factor for FMT failure on multivariate analysis [64].

The working group discussed their experience of treating patients with CDI whose disease fitted an intermediate pattern to the typical descriptions given of recurrent or refractory CDI, e.g. patients with CDI who have some (but incomplete) symptomatic improvement with anti-CDI antibiotics and worsening of disease when these are stopped. The experience of the working group was that such patients experienced excellent responses to FMT, and that these patients should be considered for FMT.

As FMT is currently an unlicensed medicine with poorly-studied long term sequelae, the working group considered that it should generally be reserved for patients who have had three or more episodes of infection. There are no studies directly comparing its effectiveness with some of the newer agents such as fidaxomicin or bezlotoxumab, hence this recommendation is made on the basis of safety. However, the working group agreed that it may be reasonable in certain patient groups with ongoing risk factors for further recurrence to offer FMT after the second episode.

Evidence:

The reviewed literature represents a wide variety of different study designs. However, regardless of design, there is consistent evidence that FMT is an effective therapy for people with recurrent CDI (quality of evidence: 1+).

Recommendation:

FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe and severe-complicated CDI (strong).
9.1.1.2. **Refractory *Clostridium difficile* infection:**

Two randomised trials allowed the recruitment of patients with refractory CDI. The first defined this as at least three weeks of ongoing severe symptoms despite standard antimicrobial therapy for CDI [17]. The second required persistent or worsening diarrhoea and one of the following: ongoing abdominal pain, fever > 38°C, or white blood cell count > 15x 10⁹/l despite oral vancomycin at a dose of 500mg four times daily for at least five days [16]. Both studies included only small numbers of patients with refractory CDI (n=4/20 (20%) and n=15/219 (6.8%), respectively). There did not appear to be any significant difference in primary outcome measure (clinical cure) in patients with recurrent or refractory CDI, although neither study was designed to assess this difference. There are also a number of case series in which FMT was given to patients with refractory CDI; however, outcome measures were not reported for these groups individually in these studies [42,43,59,65].

**Evidence:**

There is little consensus on the definition of refractory CDI, with some studies using the terms ‘refractory’ and ‘recurrent’ interchangeably (as well as other terms, e.g. ‘salvage therapy’).

Consequently, the quality of evidence for the utility of FMT in refractory cases of CDI is lower than for recurrent CDI. Standardisation of definitions will allow more robust comparison between patient cohorts (quality of evidence: 1-).

**Recommendation:**

*FMT should be considered in cases of refractory CDI (conditional).*

9.1.1.3. **FMT as initial therapy for *Clostridium difficile* infection:**

Experience of the use of FMT as initial therapy for CDI is very limited. In a case series of patients with CDI with ribotype 027, use of anti-CDI antibiotics together with nasogastric FMT within a week of diagnosis during an initial episode of CDI was associated with reduced mortality compared to using FMT only after the failure of three courses of antibiotics (mortality of 18.75% (n=3/16 patients) vs 64.4% (n=29/45 patients)) [66]. However, 37.5% (n=6/16) of the patients treated with FMT within a week of CDI diagnosis required further antibiotics and a second FMT within one month of the first FMT because of relapse [66]. In a small pilot randomised trial, patients were randomised to either
vancomycin or multi-donor FMT (administered either via upper or lower GI routes) as initial therapy for CDI; CDI resolution occurred in 88.9% (8/9) of patients with vancomycin, compared with 57.1% of patients (n=4/7) with one FMT, and 71.4% of patients (n=5/7) after two FMTs [67]. Given the small size of these studies and equivocal results, the working group concluded that the reviewed studies did not support CDI as initial therapy for CDI.

**Evidence:**

There is very little experience of FMT as use as initial therapy for CDI (quality of evidence: 3).

**Recommendation:**

**FMT should not be administered as initial treatment for CDI (strong).**

9.1.1.4. **Antimicrobial/ antitoxin therapy prior to considering FMT for patients with CDI:**

There are now at least two licensed agents (fidaxomicin and bezlotoxumab) which have been shown to significantly reduce the risk of recurrence compared with vancomycin [68,69]. There is also some evidence that pulsed/tapered dosing of vancomycin and fidaxomicin (including pulsed fidaxomicin [70]) results in fewer recurrences than with standard dosing of these agents [71,72] (although this finding has not been replicated in all studies [73]). Pre-planned subgroup analysis of patients with severe CDI in a randomised trial demonstrated a significantly lower recurrence rate when treated with fidaxomicin (13.0%, n=12/92) than when treated with vancomycin (26.6%, n=29/109) [68]; this finding was replicated in another randomised controlled trial, with 8.3% (n=4/48) and 32.6% (n=14/43) experiencing a recurrence respectively [74]. In a further randomised trial, bezlotoxumab (together with standard of care antibiotics) was shown to reduce recurrence of severe CDI compared with standard of care antibiotics alone (10.9% (n=6/55) vs 20% (n=13/65) respectively) [69].

As discussed above, the working group noted that there are no studies comparing FMT with fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT [12]. The working group agreed that in the absence of this evidence, on the balance of safety and potential risks, consideration should be given to using antimicrobial/antitoxin therapy associated with reduced CDI recurrence prior to considering the use of FMT.
Several studies specify that patients should be treated with anti-\textit{C. difficile} antibiotics for a minimum period of 10 days before diagnosing recurrent CDI and offering FMT \cite{12,15,16,18}.

\textbf{Evidence:}

There is evidence that particular antimicrobial agents reduce the likelihood of recurrence of CDI, but data comparing FMT to antimicrobial therapy is lacking (quality of evidence: 3).

\textbf{Recommendations:}

i. \textit{FMT for recurrent CDI should only be considered after recurrence of symptoms following resolution of an episode of CDI that was treated with appropriate antimicrobials for at least 10 days} (conditional).

ii. \textit{Consider treatment with extended/ pulsed vancomycin and/or fidaxomicin before considering FMT as treatment for recurrent CDI} (conditional).

iii. \textit{For those with severe or complicated CDI, which appears to be associated with reduced cure rates, consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin and bezlotoxumab), before offering FMT} (conditional).

\subsection*{9.1.2. Post-FMT follow-up, outcomes and adverse events:}

\textbf{Management of FMT failure:}

Where patients were deemed not to have responded to an initial FMT, many studies have offered repeat FMT and success rates have been excellent even in patients with a modest response to a first FMT \cite{14,15,17,18,40,48,51,56,59,75,76}. The success of a second FMT appears to be high whether treatment failure represents non-response to the first FMT, or a late failure (i.e. further relapse of CDI after an initial response); however, these terms have been defined variably between different studies (also see Section 9.1.2.5). Second FMTs have been offered as soon as 24-72 hours after an initial FMT for presumed non-response \cite{42,77,78}. For FMT failure in patients with pseudomembranous colitis, repeat FMT every three days until resolution of pseudomembranes has been a successful approach \cite{18}. Good outcomes in pseudomembranous disease have also been achieved through a protocol that routinely restarted five days of vancomycin if FMT failed, before offering another FMT \cite{78}. Other studies have demonstrated potential success in treating initial FMT failure with further antibiotics, including repeat FMT with vancomycin between procedures \cite{47}, or
anti-CDI antibiotics alone [40,47,48,50,56,75,76]. Patients unresponsive to two FMTs have been offered further FMT or antibiotic therapy [16], or even administration of intravenous immunoglobulin [40]. While the working group collectively agreed that there was strong evidence to recommend repeat FMT after initial FMT failure, they were not able to recommend a specific protocol for administering repeat FMT and/or maximum number of FMTs, given the wide heterogeneity of approach described within the reviewed literature.

**Evidence:**

Regardless of how failure is defined, there is good evidence that further FMT is efficacious at treating CDI after initial FMT failure (quality of evidence 1++).

**Recommendation:**

*Further FMT should be offered after initial FMT failure (strong).*

**9.1.2.2. General approach to follow-up post-FMT:**

Follow-up post-FMT (in terms of duration, modality and regimen for follow-up) varies considerably between studies, and is largely dependent on study design. Follow-up regimens vary not only between studies but within them too, reflecting the retrospective nature of many early FMT studies in CDI, where follow-up mostly reflected pragmatic routine clinical care.

Modalities of follow-up have included outpatient review [14,48,63,76,79,80], telephone interview [17,44,48,51,63,76,79] and case note/database review [40,44,45,47,48,50,51,54,56,59,75,76,79]. Follow-up duration has varied from 60 days [50] to 8 years [41], with very different durations used in each study. Once again, however, this variability in follow-up largely reflects the retrospective analysis of case series rather than being justified by any specific methodology. The working group decided by consensus that at least eight weeks of follow-up was appropriate post-FMT to fully assess efficacy and potential adverse events; this figure was also influenced by discussions regarding the time point after FMT at which a decision could be made regarding cure/remission of CDI (see Section 9.1.2.4).
Evidence:

The approach to following up patients after FMT varies considerably between studies, and is often pragmatically designed (quality of evidence: 3).

Recommendation:

All FMT recipients should routinely receive follow-up. Clinicians should follow-up FMT recipients for long enough to fully establish efficacy/adverse events, and for at least eight weeks in total (strong).

9.1.2.3. Management of the FMT recipient:

Procedural adverse events during administration of FMT have predominantly occurred with colonoscopic administration of FMT. These have included mild nausea and vomiting attributed to sedation for the colonoscopy, minor mucosal tears during colonoscopy [54,65], and microperforation following biopsy of an area of presumed ischaemic small bowel injury in a patient with chronically dilated small bowel (which resolved with conservative management [51]). One death occurred due to witnessed aspiration at the time of colonoscopy [65]. Faecal regurgitation and vomiting with temporal association to upper GI FMT administration has also been described (discussed further in Section 9.5.2.2) [81].

The predominant short term adverse events post-FMT for CDI are mild: self-limiting GI symptoms have been the most frequently reported adverse events. These may be related to the route of administration and include belching [15], nausea [15,16,54,65], abdominal cramps/ discomfort/ bloating/ pain [15,18,54,65,77], and diarrhoea [15,16,18,65]. One patient with a history of autonomic dysfunction experienced dizziness with diarrhoea after FMT [15]. These symptoms are typically short-lived, resolving in hours to days [15,16,18,54,77]. Minor subsequent adverse events have included a range of GI side effects including self-limiting abdominal discomfort [14,17,62,80], nausea [14,54,75], flatulence [14,16,17,46,47,54,62], self-limiting irregular bowel movements [46], C. difficile-toxin negative diarrhoea [57,60], constipation [14,15,47,60,75] and constitutional symptoms/ temperature disturbance [14,17].
As such, immediately post-endoscopic administration of FMT, most FMT centres typically manage patients using standard protocols for an endoscopic procedure [46,54], without any specific adaptations (apart from to reiterate advice about the possibility of self-limiting GI side effects, and the use of departmental infection control protocols). There is often a relatively short period of post-procedural observation [15,18]. Most studies allow patients to leave the administration site after the period of observation, although overnight observation was the protocol used for a cohort of very elderly patients with multiple comorbidities [56]. Where enteral tube administration is used, post-procedure management has ranged between removal of the tube after 30 minutes (following nasoenteral administration of 500ml of FMT [15]) to prompt post-procedure removal and oral water administration (after nasogastric administration of 90ml of FMT [77]), with no direct adverse outcomes in either case. The working group felt that removal of the tube at 30 minutes, with administration of water at this point, was a pragmatic approach.

The definition of post-FMT serious adverse events has varied between studies, but has included significant morbidity necessitating hospital admission and death in the follow-up period. Many of these events are described as not directly caused by the FMT, including the scenario of post-FMT severe CDI recurrences [77] and probable or certain CDI-related deaths [16,65,75] occurring in the context of FMT failure, or deaths related to patient comorbidities [17,60]. One patient was admitted to hospital with self-limiting abdominal pain post-FMT [65], and four patients with flares of inflammatory bowel disease [65]. Three patients underwent colectomy during the post-FMT follow-up period, with all related to ulcerative colitis and not believed to be due to CDI [65]. Other reported serious adverse events include recurrent urinary tract infection [15], fever during haemodialysis [15] and upper gastrointestinal haemorrhage after nasogastric FMT (in a patient taking non-steroidal anti-inflammatory drugs [56]), none of which were thought to be strongly linked to FMT. There have also been a number of new onset autoimmune, inflammatory and metabolic conditions described post-FMT, although these have been described from single centres only, with these findings not replicated elsewhere. Such conditions include microscopic colitis, Sjögren’s syndrome, follicular lymphoma, peripheral neuropathy, immune thrombocytopenia and rheumatoid arthritis [58,60].

Significant adverse events are therefore rare but well-described. Furthermore, the procedure is relatively novel, and longer-term follow-up data regarding safety are required. Therefore, the
working group opined that formal follow-up post-FMT to assess outcome and possible adverse events is essential.

The use of questionnaires to compare symptoms pre- and post-FMT is common. Specifically, data collected have included clinical response to symptom severity [60], stool frequency [15,17,51,60,62,77], stool consistency [14,15,77], abdominal pain or tenderness [60,62], rating of gastrointestinal symptoms [77], general well-being [60,77], days to improvement post-FMT [62], weight change [77], functional status [60], and changes in medication/use of antibiotics [62,77]. Additionally, certain patients have been given specific advice post-FMT to contact their clinical team if there is recurrence of diarrhoea or symptoms [14,40,46,48]. Where patients underwent outpatient clinical evaluation, this was generally undertaken relatively early post-FMT [44,57,80]. In one study, patients were additionally given instructions for cleaning and disinfection at home, with the aim of reducing the possibility of C. difficile reinfection [48], and counselling on the risk of recurrent CDI with future antibiotic courses [80].

Evidence:

Much of the short-term management of the FMT recipient describes general principles of best practice related to the route of administration. Many adverse events described following FMT are minor, and/or may not directly relate to the transplant itself (quality of evidence: 3).

Recommendations:

i. **Immediate management after endoscopic administration of FMT should be as per the endoscopy unit protocol (strong).**

ii. **Patients should be warned about short term adverse events, in particular the possibility of self-limiting GI symptoms. They should be advised that serious adverse events are rare (strong).**

iii. **After enteral tube administration, patients may have the tube removed and oral water given from 30 minutes post-administration (strong).**

9.1.2.4. **Definition of cure post-FMT for CDI:**
It is recognised that symptoms of CDI resolve relatively promptly after successful FMT, although this has been variably described (within hours in some studies [57], at an average of 4-5 days in others [62,76]). Treatment success post-FMT for CDI has no uniformly-agreed definition, with the time point at which cure/remission is defined on clinical grounds varying between 3-5 days [41] up to six months [47]. A consensus document from the USA recommends ‘resolution of symptoms as a primary end point; absence within eight weeks of FMT as a secondary end point’ [8]. The working group recommended that this definition should be made on a case-by-case basis; however, they agreed that an assessment for cure/remission of CDI within eight weeks post-FMT was reasonable in most cases, and therefore that this was also a reasonable minimum length of time to undertake follow-up post-FMT (see Section 9.1.2.2).

Evidence:

No universal definition exists regarding cure/remission post-FMT for CDI (quality of evidence: 4).

**Good practice point:**

*A decision regarding cure/remission from CDI should be recorded during follow-up. However, this has no uniformly-agreed definition, and should be decided on a case-by-case basis (strong).*

**9.1.2.5. Definition of treatment failure post-FMT for CDI:**

There is no uniformly-agreed definition of treatment failure/recurrence post-FMT for CDI, with varied definitions used in studies. The use of *C. difficile* toxin as a marker of treatment success or failure is variable, with some studies opting not to test for *C. difficile* toxin unless symptoms consistent with CDI recurred [54,57–59,65,77,79]. Some studies have routinely performed *C. difficile* toxin testing without specifying any action taken after a positive result [14,15,18,41,44,46], while others have tested for *C. difficile* PCR but relied on clinical criteria (even if PCR was positive) post-FMT for evaluating FMT efficacy [14]. A recent prospective study from the USA identified that only 3% (3/129) of patients who were asymptomatic at four weeks post-FMT for recurrent CDI had positive *C. difficile* PCR, again emphasising that symptoms rather than laboratory assays are more useful contributors to establishing FMT success [82].
Evidence:

No standard definition exists regarding treatment failure/recurrence post-FMT for CDI (quality of evidence: 4).

Good practice point:

Treatment failure/recurrence should be defined on a case-by-case basis. Routine testing for C. difficile toxin after FMT is not recommended, but it is appropriate to consider in the case of persistent CDI symptoms/suspected relapse (strong).

9.2. What recipient factors influence the outcome of faecal microbiota transplant when treating people with Clostridium difficile infection?

9.2.1. General approach to co-morbidities and FMT:

Most published studies had a core set of general recipient exclusions which included: significant/anaphylactic food allergy [14,17], pregnancy [12–15,17,18], breastfeeding [14], admission to intensive care or requirement for vasopressors [12,15,18], chronic diarrhoea or other infectious cause of diarrhoea [12,14,18,55], inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) [14,41], immunodeficiency due to recent chemotherapy and/or neutropenia [12,14–18,55], HIV/AIDS [14,17,18], prolonged use of corticosteroids [15,17,18], graft versus host disease [12], and decompensated cirrhosis [14,15,17,18].

The working group discussed the reported practice of several centres of treating patients with recurrent CDI and food allergies through the use of FMT prepared from a patient-directed donor instructed to avoid trigger foods before stool donation. They agreed that this seemed reasonable for patients with true adverse immunological reactions to defined food groups (e.g. gluten-free diet donor for a recipient with coeliac disease). However, the working group noted that food allergies are often poorly-defined clinically, and also expressed concerns that there was no means to verify how closely a donor had followed an exclusion diet; as such, they felt unable to make any specific recommendation about FMT in patients with food allergies in general. In contrast, while the working group were unaware of any reports in the literature of anaphylaxis attributable to FMT, they felt that the theoretical risk of a serious adverse outcome in patients with anaphylactic food allergy merited a specific recommendation that such individuals should not be offered FMT. Similarly, the working group expressed concern about the theoretical risk of adverse outcomes when administering FMT to patients with advanced decompensated chronic liver disease (including
translocation of microbial material from the intestinal tract into the portal and systemic circulations, and theoretical risk of sepsis), and felt that FMT should be used with caution in this patient group.

**Evidence:**

There is a wide range of FMT recipient exclusions listed in different studies, but little evidence on the safety of FMT administration in patients with these excluded conditions (quality of evidence: 4).

**Good practice points:**

i. *FMT should be avoided in those with anaphylactic food allergy (strong).*

ii. *FMT should be offered with caution to patients with CDI and decompensated chronic liver disease (conditional).*

9.2.2. **Immunosuppression and FMT:**

One randomised study [16] included patients with immunodeficiency (treatment with immunosuppressive therapy (azathioprine, ciclosporin, infliximab, methotrexate alone, or in combination with corticosteroids) \(n=18\), renal transplant \(n=5\), chronic haemodialysis \(n=5\), solid organ tumours \(n=3\) and haematological malignancy \(n=4\)) at the time of FMT. Clinical resolution rates after up to two FMTs were high: 27/29 (93%) for immunocompromised individuals, 5/6 (83%) for patients with IBD.

There are also limited data from case series and single case reports describing the use of FMT in immunocompromised patients. Agrawal and colleagues [60] included 46/146 (32%) patients with a history of cancer, and an additional 15/146 (10%) patients with non-cancer-related immunologic dysfunction, although primary outcome measures are not specifically reported for these groups. Overall cure at 12 weeks in a case series of 80 patients with immunocompromise was reported in 71 (89%) patients [65]. Adverse events occurred in 12 (15%) immunocompromised patients; this included two deaths (one due to respiratory failure and another due to pneumonia resulting from aspiration at the time of FMT administration) [65]; however, such adverse events have also been reported in non-immunocompromised patient populations [83]. Hefazi and coauthors described high efficacy rates in a case series of FMT for recurrent CDI and a range of haematological or solid organ malignancies (remission after one FMT in 11/12 with haematological patients, and 8/10 in solid organ malignancy patients). No significant FMT-related complications were reported [84].
further case series [50] reported FMT treatment for 75 patients with recurrent CDI and found no significant difference in primary cure rates for patients with diabetes mellitus, malignancy, or steroid use in the preceding three months.

The working group discussed the potential impact of donor EBV and CMV status for the immunocompromised FMT recipient at risk of severe infection if exposed to these viruses. Their opinion was that such recipients should only receive FMT from donors with negative EBV and CMV status.

**Evidence:**
The growing pool of experience in using FMT in CDI patients with a range of causes of immunosuppression demonstrates that it appears to be generally as safe and effective as in patients without immunosuppression (quality of evidence: 1-).

**Recommendation:**

*FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (strong).*

**Good practice point:**

*Immunocompromised FMT recipients at risk of severe infection if exposed to EBV or CMV should only receive FMT from donors negative for EBV and CMV (strong).*

**9.2.3. Other comorbidities and FMT:**

Only a limited number of cited studies included specific detail about the presence of comorbidities in patients receiving FMT. However, several studies reported median Charlson comorbidity scores [12,14,15,18,55]. One randomised study reported the presence of IBD in 10/17 (59%) FMT recipients [16], and there did not appear to be any significant difference in primary outcome measures in this group. Another randomised trial included 14/72 (33%) patients with IBD and reported clinical cure of CDI in 12/14 (86%) of these patients [13]. This study also included 64/72 (89%) patients with cardiac, respiratory, renal, central nervous system or multi-organ system comorbidities [13]; however outcomes were not stratified according to co-morbidity. Kelly and coauthors [65] reported an overall cure rate of 94% in a subset of patients with IBD. A meta-analysis
of studies in which patients with IBD received FMT (either primarily as treatment for concurrent recurrent CDI, or with the aim of treating IBD) noted a small risk of exacerbation of IBD in association with the use of FMT [85]. The working group noted the complexity of the relationship between IBD and CDI, given that IBD is itself a risk factor for CDI.

Other exclusions have been more directly related to the mode of administration. For upper gastrointestinal delivery, exclusion criteria have included delayed gastric emptying, chronic aspiration, ‘swallow dysfunction’, and dysphagia [17,55]. Exclusions for lower GI administration have included colostomy/ileostomy [16,55], significant bleeding disorders [12], untreated colorectal cancer [14,41,59], and ileus/small bowel obstruction [55].

In summary, the working group noted that co-morbidities among patients with recurrent CDI are common. Most studies did not analyse primary outcome measures according to co-morbidity; however, a small number of studies have analysed primary outcome measures (clinical cure) for patients with IBD receiving FMT for recurrent CDI and have found no significant difference compared with those without IBD, along with no overall significant worsening of IBD activity.

**Evidence:**

There is growing evidence that FMT is safe and efficacious as treatment for CDI in people with concomitant inflammatory bowel disease, but that there is the potential for FMT to cause a flare in IBD activity (quality of evidence: 1+).

**Recommendations:**

i. **FMT should be offered to those with recurrent CDI and inflammatory bowel disease, but patients should be counselled about a small but recognised risk of exacerbation of IBD (strong).**

ii. **FMT should be considered for appropriate patients with recurrent CDI regardless of other comorbidities (conditional).**

9.3. **What donor factors influence the outcome of faecal microbiota transplant when treating people with* Clostridium difficile* infection?**

9.3.1. **General approach to donor selection:**
Excellent efficacy has been shown in treating recurrent CDI using FMT derived from both related [14,41,43,45,46,50,51,54,58,59,62,64,66,86,87] and unrelated [14–17,40,42,43,46,58,62,64,66,77,79,86–91] donors. To date, there have been no randomised studies comparing differences in efficacy. Case series have tended to rely more on donation of stool from healthy family members. In randomised studies using FMT, all donors were healthy unrelated individuals [12–18,92]. Three case series used donor stool from healthcare professionals [44,66,89]; no randomised studies have used stool from this cohort. However, the working group noted that there were clear advantages to using FMT from a screened anonymous donor, in particular with regards to monitoring and traceability, as discussed further later.

Evidence:

Both related and unrelated donors have been shown to be acceptable as donors, but there has been no comparative study of the two groups (quality of evidence: 3).

Recommendation:

Related or unrelated donors should both be considered acceptable. However, where possible, FMT is best sourced from a centralised stool bank, from a healthy unrelated donor (conditional).

9.3.2. Age and BMI restrictions for potential donors:

There are no well-defined age restrictions on donors. Randomised studies have used donors of ≥18 [12,77] and ≤60 years old [15,17,18] with satisfactory outcomes. Two of the reviewed case series defined age limitations for donors as ≥18 and ≤ 50 years [77,93]. A recent study demonstrated that the Bacteroidetes: Firmicutes ratio and microbial diversity was similar for donors older and younger than 60 years, and their stool donations had similar clinical efficacy as FMT; however, there were losses of the phylum Actinobacteria and family Bifidobactericeae from donors older than 60 years [94]. On balance, the working group agreed that an age range of 18 – 60 years was appropriate for donors.
A widely-reported case study noted apparent weight gain in a recipient of FMT for treatment of CDI when an overweight donor was used [95], but any association between a donor with a raised BMI and weight gain post-FMT has not been replicated elsewhere in the literature [96]. Whereas most randomised studies did not report donor-specific BMIs, some have excluded those without a ‘normal’ BMI [13,17]. The working group considered an acceptable BMI as between ≥18 and ≤30 kg/m².

**Evidence:**

There is considerable variability between studies with regards to age and BMI restrictions for donors, and no comparative studies (quality of evidence: 3).

**Recommendation:**

*People should only be considered as potential FMT donors if they are ≥18 and ≤60 years old, and have a BMI of ≥18 and ≤30 kg/m² (conditional).*

**9.3.3. General approach to the donor screening assessment:**

There is a clear theoretical risk of the transmission of infection by FMT; furthermore, given the large number of conditions in which perturbation of the gut microbiota has been described [97], there is a concern regarding a risk of transmission of microbiota associated with vulnerability to disease.

While FMT is efficacious for recurrent CDI, adverse events may be associated with its use (discussed further later), and long-term safety follow-up is lacking. The aim of a donor screening questionnaire and interview is to minimise post-FMT adverse events by excluding potential donors from whom FMT may be associated with risk to recipients. Randomised studies performed to date used various pre-screening questionnaires, including self-screening questionnaires which focused on high risk behaviours for blood-borne infections [12–16], questionnaires that focused on previous potential transferable medical conditions [18], and adaptations from the American Association of Blood Banks Donor Questionnaire [14,17]. One randomised study used the OpenBiome questionnaire as a screening questionnaire [98]. Some studies have suggested excluding potential donors who have recently travelled to defined regions (typically tropical areas), varying between 3-6 months prior to donation [43,44,54,57,60,64,79,91]; this is also the protocol employed in randomised studies [14,16,18]. Another important point for assessment is recent use of medications by potential donors.
donors. In particular, given the profound effects of antimicrobials on the gut microbiota [99–102] (along with the theoretical concern that recent antimicrobials might precipitate gut colonisation with antimicrobial-resistant bacteria that could be transferred during FMT) studies advocate either a three month [14,51,58–60,62,66,79] or six month [16,17,104,18,40,43,44,54,86,89,103] period without antimicrobial use prior to FMT donation.

The working group agreed that, given the growing evidence for the contribution of the gut microbiota to the aetiopathogenesis of colorectal carcinoma, patients with a significant personal or family history of (or risk factors for) this condition should be excluded as donors (Table 1). However, the working group noted an added complexity, in that their recommendation was that potential donors may be up to 60 years of age, but bowel scope screening for colorectal carcinoma currently begins within the UK at 55 years of age, and formal NHS bowel cancer screening starts at the age of 60 years [105]. The working group agreed that potential donors living in countries with bowel cancer screening programmes that start before the age of 60 years should have therefore completed appropriate screening with negative/normal tests before they are considered further as donors.

The working group was of the opinion that a screening process is mandatory; any positive responses should usually result in exclusion from donation, although this will depend on the particular circumstances/answers given. A donor screening questionnaire should be performed both prior to considering a person as a donor, and also at a further point in time (discussed further in Section 9.3.5).

Evidence:

Based on the principles derived from blood transfusion, a donor screening questionnaire has become standard practice (quality of evidence: 3).

Recommendation:

It is mandatory to screen potential donors by questionnaire and personal interview, to establish risk factors for transmissible diseases and factors influencing the gut microbiota (Table 1) (strong).
9.3.4. Laboratory screening of potential donors:

Currently, there are no known confirmed cases of blood-borne pathogens being transmitted by FMT, but strict preventative measures are important, as the potential risk of transmission is unknown. Many of the suggestions are extended from established blood screening guidelines [106]. Case series almost universally screen for HIV, hepatitis B and hepatitis C as a minimum [40–42,44–47,51,54,57–60,64,66,77,79,86,88,91,107]; other studies (including the randomised trials) have a more thorough blood screening process [14–18]. Many studies have also included a ‘metabolic/general blood screen’, to select out donors with hitherto undiagnosed chronic illness. Table 2 shows the suggested blood screening protocol of the BSG/HIS working group.

The working group specifically discussed the role of screening donors for their EBV and CMV status; the importance of the rationale for this is discussed in Section 9.2.2. They agreed that EBV and CMV testing was only required where there is the potential that the FMT prepared from that donor would be administered to immunosuppressed patients at risk of severe infection if exposed to CMV and EBV.

The primary aim of stool screening of potential donors is to minimise the risk of transmission of pathogens; again, the relative novelty of FMT for CDI means that these risks are not currently well-defined. Stool screening protocols are universal among published studies, although widely-variable protocols have been used. Table 3 displays the suggested stool screening protocol of the working group. The working group discussed stool screening for multi-drug resistant bacteria carriage, and agreed that carbapenemase-producing Enterobacteriaceae (CPE) should be screened for. Although these bacteria are carried only by a minority of the UK population, transfer into debilitated patients with CDI is clearly undesirable given that CPE are potentially so difficult to treat. They also agreed that extended-spectrum beta-lactamase (ESBL)-producing organisms could also potentially cause severe disease (with limited antimicrobial options) if transplanted into patients with CDI, and so should also be screened for. While vancomycin-resistant Enterococci (VRE) carriage is relatively common in the community (probably related to food consumption) [108], community strains of VRE are genetically distinct from (and generally of much lower pathogenicity than) those found nosocomially [109]; as such, the working group thought that routine screening was not justified. The working group also noted that methicillin-resistant Staphylococcus aureus (MRSA) carriage is very
rare in healthy adults in non-healthcare settings (with significant intestinal carriage even rarer), and so did not justify routine screening. However, the working group acknowledged that the potential infection risk from VRE and MRSA would vary regionally dependent on local prevalence and pathogenicity, and as such recommended that a risk assessment is performed to assess whether screening for these organisms should be considered.

A donor laboratory screening should be performed both prior to considering a person as a donor, and also at a further point in time (discussed further in Section 9.3.5).

Evidence:

Blood and stool screening is performed uniformly as a part of FMT donor selection, but with varying protocols between studies (quality of evidence: 3).

Recommendation:

**Blood and stool screening of donors is mandatory (Tables 2 and 3) (strong).**

9.3.5. Repeat donor checks, and donation pathway:

Almost all reviewed studies have repeated at least some elements of the initial donor screening process either at the time of donation of each stool sample used to prepare FMT, or at the end of a period of donation to assess ongoing suitability for inclusion. However, protocols have differed widely between studies.

The opinion of the working group was that when a donor had met criteria for donation (both with an acceptable health questionnaire and satisfactory laboratory tests), they were suitable to begin donation of stool that may be prepared into FMT. Repeat donor screening was also deemed necessary. In centres where frozen FMT is being prepared, stool may be collected and processed immediately after the first donor screen is successfully completed, but should be stored in ‘quarantine’ pending further donor screening, rather than used immediately for clinical use. At the end of the locally-defined period of donation, potential donors should undergo repeat testing, with a
further health questionnaire and laboratory screening. If the donor’s health questionnaire remains acceptable and repeat laboratory screening is negative at this point, then the frozen FMT may be released from ‘quarantine’, and used. The working group thought that donor screening both before and after donation was the safest route possible, and that this represented the preferred scenario. A proposed summary pathway for donor screening in this scenario is provided in Figure 1.

In centres using fresh FMT, the working group agreed that a repeat health questionnaire should be completed at the time of donation of each stool sample used to prepare FMT. Formal repetition of both the personal interview/ health questionnaire and laboratory screening tests should occur at regular intervals to ensure ongoing suitability for inclusion as a donor. The working group’s opinion was that this repetition of the screening process should occur at least once every four months.

Evidence:

Repetition of some or all elements of initial donor screening at a later point is standard practice, though the means of assessment differs between studies (quality of evidence: 3).

Recommendations:

i. In centres using frozen FMT, before FMT may be used clinically, donors should have successfully completed a donor health questionnaire and laboratory screening assays both before and after the period of stool donation. This is the preferred means of donor screening (strong).

ii. In centres using fresh FMT, a repeat health questionnaire should be assessed at the time of each stool donation. To ensure ongoing suitability for inclusion as a donor, the donor health questionnaire and laboratory screening should be repeated regularly (strong).

9.4. What factors related to the preparation of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?

9.4.1. General principles of FMT preparation:
There is very little evidence or guidance on the collection of donor stool. Critical steps during this process centre on the reduction of environmental cross-contamination risk, so the use of clean collection devices and clean collection procedures is advocated. To promote standardised practice and a safe and effective product, clear instructions should be provided to the donor for stool collection (Table 5).

Regardless of the methods used to prepare FMT, stool donations should be processed within six hours of defaecation. The period of six hours has been generally applied across many successful studies of FMT treatment in CDI [14,18,40,44,48,57], although no formal comparative study has been undertaken. This strategy aims to minimise sample degradation and alteration over time, which may occur due to the complex metabolic and environmental requirements of the faecal microbiota.

There are no comparative trials of anaerobically versus aerobically prepared FMT in the treatment of recurrent CDI. With the exception of small observational studies [46,79], the vast majority of FMT preparation has been undertaken aerobically for the treatment of CDI and has proved highly efficacious. There appears to be no clear need to process anaerobically, a method which introduces complexity and cost for the treatment of CDI.

The reviewed randomised studies reported variable amounts of stool used in the preparation of each FMT aliquot, and the lack of comparative data means that it is not possible to link stool mass to outcome from these studies. However, a previous systematic review of case series using FMT as treatment for recurrent CDI reported similar rates of treatment efficacy, but an approximate fourfold increase in recurrence rates, if <50g of stool was used compared with ≥50g [110]. Similarly, the initial volume of diluent used to create the faecal emulsion is variable between studies, although the most common practice appears to be creation of a stool: diluent ratio of approximately 1:5. The overwhelming majority of the reviewed studies used stool from only a single donor per FMT (rather than stool pooled from a mixture of donors), and there are no comparative studies of outcomes of CDI from single donor versus pooled donor FMT; as such, the working group found no justification to recommend donor stool pooling for FMT for CDI.
The majority of studies have used preservative-free sterile 0.9% saline as the diluent for FMT production, although there have been a handful of reports of other diluents including potable water [16,40,48]. There have been no comparative studies of FMT diluent. In cases where frozen FMT is prepared, an appropriate cryoprotective substance should be added prior to freezing. Most studies use glycerol at a final concentration of ~10% [16,46]. It has been demonstrated that storing stool at -80°C for up to six months in saline without glycerol decreases viable aerobic and anaerobic bacterial counts; the reduction was statistically significant in all bacterial groups with the exception of *E. coli* and total anaerobes. When stored with glycerol, no significant reduction in viable counts was observed [79].

A variety of homogenisation and open filtration systems have been used, with no apparent major variation in efficacy. Open filtration systems such as gauze [16,42,45,60], filter paper [44] and strainers/sieves [17,46] are unpleasant to use and pose a risk of external contamination. In order to best comply with GMP standards, a sterile, single-use closed homogenisation and filtration system is recommended. An example of such a system includes the use of sterile filter bags inside a laboratory paddle homogeniser.

**Evidence:**

The mechanics of stool preparation vary widely between different studies. There are almost no comparative data for any of these variables (quality of evidence: 3).

**Recommendations:**

i. **Donor stool collection should follow a standard protocol (strong).**

ii. **Donor stool should be processed within 6 hours of defaecation (strong).**

iii. **Both aerobically and anaerobically prepared FMT treatments should be considered suitable when preparing FMT for the treatment of recurrent CDI (strong).**

iv. **Sterile 0.9% saline should be considered as an appropriate diluent for FMT production, and cryoprotectant such as glycerol should be added for frozen FMT (strong).**

v. **Use ≥50g of stool in each FMT preparation (strong).**
**Good practice points:**

1. **Stool should be mixed 1:5 with diluent to make the initial faecal emulsion (conditional).**
2. **Homogenisation and filtration of FMT should be undertaken in a closed disposable system (conditional).**

### 9.4.2. Fresh vs frozen FMT:

Two randomised studies have examined this area. One double-blind randomised study concluded that enema-administered frozen FMT \( (n=91) \) was non-inferior for clinical resolution of diarrhoea to fresh FMT \( (n=87) \) for the treatment of recurrent or refractory CDI \[16\] (with frozen FMT in this study stored at \(-20^\circ\text{C}\) for up to 30 days). A further randomised study demonstrated statistically comparable remission rates for recurrent CDI with fresh or frozen FMT delivered colonoscopically \( (n=25/25 \text{ vs } 20/24 \text{ respectively, } p=0.233) \) (using frozen FMT stored at \(-80^\circ\text{C}\) for up to six months). These data support the findings of earlier small observational studies \[40,46\]. Frozen FMT is also preferable to fresh FMT on logistical and cost grounds \[16\]. Banked frozen FMT also enables the window period for donor screening to be minimised, allowing centres to more closely meet regulatory requirements (also see Section 9.3.5).

**Evidence:**

There is randomised trial evidence demonstrating that fresh and frozen FMT have comparable efficacy (quality of evidence: 1+).

**Recommendation:**

*The use of banked frozen FMT material should be considered preferable to fresh preparations for CDI (strong).*

### 9.4.3. Use of frozen FMT:

Frozen FMT has been used up to six months after storage at \(-80^\circ\text{C}\) \[17,46,79\], with high efficacy rates (>70%) observed in the cases treated. However, there have been no comparative trials investigating
storage durations. As already described, a reduction in the viability of certain gut microbiota taxa was noted when faecal aliquots were frozen in 10% glycerol for six months [79], and as such, the working group agreed that six months was the acceptable limit for freezing of an FMT in glycerol. Storage at -80°C is recommended rather than -20°C to minimise sample degradation.

Warm water baths have been recommended to speed thawing [6]; however, the working group thought that this should be strongly discouraged, as this may introduce risks of cross contamination by *Pseudomonas* species (and other contaminants) from the water bath [111,112], and may reduce bacterial viability in the FMT. Repetitive freeze thawing of FMT samples should be avoided as bacterial numbers will be reduced during this process [113].

**Evidence:**

Frozen FMT remains an efficacious treatment for CDI after six months frozen, but it has not been assessed at longer time points. There are little published data addressing optimal thawing of frozen FMT (quality of evidence: 3).

**Recommendation:**

*FMT material stored frozen at -80°C should be regarded as having a maximum shelf life of six months from preparation (strong).*

**Good practice points:**

1. Consider thawing frozen FMT at ambient temperature, and use within six hours of thawing (conditional).

2. Do not thaw FMT in warm water baths, due to the risks of cross contamination with *Pseudomonas* (and other contaminants) and reduced bacterial viability (strong).

9.5. **What factors related to administration of the transplant influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?**
9.5.1. Use of specific medications in the period around FMT administration:

9.5.1.1. General principles of FMT administration:

Bowel purgatives have been proposed pre-FMT as a means of removing residual antibiotics that may affect engraftment of transplanted microorganisms, and as a means of removing any residual C. difficile toxin, spores and vegetative cells [114–118]. Furthermore, bowel purgatives pre-colonoscopic FMT delivery facilitate safe endoscopy. Various bowel purgatives have been used in colonoscopic FMT studies, including polyethylene glycol (PEG) (often 4 litres) [14,17,40,46,51,59–61,86,103,119–121], MoviPrep® [40,46], and macrogl [13,15,18,64]. In those studies that used an upper GI route for FMT, PEG [59,60,88] and Klean-Prep® [15,66] were used. FMT without bowel preparation has also been used as treatment for recurrent CDI without any apparent reduction in efficacy, including in randomised studies [16].

The rationale for the use of proton pump inhibitors (PPI) prior to upper GI FMT is to minimise acidity which may impair engraftment of transplanted microorganisms; however, PPIs have been shown to alter the gut microbiota [122,123], and have also been associated with primary and recurrent CDI [124,125]. Some studies advocate the use of PPI prior to receiving FMT via the upper GI route [42,44,50,88,89,126,127], but there appears to be comparable efficacy data in studies where it has not been used. Certain studies have also given recipients PPI prior to receiving colonoscopic FMT [17,91].

The use of prokinetics (such as metoclopramide) has been described prior to FMT delivery via the upper GI tract route, but only in a very small number of studies [89]. Given the potential risk of regurgitation/aspiration associated with upper GI administration of FMT, the working group felt that its use should be considered where appropriate.

A single dose/short course of loperamide has been used following FMT (predominantly for lower GI administration) in an attempt to prolong the exposure of the FMT to the mucosa, and to aid retention of the FMT within the GI tract [13,51,54,60,88,127]. One study utilised diphenoxylate with atropine [59] instead. However, no studies have compared FMT with and without anti-motility drugs.
The working group also discussed infection control aspects as they apply to FMT administration. Specifically, they agreed that recipients should ideally be cared for in a single room with en-suite bathroom facilities and, where appropriate, be placed at the end of an endoscopy list, to facilitate enhanced environmental decontamination and prevention of transmission of *C. difficile* spores. Protocols for decontamination of endoscopes should follow national guidance [128,129], using a sporicidal agent. Best practice for prevention of transmission of healthcare-associated infections, as described in national guidelines [130], should also be applied throughout.

**Evidence:**

These different classes of medications have all been used variably pre-FMT between different studies. They do not appear to adversely affect the efficacy of FMT, and there are sound reasons to expect that they may be beneficial (quality of evidence: 3)

**Recommendations:**

i. *Bowel lavage should be administered prior to FMT via the lower GI route, and bowel lavage should be considered prior to FMT via the upper GI route; polyethylene glycol preparation is preferred (conditional).*

ii. *For upper GI FMT administration, a proton pump inhibitor should be considered, e.g. the evening before and morning of delivery (conditional).*

iii. *A single dose of loperamide (or other anti-motility drugs) should be considered following lower GI FMT delivery (conditional).*

**Good practice point:**

i. *Prokinetics (such as metoclopramide) should be considered prior to FMT via the upper GI route (conditional).*

ii. *Best practice for prevention of further transmission of CDI should be applied throughout when administering FMT to patients with CDI (nursing with enteric precautions, sporicidal treatment of endoscope, etc).*
9.5.1.2. Additional antibiotics pre-FMT:

Many studies have given further courses of conventional antimicrobial C. difficile treatment prior to FMT. Regimens have included vancomycin alone [12,14,18,40,44,60,64,90,121], metronidazole or vancomycin [45,46,86,126], or alternatively vancomycin, fidaxomicin or metronidazole [61], with one study using a range of regimens which included rifaximin [127]. The length of treatment was also variable, ranging from 24 hours [59] up to four days prior to receiving FMT [44,50]; however, comparative studies have not been undertaken.

Evidence:

In many studies, additional anti-CDI antibiotics have been used pre-FMT, with the aim of further reducing the burden of C. difficile (quality of evidence: 3).

Recommendation:

Administer further antimicrobial treatment for CDI for at least 72 hours prior to FMT (strong).

9.5.1.3. Washout period between antibiotic use and FMT:

Nearly all studies specified a washout period after completing anti-CDI antibiotics and before administration of FMT. However, this time period appeared to be arbitrarily selected and varied from as little as four [51] or 12 hours [56], up to 72 hours [41]. The majority of studies specified either 24 hours [15,42,44,45,50,59,131] or 48 hours [46,47,54,65], however some allowed a range from 1-3 days [16,49,57,58,60]. One study appeared to allow co-administration of vancomycin with bowel preparation, without a washout period [18].

The working group discussed the challenging scenario of providing FMT to patients with recurrent CDI, but who also had a strong indication for long-term non-anti-CDI antibiotics (e.g. splenectomy, osteomyelitis, or infective endocarditis), or patients who develop an indication for antibiotics for a reason other than CDI shortly after receiving FMT. The concern in this instance is that the use of antibiotics may limit engraftment of microbial communities derived from the FMT, and therefore reduce its effectiveness. The working group discussed a recent retrospective study demonstrating
that exposure to non-anti-CDI antimicrobials within eight weeks of FMT is associated with an
approximate threefold risk of FMT failure (n=8/29 failures with antibiotic exposure vs 36/320 failures
without antibiotic exposure) [132]. Similarly, the experience of the large pan-Netherlands stool bank
[133] was that ~50% of their failures of FMT in the treatment of recurrent CDI occurred in patients
who had received antibiotics within one month of their FMT. For patients requiring long-term
antibiotics, the working group’s expert opinion was that such patients should still be eligible for FMT,
but that the regimen for the use of non-anti-CDI antibiotics should be decided on a case-by-case
basis, based on factors including response to FMT and/or strength of indication of antibiotics. Both
in this scenario, and the scenario in which antibiotics are required shortly after receiving FMT, the
working party agreed that infectious diseases specialists/medical microbiologists should be involved
in making decisions regarding the choice of agents used.

Evidence:

A washout period between the end of antibiotic use and administration of FMT is usually described.
However, no formal trial assessment as to the optimal length of this period has been undertaken
(quality of evidence: 3).

Recommendation:

To minimise any deleterious effect of antimicrobials on the FMT material, there should be
a minimum washout period of 24 hours between the last dose of antibiotic and treatment
with FMT (strong).

Good practice point:

Consider consultation with infectious disease specialists or medical microbiologists for
advice whenever FMT recipients also have an indication for long-term antibiotics, or have
an indication for non-CDI antibiotics within eight weeks of FMT (conditional).
FMT can be delivered via the lower GI route (retention enema, colonoscopy), upper GI route
(endoscopically, or via nasogastric tube, nasoduodenal or nasojejunal tube), or via capsules
(containing either frozen FMT or lyophilised faecal material). Systematic reviews with meta-analysis
suggest that FMT for recurrent CDI via colonoscopy may have slightly higher efficacy compared with
upper GI administration [131,134–136] with similar safety profiles, but also note the trend towards
using larger amounts of stool or ‘higher concentration’ FMT in lower GI administration. One
systematic review (reviewing principally case series, and including only one randomised study)
compared remission rates for CDI using FMT delivered to different areas of the GI tract, and
reported that for FMT infused into the stomach, duodenum/jejunum, caecum/ascending colon, and
rectum the rates of cure rate were 81%, 86%, 93%, and 84%, respectively [135].

In the only randomised study that directly compared upper and lower GI administration, there was
no significant difference in overall cure rate ($p = 0.53$) [17].

9.5.2.2. **Upper gastrointestinal tract administration of FMT:**

FMT has been shown to be safe and efficacious in the treatment of *C. difficile* when administered via
nasogastric tube [42,44,50,66,87,127], nasoduodenal tube [15,88,89], enteroscopy [126,127], or via
the infusion channel on a gastroscope [45,50]. In a randomised trial, nasoduodenal donor FMT has
been shown to be more efficacious than vancomycin in treating recurrent CDI [15]. Furthermore, it
has been shown that FMT can also be safely and effectively delivered via a percutaneous endoscopic
gastrostomy tube [50,87]. The working group noted that upper GI administration of FMT may be
particularly suitable for certain patient groups, such as those in whom there are contraindications or
who would find it difficult to tolerate lower GI endoscopy, and/ or patients unlikely to be unable to
retain enemas.

Typically, smaller volumes of faecal suspension are administered to the upper GI tract compared
with lower GI administration, with quoted volumes ranging from 25ml [44] up to 150ml [88]– 250ml
[42,89]. Up to 500ml of suspension has been given safely and effectively via the upper GI route
[15,81]. However, the working group expressed concerns regarding the risk of regurgitation and
aspiration if large volumes of FMT are administered to the upper GI tract, and also discussed cases in
which this has been described with adverse outcomes [83]. This included a reported death from
aspiration, after 100-150ml of FMT was delivered by enteroscope into the distal duodenum under
A further report described a case of fatal aspiration pneumonitis likely related to a 500ml FMT via nasoduodenal tube; this patient had a swallowing disorder following oropharyngeal radiation after surgical removal of a maxillary carcinoma two years previously [81]. Based on their expert opinion, the working group recommended that upper GI FMT should be used with caution in those at risk of regurgitation (e.g. known large hiatus hernia, gastro-oesophageal reflux disease, etc.) and/or with swallowing disorders (although administration via a gastrostomy tube would be acceptable). They also recommend that no more than 100ml of FMT should be administered to the upper GI tract to minimise these risks.

Evidence:

There is randomised trial evidence demonstrating that upper GI administration of FMT for CDI is effective, although there are concerns about the possibility of aspiration and vomiting associated with its use (quality of evidence: 1+).

Recommendation:

i. **Upper GI administration of FMT as treatment for recurrent or refractory CDI should be used where clinically appropriate** (strong).

ii. **Where upper GI administration is considered most appropriate, FMT administration should be via nasogastric, nasoduodenal, or nasojejunal tube, or alternatively via upper GI endoscopy. Administration via a permanent feeding tube is also appropriate** (strong).

Good practice points:

i. **It is recommended that no more than 100ml of FMT is administered to the upper GI tract** (conditional).

ii. **Upper GI administration of FMT should be used with caution in those with swallowing disorders** (strong).

9.5.2.3. Lower gastrointestinal tract administration of FMT:
FMT via enema: Successful treatment of *C. difficile* with FMT enema has been demonstrated [16,43,47,58,60,87,90] but enema appears to have a lower efficacy than other routes of FMT administration. Specifically, in a randomised study primarily comparing the efficacy of fresh and frozen FMT in the treatment of recurrent CDI, only 52.8% of patients in the ‘frozen’ arm and 50.5% of patients in the ‘fresh’ arm of the study (n= 57/108 and 56/111 respectively) experienced resolution of symptoms after a single enema, by modified intention to treat analysis [16]. However, resolution rates in both arms only reached >80% after at least three enemas [16]. A recent randomised study demonstrated similar rates of recurrence of CDI in patients with recurrent CDI treated with either a single FMT enema or a six week vancomycin taper (9/16 patients with recurrence vs 5/12 respectively) [12]. Notwithstanding this, enemas do have specific advantages, such as being a treatment option where full colonoscopy is contraindicated. It is also possible to give multiple infusions relatively easily and outside a hospital setting.

FMT via colonoscopy: Randomised study evidence has demonstrated that colonoscopic FMT has higher efficacy in treating recurrent CDI than vancomycin [18]. Efficacy is similar whether FMT is fresh or frozen, but modestly reduced when using a lyophilised FMT product [13]. Colonoscopic delivery of donor FMT into the ileum or caecum was associated with a 91% cure rate for recurrent CDI [14]. Observational studies highlighted similar success, describing cure rates of 88% (n=14/16) [79] and 91% [51] (n=21/23) in response to infusion of donor FMT into the caecum or terminal ileum. A further advantage of using colonoscopy to administer FMT has been to allow assessment for the presence of pseudomembranes; in certain reviewed studies, the presence or absence of pseudomembranes has influenced the FMT regimen used [18,78]. However, the working group noted that many patients with CDI are frail and elderly, and as such it will not always be safe or feasible to undertake colonoscopy in this particular group of patients. Flexible sigmoidoscopy appears to be an feasible option where full colonoscopy cannot be performed e.g. unable to tolerate colonoscopy, severity of colitis [61,65].

The amount of faecal suspension via enema has varied between 150-500mls [16,43,47,60,90]. The amount of faecal suspension delivered via colonoscopy has been similarly variable, with some studies suggesting as little as 100ml can be used with success rates of 94% [86]. 250ml-400ml had a success rate of 100% [41], whereas infusions of up to 500-700ml were associated with cure rates of 92% [51]. However, the working group noted that it is difficult to compare ‘concentration’ of FMT in different studies as different protocols used varied starting amounts of faecal material. Currently,
there are no randomised studies that compare concentration/volume of colonoscopic or enema FMT. As such, no recommendation was made to this regard.

Evidence:

Randomised trial evidence demonstrates the efficacy of FMT as treatment for CDI when administrated either as enema or via colonoscopy (quality of evidence: 1+).

Recommendations:

i. Colonoscopic administration of FMT as treatment for recurrent or refractory CDI should be used where appropriate (strong).

ii. Where colonoscopic administration is used, consider preferential delivery to the caecum or terminal ileum, as this appears to give the highest efficacy rate (conditional).

iii. FMT via enema should be used as a lower GI option when delivery using colonoscopy or flexible sigmoidoscopy is not possible (strong).

9.5.2.4. Capsulised FMT:

Capsulised FMT aims to remove some of the concerns regarding conventional FMT, such as the invasive means of administration and palatability. The largest case series describing the use of capsules as treatment for recurrent CDI [77,93] noted clinical resolution at eight weeks off antibiotics for CDI in 82% of cases (n=147/180) after one course of capsules, and 91% (n=164/180) after two courses. The capsules contained frozen FMT prepared in a diluent of saline with 10% glycerol; 15 capsules were administered each day for two consecutive days (equating to a mean 48g of original crude stool). Other smaller case series have demonstrated comparable results [91,127,138], including when lyophilised stool is used instead of frozen whole FMT [138].

The working group reviewed two randomised studies which have examined the efficacy of capsulised FMT in treating recurrent CDI. In one study, published in abstract form [98], a ‘high dose’ regimen of frozen FMT capsules (30 capsules each day for two days) was compared with ‘low dose’ (30 capsules in one day). CDI resolution was comparably high in both arms with one treatment
course (77\% (n=7/9) in the ‘high dose’ arm vs 70\% (n=7/10) in the ‘low dose arm’. Four of five initial non-responders entered remission after a second capsule course with the ‘high dose’ regimen [98].

In a recent large randomised trial, patients with recurrent CDI were randomised to receive thawed frozen FMT either via colonoscopy or via capsules (one treatment of 40 capsules) [11]. On per protocol analysis, remission at 12 weeks after a single treatment occurred in 96\% in both arms (n=51/53 by capsule, n=50/52 by colonoscopy).

The working group discussed certain unresolved issues regarding capsules. Specifically, capsules are often large, and swallowing 30 capsules in a single day may be a significant undertaking for patients with CDI, such as the frail elderly with an existing high pill burden. They also noted that follow-up data post-capsule administration is relatively short compared with other modalities of FMT.

**Evidence:**

Case series and RCT evidence demonstrate that capsulised FMT is efficacious in treating recurrent CDI, with comparable efficacy to other modalities of administration. However, capsules are a relatively new modality of administration, and further data are awaited on longer term efficacy and safety, and the optimal mechanics of preparation and administration (quality of evidence: +1).

**Recommendation:**

*Capsulised FMT holds promise as a treatment option for recurrent CDI and should be offered to patients as a potential treatment modality where available. Capsule preparations should follow a standard protocol. Further evidence regarding optimal dosing and formulation is required (conditional).*

**9.6. What is the clinical effectiveness of FMT in treating conditions other than *Clostridium difficile* infection?**

**9.6.1. Introduction:**

In current clinical practice, FMT is used predominantly in the treatment of recurrent CDI. Its success has led to exploration of its efficacy in other GI diseases, primarily ulcerative colitis (UC), where perturbation of the gut microbiota has been observed and implicated in disease pathogenesis [139].
Due to variability of the quality, methodology and cohorts of patients recruited in trials of FMT for non-CDI indications, and in order to control for significant confounding factors, the working group only included randomised trials involving patients with well-defined conditions and in which there was a primary clinical outcome. To date, there have been a total of 71 such studies investigating the role of FMT in IBD; of these, only four are prospective randomised controlled trials, limited to patients with ulcerative colitis [140–143]. Five other reviewed randomised studies investigated the use of FMT in irritable bowel syndrome [144], slow transit constipation [145], hepatic encephalopathy [146] and metabolic syndrome [147,148]. Another study [147] compared the effect of autologous vs healthy donor FMT on people with metabolic syndrome, but this was deemed to be a pilot scientific study rather than a formal randomised FMT clinical trial, so was not considered further.

9.6.2. **Use of FMT for ulcerative colitis:**

9.6.2.1. **Efficacy:**

All four RCTs, with a total of 277 subjects, included patients with mild to moderate UC (Mayo score 3–11 and endoscopic sub-score of at least 1). Participants were aged between 27 and 56 years and largely included patients on stable immunosuppressive therapy (only one study excluded patients using biologic treatments and methotrexate within the preceding two months) [140]. Three studies included patients on oral corticosteroids at the time of FMT, however only two required a mandatory wean of these to meet eligibility. Studies generally included patients with all disease distributions found in UC. Time to evaluation of response to FMT in these studies varied between seven and twelve weeks. Two studies used autologous FMT as placebo [140,143]. Three of the four studies demonstrated that patients receiving donor FMT were significantly more likely to achieve clinical and endoscopic remission compared with placebo [141–143]. The pooled rate of combined clinical and endoscopic remission was 27.9% for donor FMT and 9.5% for placebo. A pooled risk ratio for failure of FMT to achieve these combined outcomes was 0.8 (95% CI: 0.7-0.9). Deep remission (histological) was only reported in one RCT: 18.4% of patients receiving FMT achieved this outcome compared with 2.7% of those receiving placebo [141].

9.6.2.2. **Characteristics of FMT preparation and delivery:**

The four RCTs varied in their FMT preparation and delivery methodology. Two RCTs delivered frozen FMT, one fresh FMT and one used a combination. Three RCTs with a positive outcome delivered the FMT via the lower GI route; these studies used a high intensity protocol ranging from a total of three
infusions in one week to 40 FMTs over an eight week period [141–143]. The other RCT (that failed to show efficacy of FMT for UC) had adopted a low intensity protocol of two nasoduodenal infusions given three weeks apart [140]. Interestingly, the only RCT that prepared stool in anaerobic conditions demonstrated the highest rate of steroid-free clinical remission and steroid-free clinical response with donor FMT [143]. A further interesting observation in one study was a trend towards higher rates of remission with one particular donor [141].

9.6.2.3. Adverse events:
Short-lived GI symptoms such as abdominal bloating, cramps, diarrhoea and fever were reported in patients receiving FMT for UC. There were no significant differences in serious adverse events between patients receiving FMT compared with placebo (10 vs 7 respectively). Most of the serious adverse events were a consequence of worsening colitis: one patient who received FMT required a colectomy [140]. In addition, one patient developed concurrent CDI [141]. No deaths were reported in any of the studies.

9.6.3. Use of FMT in functional bowel disorders:
Two RCTs have investigated the role of FMT in functional bowel disorders. In a double-blind placebo controlled RCT that recruited 90 patients with IBS with diarrhoea or with diarrhoea and constipation [144], the primary endpoint only just reached statistical significance in inducing symptom relief (as assessed by 75 point reduction in IBS-severity scoring system at three months following a single infusion FMT by colonoscopy) \( p=0.049 \). The second RCT randomised 60 patients with slow transit constipation to either six consecutive days of nasogastric-delivered FMT or conventional treatment [145]. This demonstrated that a significant proportion of patients achieved the primary endpoint of a mean of at least three complete spontaneous bowel movements per week (53.3% vs. 20.0%, \( p=0.009 \)) along with improvement in stool consistency score and colonic transit time. However, the intervention group had more treatment-related adverse events than the control group (total of 50 vs 4 cases).

9.6.4. Use of FMT in hepatic encephalopathy:
One small study has investigated the role of FMT in the management of hepatic encephalopathy (HE) [146]. This RCT randomised 20 male patients with cirrhosis with refractory HE to receive either five days of broad-spectrum antibiotic pre-treatment followed by a single FMT enema or standard of
care. Patients in the FMT arm had a significantly lower incidence of serious adverse events and improved cognition. The Model for End-Stage Liver Disease (MELD) score, however, transiently worsened post-antibiotics in the FMT arm. The study was potentially confounded as patients in the FMT arm continued to receive lactulose and/or rifaximin for treatment of their HE.

9.6.5. Use of FMT for metabolic syndrome:

Two randomised studies [147,148], with a combined total of 56 patients, demonstrated an improvement in peripheral (but not hepatic) insulin sensitivity in Caucasian male obese patients with metabolic syndrome following one or two infusions via nasoduodenal tube of FMT obtained from lean donors. This improvement was observed at six weeks post-FMT, but was no longer present by 18 weeks. No improvement in insulin sensitivity was identified in patients transplanted with autologous FMT (i.e. patients transplanted with their own collected faeces). The improvement in peripheral insulin sensitivity in the lean donor FMT group was accompanied by a small but significant improvement in HbA1c at six weeks [148], but no improvements in other metabolic parameters, such as weight. While these data are of interest, the working group felt that the limited, transient nature of the benefits seen and small size of the studies meant that FMT could not be recommended as treatment for metabolic syndrome.

9.6.6. Future directions for randomised trials of FMT for non-CDI indications:

Currently there are a large number of randomised trials (including RCTs) being undertaken globally, to evaluate the potential role of FMT as treatment for a wide range of conditions. The working group concluded that until there are more reliable data to inform decision-making, the best practice principles described in this document for the governance of an FMT service for recurrent CDI should also be applied to FMT clinical trials for other conditions. However, specific adaptations may be considered depending on the condition being studied, e.g. consideration of using anaerobic conditions for the preparation of FMT in trials for the treatment of UC, as described above.

Evidence:

FMT has the potential to be an effective treatment option for mild to moderate ulcerative colitis, and appears to be safe despite the use of immunosuppressive therapy. FMT may also have a potential role in the treatment of functional bowel disorders. However, recommendations for clinical use for both of these indications cannot be made until there is clearer evidence of the most
appropriate patient characteristics, preparation methodology, route of delivery and intensity of administration of FMT (quality of evidence: 1+). The evidence for the use of FMT in hepatic encephalopathy and metabolic syndrome is currently limited, and further well-designed RCTs are needed to evaluate its potential role here (quality of evidence: 1-).

**Recommendation:**

*FMT is not currently recommended as treatment for inflammatory bowel disease. Apart from CDI, there is insufficient evidence to recommend FMT for any other gastrointestinal or non-gastrointestinal disease (strong).*

9.7. **Basic requirements for implementing a FMT service**

As discussed above, there is an absence of published studies to support the recommendations in this section (although the experience of setting up a nationwide stool bank has recently been reported from the Netherlands [133]). This section is therefore based on the working group’s expert opinion and experience of developing FMT services.

9.7.1. **General considerations:**

Although it is possible to prepare and administer FMT on an individual patient basis in a single hospital, the regulatory requirements are more readily fulfilled by a specialist centre approach for the production of a safe FMT product. This particularly applies to record keeping and staff expertise in quality control and production. Recent European consensus advice suggests that FMT should be administered in a referral centre [6], however an alternative approach which limits the need for patient transfer is to undertake controlled production in a large centre and transport treatment to the patient, a supply model which has been well established in the USA (OpenBiome) [149] and has also been successfully replicated in the UK in a large centre in Birmingham, which has supplied FMT to nine NHS Trusts across three regions [28]. This service design only requires that a responsible clinician is capable of administering the FMT safely at the satellite clinical site. It also eliminates the need for patient transfer between clinical sites, which in the case of severe CDI may not be practical.

The working group encouraged the use of frozen FMT material supplied from a carefully controlled production site. This allows donor screening more closely to meet regulatory requirements,
ensuring that the window period between donor testing and FMT production is maintained to a minimum. The costs of donor screening are substantially reduced using this supply model, as a single donor can provide multiple FMT donations under a single screening period.

The working group also noted that given the novelty of FMT, awareness of this as a potential treatment option for recurrent or refractory CDI may be low amongst certain groups of clinicians. For instance, clinicians working in primary care, or those whose practice is not located near to an FMT centre, are likely to have less knowledge about the potential suitability of FMT for patients with CDI, or be unaware of referral pathways. As such, there is a responsibility for FMT centres to raise awareness and educate as wide a range of clinicians as possible about the potential role for FMT. Furthermore, microbiology staff processing stool samples for *C. difficile* assays from the community should proactively liaise with primary care teams where recurrent positive tests are received from a single patient to raise awareness and suggest the option of FMT.

Similarly, given the expectation that FMT and/ or other ‘microbiome therapeutics’ are likely to play an increasing role within medicine over future years, there is also an expectation for FMT centres to not only educate about the potential role for FMT, but also to train relevant healthcare professionals in the practicalities of delivering an FMT service, to enable longer-term ongoing provision of services. This is likely to be most of relevance to specialty trainee and consultant physicians specialising in gastroenterology, infectious diseases and/ or medical microbiology, but potentially to other healthcare professionals too, including infection prevention and control nurses, infectious diseases pharmacists, etc.

**Evidence:**

Working group consensus opinion (quality of evidence: 4).

**Good practice points:**

1. **The development of FMT centres should be encouraged** (strong).

2. **FMT centres should work to raise awareness about FMT as a treatment option amongst clinicians caring for patients with CDI, and provide training to relevant healthcare professionals on the practicalities of delivering an FMT service** (conditional).
9.7.2. Legal aspects and clinical governance:

In the United Kingdom, FMT is now considered a medicinal product based on the definitions of purpose and efficacy, in The Medicines Directive 2001/83 and The Human Medicines Regulations [19]. As the competent authority for medicines regulation, the Medicines and Healthcare products Regulatory Agency (MHRA) has indicated that the approach to regulation will be proportionate, depending on factors such as supply being within or outside a legal entity and FMT production scale. Specifically:

- When FMT is supplied on prescription on a named patient basis, then supply under a pharmacy exemption may be used subject to ensuring proper governance and traceability [19].
- If production scale reaches an ‘industrial’ level, defined ‘by virtue of the batch sizes, the extent of processing and/or whether potential use includes supply between legal entities’ [19], the route to regulation is via adherence to HMR and formal Manufacturer’s ‘Specials’ (MS) license.
- If a supply is to a clinical trial, then an MIA (IMP) manufacturing license is required (further information on license applications [150] and specials [151] is available online).

Centres establishing an FMT service should undertake steps to ensure practice meets the required compliance levels and seek guidance from the MHRA. If pharmacy exemption is applied, there should be justifiable processes in place to ensure traceability, health and safety, governance and to prevent cross-contamination. FMT is regulated as a medicine, rather than a tissue, but no products have been licensed following an assessment against the criteria of safety, quality and efficacy, for there is a possible risk that donor screening protocols will not be sufficiently considered, a step which is critical to the quality of the product and therefore safety of the patient [152]. To mitigate this, it is advisable that donor screening protocols are under regularly review and risk assessment, and to ensure that consideration is also given to the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment, particularly Annex B related to donor testing [153]. When formal licencing is sought, this is overseen by a Production Manager and Quality Control Manager if under an MS, or by a Qualified Person if under an MIA (IMP). Both should follow the Good Manufacturing Practice (GMP) guidelines, found within The Orange Guide Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017 [154], or at: https://ec.europa.eu/health/documents/eudralex/vol-4_en.
The working group noted that outside the UK, the legal and regulatory framework relating to FMT was highly variable between different countries. They agreed that FMT should only be administered after appropriate approval from the competent body of each country.

Evidence:
Working group consensus opinion and legal requirement (quality of evidence: 4).

Good practice point:

In the UK, FMT must be manufactured in accordance with MHRA guidance for human medicines regulation. When FMT is supplied on a named patient basis, within a single organisation, a pharmacy exemption may be used, subject to ensuring proper governance and traceability. All centres that are processing and distributing FMT should seek guidance from the MHRA and where necessary obtain appropriate licenses prior to establishing an FMT service. This is a legal requirement. In countries other than the UK, FMT should only be manufactured following appropriate approval from the national authority of that country (strong).

9.7.3. Multidisciplinary teams:

To promote safe and high quality FMT supply, it is strongly recommended that providers adopt a multidisciplinary team approach. The choice of the team required is subject to the scale of production, but should involve as a minimum a clinical gastroenterologist, microbiologist/infectious diseases clinician, state-registered experienced healthcare scientist and pharmacist. Governance and quality expertise will be required, which may be provided by consultation. If FMT production is to be under a ‘specials’ licence, the team should be expanded to include a Qualified Person, Quality Manager and Production Manager, all with GMP training.

Evidence:
Working group consensus opinion (quality of evidence: 4).

Good practice point:

A multidisciplinary team should be formed to deliver FMT services (strong).
9.7.4. **Infrastructure:**

Dedicated laboratory facilities for FMT production are recommended to ensure that the process adheres to Health and Safety requirements, to reduce the risk of cross-contamination, and to facilitate standardisation of the production process. In some studies, FMT has been prepared in a clinical environment [80]; however, this may not be advisable because of the risks of cross-contamination. The manipulation of human stool should be conducted in a Containment Level 2 laboratory according to current Health and Safety guidance (Health and Safety at Work Act 1974, COSHH Control of Substances Hazardous to Health Regulations, 2002), and at least within a microbiological safety cabinet which provides user protection (Class I) or, ideally, user and product protection (Class II). To meet the requirements of GMP, this facility should be sole use or be risk assessed for multipurpose use with adequate separation of different activities. The working group recommend that the facility complies with the new GMP production facility classification of ‘clean not sterile’. The use of personal protective equipment - such as laboratory coat, gloves and face mask - is also recommended to prevent production contamination. It is essential to risk assess the process and develop control measures to reduce microbial ingress into the facility and monitor the microbiological cleanliness of the production suite. FMT preparation under a ‘specials’ licence should ensure that the production process is integrated into a Quality Management System, to safeguard production and maintain the minimum criteria for audit, monitoring, standard operating procedures, document control, training, facilities, equipment and storage. With regard to storage, it is essential that the freezer system has real-time temperature monitoring which provides notification outside pre-set limits.

**Evidence:**

Working group consensus opinion (quality of evidence: 4).

**Good practice point:**

*Utilise suitable laboratory facilities and infrastructure for FMT production (strong).*

9.7.5. **FMT manufacturing:**

It is strongly recommended to employ a batch numbering system to track FMT preparations from production to use. It should be possible from records to identify an individual FMT aliquot, trace it
to a specific donation, and identify all other FMT aliquots prepared from the same donation. It must also be clear which FMT aliquots patients have received, which should be verifiable from the donor to the patient and vice-versa. It is therefore strongly recommended that a treatment directory be maintained documenting all production and use of FMT, and that an unambiguous record is created in the patients’ clinical notes to identify the specific FMT batch number. Further to this, it is also recommended that treatment directories also record clinical outcome, such as that developed in the USA [155] and Germany [156] to standardise and improve future clinical practice.

**Evidence:**
Working group consensus opinion (quality of evidence: 4).

**Good practice point:**

**Ensure traceability of supply (strong).**

**9.7.6. FMT production quality control:**
Safety and clinical governance is a central responsibility for FMT centres, particularly in light of the absence of phase III licensing trials for FMT, which would normally be required for a novel medicinal product. Reporting and investigating adverse events and reactions contributes to knowledge of the FMT safety profile, while also identifying previously unknown safety issues. Governance structures and processes must be in place to monitor, notify and investigate all FMT-related adverse events or reactions locally, and FMT users are encouraged to use the MHRA Yellow Card Scheme for formal notification. FMT supply should be suspended if serious adverse events or reactions occur which are directly attributable to FMT, and there should be a clear documented pathway to achieve this. To facilitate a ‘look-back exercise’ if required, it is advisable to store documentation and reference samples, both product-based and donor/patient-based. Specifically, retention of production documentation should be for at least five years after the use of the batch; retention of reference FMT samples (and stool samples from donors and recipients) should be for at least one year after the last use. Retention of excipient samples should be for at least one year after expiry of the excipient.

**Evidence:**
Working group consensus opinion and legal requirement (quality of evidence: 4).
Good practice point:

Monitor, notify and investigate all adverse events and reactions related to FMT (strong).

9.7.7. Donor screening governance:

The testing requirements for donor screening have been discussed previously; however, it is worth noting here the pertinent clinical governance issues which should be addressed. Donor anonymity should be maintained at all times. The laboratory undertaking testing of donor samples should be competent for such activity, demonstrable by accreditation with the United Kingdom Accreditation Service (UKAS). The results of donor testing should remain confidential. There should be appropriate standard operating procedures to ensure that the outcome of donor screening is built into a robust FMT batch release process. To ensure unbiased autonomy during donor screening, it is suggested that a clinician independent to the FMT production team is responsible for ratifying FMT donors prior to donation. Finally, the duration of donor follow-up should be considered and extend beyond the period of active donation to capture acute and chronic health changes.

Evidence:

Working group consensus opinion (quality of evidence: 4).

Good practice point:

Ensure the clinical governance of donor screening (strong).

10. Conclusions:

FMT has become an accepted, efficacious treatment for recurrent and/or refractory CDI. In developing this guideline, the evidence for the technique has been reviewed in the context of other available treatments. Specific guidance for best practice for an FMT service is provided.

11. Further research:
As described within this guideline, many aspects of the terminology of CDI are used variably between studies, and end-points in FMT trials are inconsistent. The working group noted the need to standardise this terminology to allow more robust comparisons between studies.

Given the relative novelty of FMT as a procedure, any potential long-term adverse events associated with its use are poorly-defined. The establishment of formal FMT registries should be considered. While this would primarily act as an important tool for defining the safety and efficacy of FMT, it would also be a valuable database for researchers within the field. Standardisation of other key documentation related to FMT administration (e.g. establishment of a proforma for assessing eligibility for FMT and/or follow-up after FMT) would also be advantageous for the same reasons.

The working group noted the lack of consistency in definitions related to the severity of CDI disease and to response or failure to FMT. This limited interpretation of the published studies. As such, the working group thought that standardisation of these definitions would allow more accurate delineation of the factors influencing the efficacy of FMT for CDI. The working group also noted that only one reviewed study had reported the relationship between C. difficile ribotype and FMT outcome, and that recording of this information should be encouraged better to evaluate its influence.

Further well-designed clinical trials (in particular, RCTs) are required to identify the optimal means of administration of FMT as treatment for recurrent and/or refractory CDI.

The working group noted that even capsulised FMT may be associated with potential drawbacks. They also noted that there are many patients with recurrent CDI for whom FMT (or any form of ‘bacteriotherapy’) may be inappropriate, including those with very marked immunosuppression, and/or multi-organ disease. Despite high levels of efficacy, there is a small but appreciable FMT failure rate and it is not currently understood whether this is due to underlying donor or recipient factors. Therefore, a research priority should be in basic and translational studies better to define the mechanisms underlying the efficacy of FMT in CDI. This includes comparing the structure and function of the microbiota of donors to patients pre-FMT and post-FMT, via techniques including next-generation microbial sequencing, metabolic profiling, and immunological assays. This would allow the refinement of FMT from its current state to a more targeted therapy, removing the concerns associated with FMT.

The working group identified a need for further well-designed RCTs to investigate the potential role of FMT for non-CDI indications.
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HIS/ BSG FMT Guideline: Main Document.


13. **Appendices**

**Appendix 1: Glossary**

*Clostridium difficile* infection (CDI) - Symptomatic infection caused by the spore-forming, toxin-secreting bacterium, *Clostridium difficile*. It is the most common cause of antibiotic-associated diarrhoea, and symptoms include watery stools, fever, nausea, and abdominal pain.
Refractory CDI – Failure of an episode of CDI to respond to metronidazole and oral vancomycin, although no uniform definition.

Recurrent CDI – Defined in ESMID guidelines as ‘when CDI re-occurs within 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment’[4]; however, defined more variably within the reviewed literature within this guideline.

Faecal microbiota transplant – A procedure in which faecal matter (stool) is collected from a healthy screened donor, homogenised, strained, and introduced into the gastrointestinal tract of a patient.

Donor – In the context of FMT, this is a healthy screened individual that provides stool for the use in preparation of FMT.

Nasogastric – A means of reaching/ supplying the stomach via the nose for the purpose of treatment or investigation. This is usually achieved by the insertion of a tube.

Enema – A procedure in which liquid (or gas) is infused into the rectum as means for treatment or investigation.

Gut microbiota - Population of microorganisms that live in the gastrointestinal tract including bacteria, viruses and fungi.

Inflammatory bowel disease – Describes a group of chronic disorders (ulcerative colitis and Crohn’s diseases) in which the gastrointestinal tract becomes inflamed. The exact cause is unknown but it is thought to result from a combination of factors that trigger the body’s immune system to produce an inflammatory reaction in the gastrointestinal tract.

Medicines and Healthcare Products Regulatory Agency - An executive agency of the Department of Health in the United Kingdom which is responsible for ensuring that medicines and medical devices are efficacious and are acceptably safe.

Appendix 2: Guideline Development

Introduction

The need for a guideline within this area was agreed at a HIS guideline scoping day, and a BSG Gut Microbiota for Health (GMfH) panel teaching/meeting day, both in September 2015, and further meetings between both bodies confirmed the establishment of a working group. Members were chosen to reflect the range of stakeholders, but were not limited to members of BSG or HIS.
Feedback from the HIS guideline scoping day (including patient representatives) was used to establish a basis for PICO questions, with the final structure of PICO questions agreed collectively by teleconference in July 2017. No payment was made to anyone involved in this guideline.

**Conflict of interest**

Conflict of interest was registered from all working group members and underwent ongoing review up until the point of completion. In the event of a potential conflict being identified, the working group agreed that the member should not contribute to the section affected.

**Search Strategy & Results**

**i. Literature search strategy: PICO Review Questions:**

Review Question 1: Which patients with *Clostridium difficile* infection should be considered for faecal microbiota transplant, and how should they be followed up after treatment?

**Populations:** Adults (18 years and over) with *Clostridium difficile* infection

**Intervention:** Faecal microbiota transplant

**Comparison:** Placebo

Vancomycin

Metronidazole

Fidaxomicin

Intravenous immunoglobulin

Bezlotoxumab

Probiotics

Cessation of antibiotics for alternative indication

**Outcomes:** **Critical:** Cessation of diarrhoea and other symptoms/ relapse

Quality of life

Serious adverse events
Important: Negative tests for *Clostridium difficile* infection

Adverse events

Study design: Randomised trials

If no randomised trials identified – prospective cohort studies and retrospective case series

**Review Question 2: What recipient factors influence the outcome of faecal microbiota transplant when treating people with *Clostridium difficile* infection?**

**Populations:** Adults (18 years and over) with *Clostridium difficile* infection

**Intervention:** Faecal microbiota transplant

**Comparison:** Preparation of patient:

- Use of bowel purgatives vs no bowel purgatives
- For upper GI administration - use of PPI/ acid suppression prior to procedure vs no acid suppression
- Use of agents affecting GI motility (e.g. metoclopramide for upper GI/ loperamide for lower GI) vs no use
- Time before procedure that anti-CDI antibiotics are used and stopped (comparing time courses)

**Comorbidities:**

- Severe CDI/ toxic megacolon vs non-severe disease
- Co-existing inflammatory bowel disease (IBD) vs no IBD
- Immunosuppression vs no immunosuppression
- Chronic liver disease/ cirrhosis vs no chronic liver disease

**Outcomes:**

- Critical: Cessation of diarrhoea and other symptoms/ relapse
- Quality of life
Serious adverse events

Important: Negative tests for Clostridium difficile infection

Adverse events

Study design: Randomised trials

If no randomised trials identified – prospective cohort studies, retrospective case series

Review Question 3: What donor factors influence the outcome of faecal microbiota transplant when treating people with Clostridium difficile infection?

Populations: Adults (18 years and over) with Clostridium difficile infection

Intervention: Faecal microbiota transplant

Comparison: Related vs unrelated donor

Donor working in healthcare setting vs donor not from healthcare setting

BMI (comparing cut-offs used)

Age (comparing ages)

Length of time since donor had antibiotics (comparing cut-offs used)

Outcomes: Critical: Cessation of diarrhoea and other symptoms/ relapse

Quality of life

Serious adverse events

Important: Negative tests for Clostridium difficile infection

Adverse events

Study design: Randomised trials

If no randomised trials identified – prospective cohort studies and retrospective case series
Review Question 4: What factors related to the preparation of the transplant influence the outcome of faecal microbiota transplant when treating people with Clostridium difficile infection?

Populations: Adults (18 years and over) with Clostridium difficile infection

Intervention: Faecal microbiota transplant

Comparison: Time after delivery when transplant is prepared (comparing time points)
- Anaerobic preparation vs preparation in ambient air
- Manual preparation vs use of blender/ homogeniser
- Diluent used (comparing normal saline, phosphate-buffered saline, water, milk/ yoghurt and others)
- Amount of stool/ transplant administered (comparing amounts)
- Fresh preparation vs frozen preparation:
  - comparing glycerol vs other cryopreservative
  - comparing concentration of cryopreservative used
  - comparing length of time that frozen for before use

Outcomes: Critical: Cessation of diarrhoea and other symptoms/ relapse
- Quality of life
- Serious adverse events

Important: Negative tests for Clostridium difficile infection
- Adverse events

Study design: Randomised trials
- If no randomised trials identified – prospective cohort studies and retrospective case series

Review Question 5: What factors related to administration of the transplant influence the outcome of faecal microbiota transplant when treating people with Clostridium difficile infection?

Populations: Adults (18 years and over) with Clostridium difficile infection
Intervention: Faecal microbiota transplant

Comparison: Upper GI administration (nasogastric, nasoduodenal or nasojejunal tube; upper GI endoscopy) vs lower GI administration (enema, rectal catheter, colonoscopy)

Encapsulated vs full transplant

Outcomes: Critical: Cessation of diarrhoea and other symptoms/ relapse

Quality of life

Serious adverse events

Important: Negative tests for *Clostridium difficile* infection

Adverse events

Study design: Randomised trials

If no randomised trials identified – prospective cohort studies, and retrospective case series

Review Question 6: What is the clinical effectiveness of faecal microbiota transplant in treating conditions other than *Clostridium difficile* infection?

Populations: Adults (18 years and over) with conditions of interest (e.g. inflammatory bowel disease)

Intervention: Faecal microbiota transplant

Comparison: Standard care for the condition of interest

Autologous faecal microbiota transplant

Outcomes: Critical: Clinical improvement

Improvement in laboratory/ radiological/ endoscopic tests

Quality of life

Serious adverse events

Important: Adverse events

Study design: Randomised trials
ii. **Literature search terms:**

**Review Questions 1 – 5:**

**EMBASE**

1. exp Clostridium difficile infection/ or exp Clostridium difficile toxin B/ or exp Clostridium difficile toxin A/
2. clostridium difficile.ti,ab.
3. c diff*.ti,ab.
4. (CDAD or RCDI or CDI).ti,ab.
5. pseudomembranous.ti,ab.
6. exp pseudomembranous colitis/
7. (antibiotic* adj2 (diarrhea or diarrhoea or colitis)).ti,ab.
8. (FMT or HPI).ti,ab.
9. ((fecal or faecal or feces or faeces or stool or microbiota) adj2 (transplant* or infus* or transfus* or implant* or instil* or donat* or donor* or reconstitut* or therap* or bacteriotherapy or encapsulated* or capsul*)).ti,ab.
10. (fecal or faecal or feces or faeces or stool or microbiota).ti,ab.
11. transplant*.ti,ab.
12. exp transplantation/
13. 8 or 9
14. 10 and (11 or 12)
15. 13 or 14
16. or/1-7
17. 15 and 16

**MEDLINE**
1. Clostridium difficile/
2. clostridium difficile.ti,ab.
3. c diff$.ti,ab.
4. Enterocolitis, Pseudomembranous/
5. (antibiotic$ adj2 (diarrhoea or colitis)).ti,ab.
6. (antibiotic$ adj2 (diarrhoea or colitis)).ti,ab.
7. pseudomembranous.ti,ab.
8. (CDAD or CDI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. RCDI.ti,ab.
10. Clostridium Infections/
11. FMT.mp. or HPI.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12. ((fecal or faecal or feces or faeces or stool or microbiota) adj2 (transplant$ or infus$ or transfus$ or implant$ or instil$ or donat$ or donor or reconstitut$ or therap$ or bacteriotherapy or encapsulated$ or capsul$)).ti,ab.
13. (fecal or faecal or feces or faeces or stool or microbiota).ti,ab.
14. (transplant$ or infus$ or transfus$ or implant$ or instil$ or donat$ or donor or reconstitut$ or therap$ or bacteriotherapy or encapsulated$ or capsul$).ti,ab.
15. Transplantation/
16. Transplants/
17. 11 or 12
18. 14 or 15 or 16
19. 13 and 18
20. 17 or 19
HIS/ BSG FMT Guideline: Main Document.

21. or/1-10

22. 20 and 21

Limits:
2. Studies in English only.
3. Human studies only.
4. Exclude case reports.
5. Exclude case series with less than 10 patients.

Review Question 6:

EMBASE

1. (FMT or HPI).ti,ab.

2. ((fecal or faecal or feces or faeces or stool or microbiota) adj2 (transplant* or infus* or transfus* or implant* or instil* or donat* or donor* or reconstitut* or therap* or bacteriotherapy)).ti,ab.

3. (fecal or faecal or feces or faeces or stool or microbiota).ti,ab.

4. transplant*.ti,ab.

5. exp transplantation/

6. 1 or 2

7. 3 and (4 or 5)

8. 6 or 7

9. (clostridium difficile or CDAD or RCDI or CDI).ti.

10. 8 not 9

11. limit 10 to (clinical trial or randomized controlled trial or controlled clinical trial)

MEDLINE
1. FMT.mp. or HPI.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

2. ((fecal or faecal or feces or faeces or stool or microbiota) adj2 (transplant$ or infus$ or transfus$ or implant$ or instil$ or donat$ or donor or reconstitut$ or therap$ or bacteriotherapy)).ti,ab.

3. (fecal or faecal or feces or faeces or stool or microbiota).ti,ab.

4. Transplantation/

5. Transplants/

6. transplant$.ti,ab.

7. Fecal Microbiota Transplantation/

8. 4 or 5 or 6

9. 3 and 8

10. 1 or 2 or 7 or 9

11. (clostridium difficile or cdiff or CDAD or RCDI or CDI or pseudomembranous).ti.

12. 10 not 11

13. limit 12 to (clinical trial or randomized controlled trial or controlled clinical trial)

**Limits:**

2. Studies in English only.
3. Human studies only.
4. Randomised trials only.

**iii. Summary of the data extraction and literature review process (includes Q1-6):**

![Flowchart showing the process of records identified, duplicates removed, studies included, and records excluded.](chart.png)
Appendix 3: Consultation Stakeholders:

Individuals or organisation who were invited to and/or attended the scoping day for these guidelines (as well as to provide feedback in stakeholder consultation) included:

- HRPA (Ireland) (Dr Eadaoin Griffin attended)
- Human Tissue Authority (Dr Robert Watson attended)
- NHS Wales
- NHS Scotland
- ECDC
- Royal College of Pathologists
- Royal College of General Practitioners
- Infection Prevention Society
- Public Health England
- Royal College of Physicians
- Royal College of Nursing
- Royal College of Surgeons
- ESCMID
- MRSA Action
- HSCNI
- Institute of Microbiology and Infection, University of Birmingham (Prof Peter Hawkey and Dr Victoria McCune attended)
- Microbiology, Royal Devon and Exeter NHS Foundation Trust (Dr Ray Sheridan, Dr Alaric Colville, Dr Robert Porter and Dr Melissa Baxter attended)
- C diff support (Ms Graziella Kontkowski attended)
- OpenBiome (Dr Majdi Osman and Dr Carolyn Edelstein attended)
- Dr Sally Cudmore (University College Cork) attended
- Dr Ngozi Elumogo attended (Microbiology, Norfolk & Norwich University NHS Trust)
- Dr Vanya Gant (University College London Hospitals)
- Dr Simon Goldenberg attended (Guy’s and St Thomas’ NHS Foundation Trust)
- Dr Bram Goorguis attended (Academic Medical Centre, Amsterdam)
• Dr Geraldine Moloney attended (Microbiology, Trinity College Dublin)
• Dr Benjamin Mullish attended (Imperial College Healthcare NHS Trust)
• Dr Laura Prtak attended (Sheffield Teaching Hospitals NHS Trust)
• Mr Glenn Taylor attended (Taymount Clinic)
• Dr Mark Wilks attended (Microbiology, Barts and The London NHS Trust)

Appendix 4. Continuing Professional Development material

1) In which of the following settings would you most strongly avoid giving a patient FMT?
   a) Immunocompromised patients
   b) Decompensated liver disease
   c) Heart failure
   d) History of anaphylactic food allergy
   e) A previous failed FMT

Answer: d

2) Where is FMT best sourced, if available?
   a) Related healthy donor
   b) Health care professional
   c) Centralised stool bank
   d) Pooled from multiple donors
   e) Any of above

Answer: c

3) What is the maximum recommended length of time between stool donation and stool processing?
   a) 6 hours
   b) 7 hours
   c) 8 hours
   d) 9 hours
   e) 10 hours

Answer: a
4) For which non-CDI condition is FMT currently recommended?
   a) Irritable bowel syndrome
   b) Obesity and metabolic syndrome
   c) Parkinson’s disease
   d) Ulcerative colitis
   e) None of the above

   Answer: e

5) When considering setting up an FMT service in the UK, which organisation should be contacted to seek guidance in establishing the service?
   a) Medicines and Healthcare Products and Regulatory Agency
   b) Medicines and Healthcare Products Regulatory Authority
   c) Medical Drugs and Healthcare Products and Regulatory Agency
   d) Medical Drugs and Healthcare Products Regulatory Authority
   e) None of the above

   Answer: b

Additional Appendices:

A: Scope.
B: Declarations of interest.
C: Clinical evidence tables.
D: Excluded clinical studies.
E: Peer review.
14. Figure legends and tables:

Figure 1: Proposed summary pathway for donor screening for centres preparing frozen FMT from recurring donors.

Table 1: Recommended donor history/ questionnaire: A positive response to any of these questions would usually result in exclusion from further consideration as a donor, although this would depend upon the particular circumstances/ answers given.

<table>
<thead>
<tr>
<th>Question</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of antimicrobials within the past three months.</td>
<td></td>
</tr>
<tr>
<td>Known prior exposure to HIV and/ or viral hepatitis, and known previous or latent tuberculosis.</td>
<td></td>
</tr>
<tr>
<td>Risk factors for blood-borne viruses - including high risk sexual behaviours, use of illicit drugs, any tattoo/ body piercing/ needlestick injury/ blood transfusion/ acupuncture, all within the previous six months.</td>
<td></td>
</tr>
<tr>
<td>Receipt of a live attenuated virus within the past six months.</td>
<td></td>
</tr>
<tr>
<td>Underlying gastrointestinal conditions/ symptoms (e.g. history of IBD, IBS, chronic diarrhoea, chronic constipation, coeliac disease, bowel resection or bariatric surgery) - also including acute diarrhoea/ gastrointestinal symptoms within the past two weeks.</td>
<td></td>
</tr>
</tbody>
</table>
6. Family history of any significant gastrointestinal conditions (e.g. family history of IBD, or colorectal cancer).
7. History of atopy (e.g. asthma, eosinophilic disorders).
8. Any systemic autoimmune conditions.
9. Any metabolic conditions, including diabetes and obesity.
10. Any neurological or psychiatric conditions, or known risk of prion disease.
11. History of chronic pain syndromes, including chronic fatigue syndrome and fibromyalgia.
12. History of any malignancy.
13. Taking particular regular medications, or such medications within the past three months, i.e. antimicrobials, proton pump inhibitors, immunosuppression, chemotherapy.
14. History of receiving growth hormone, insulin from cows, or clotting factor concentrates.
15. History of receiving an experimental medicine or vaccine within the past six months.
16. History of travel to tropical countries within the past six months.

Table 2: Recommended blood screening for stool donors: *EBV and CMV testing is only recommended where there is the potential that the FMT prepared from that donor will be administered to immunosuppressed patients at risk of severe infection if exposed to CMV and EBV.
Table 3: Recommended stool screening for stool donors: *Whilst CPE and ESBL are the only multi-drug resistant bacteria that are recommended to be screened for universally, consider testing for other resistant organisms (including vancomycin-resistant Enterococci (VRE) and/or methicillin-resistant Staphylococcus aureus (MRSA)) based upon risk assessment and local prevalence.
Table 4: Evidence statements and recommendations. A. Levels of evidence for intervention studies; B. Recommendation grading.

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.</td>
</tr>
</tbody>
</table>

- *Clostridium difficile* PCR
- *Campylobacter, Salmonella, and Shigella* by standard stool culture and/or PCR
- Shiga toxin-producing *Escherichia coli* by PCR.
- Multi-drug resistant bacteria, at least carbapenemase-producing *Enterobacteriaceae* (CPE) and extended-spectrum beta-lactamases (ESBL)*.
- Stool ova, cysts and parasite analysis, including for *Microsporidia*.
- Faecal antigen for *Cryptosporidium* and *Giardia*.
- Acid fast stain for *Cyclospora* and *Isospora*.
- *Helicobacter pylori* faecal antigen.
- Norovirus, Rotavirus PCR.
<table>
<thead>
<tr>
<th>Bias Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High-quality systematic reviews of case-control or cohort studies</td>
</tr>
<tr>
<td></td>
<td>High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series.</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

### B. Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the ‘strength’ of the recommendation).

The ‘strength’ of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

For ‘strong’ recommendations on interventions that ‘should’ be used, the working group is confident that, for the vast majority of people, the intervention (or interventions) will do more
good than harm. For ‘strong’ recommendations on interventions that ‘should not’ be used, the working group is confident that, for the vast majority of people, the intervention (or interventions) will do more harm than good.

For ‘conditional’ recommendations on interventions that should be ‘considered’, the working group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person’s values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

**Good practice points** are recommended best practice based on the clinical experience of the guideline working group.

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**Table 5: Criteria for stool collection:**

Clear instructions should be given to donors regarding hand hygiene.
Collect stool donations in a sealable clean container. A number of specifically designed devices are available commercially.

Stool should ideally be passed directly into the clean container for collection; alternatively, it may be collected in clean tissue and transferred to the clean container.

Stool should be transported to the FMT production site as soon as possible post defaecation (and within six hours); however, if a short period of storage is necessary, this should be at 4°C.
The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

Additional Appendices:

Appendix A. Scope

1. Guideline title

The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

1.1. Short title

The use of faecal microbiota transplant

2. The remit

i. To review the evidence (include randomised trial evidence) for the efficacy of faecal microbiota transplant (FMT) in the treatment of adults (≥18 years), both in *Clostridium difficile* infection (CDI) and in other clinical conditions, and use this to make recommendations about optimal recipient selection and management, donor assessment, material preparation and administration, and other key elements of FMT delivery.

ii. To provide specific guidance about best practice for an FMT service within the context of the regulatory framework for the intervention as it currently exists in the UK and beyond.

Whilst this is not a guideline specifically addressing the management of *Clostridium difficile* infection (CDI), the working group will include consideration of where FMT should be considered within the conventional treatment algorithm of patients with CDI (specifically, in which patients it should be considered, and at which point in their care).

The working group agreed that for the purposes of this guideline, faecal microbiota transplant would be defined as treatment that involves the administration of manipulated.
whole stool. There is a growing literature of the use of ‘bacteriotherapy’ originally deriving from healthy donor stool as a potential alternative to FMT (including commensal bacteria, spores, bacteriophages and/or bacterial proteins or metabolites). However, the working group considered this to still be at the research stage, and would not be considered further.

2.1. Population

2.1.1. Groups that will be covered

Adults (≥18 years) in whom:

i. FMT has been used as treatment for CDI.

ii. FMT has been used as treatment for a non-CDI indication.

Given the variability in the means used to diagnose CDI within different studies, the working group agreed to consider the suitability of the definition used on a study-by-study basis.

2.1.2. Groups that will not be covered

Children and young people (<18 years).

2.2. Healthcare setting

All settings in which National Health Service care is received, and/or clinical trials are undertaken.

2.3. Clinical management

2.3.1. Key clinical issues that will be covered

a) Appropriate selection of patients with CDI for FMT, and best practice in their management post-FMT.

b) Optimal selection of donors of faecal material, and maintenance of a donor pool.

c) Identification of the preferred means of preparation and administration of FMT to recipients.

d) Evaluation of the safety and efficacy of FMT in treating non-CDI indications.

e) Best practice in the development and delivery of an FMT service.

2.3.2. Clinical issues that will not be covered

a) General management of CDI.
Additional Appendices

b) General management of non-CDI conditions in which FMT may have a role in therapy.

2.4. Main outcomes

Recommendations for practice

a) Patient/recipient selection, and peri-FMT management
b) Donor selection
c) Preparation and administration of FMT
d) Efficacy and safety of FMT for non-CDI indications
e) Provision of an FMT service

2.5. Economic aspects

Where FMT is being provided under a MHRA license according to Good Manufacturing Practice (GMP) standards, there are significant costs associated with initial setup and maintenance of the service. These include the cost of obtaining the relevant license, laboratory design and equipment to enable quality assurance, storage facilities for samples, etc. However, there is counterbalance to this, as the expectation of the working group is that the publication of this guideline may encourage provision of FMT as treatment for recurrent or refractory CDI. This has consistently been shown to be cost effective in comparison with anti-*C. difficile* antimicrobial therapy^{31–34}, so overall costs associated with treating the condition may actually decrease. Furthermore, there may be changes to the practice of clinicians already offering the service. For example, encouraging the use of healthy unrelated donors (who can provide multiple stool donations after one screening) reduces the cost of screening when compared to the use of an FMT recipient’s relative as donor, who is likely to provide one donation only.

2.6. Status

2.6.1. Scope

This is the final scope.

2.6.2. Timing

The development of the guideline recommendation will begin in July 2017.
3. Related NICE guidance


4. Further information

*Guideline development process*

Appendix B. Declarations of interest

B.1. Introduction
All members of the Working Group were required to make formal declarations of interest at the outset, and these were updated throughout the development process. No interests were declared that required any actions.

B.2. Tariq Iqbal
First meeting 19/07/17: no declarations of interest; second meeting 04/10/17: no change.

Third meeting 19/10/17: consultant, advisor or speaker for: Pharmacosmos and Shield Therapeutics.

B.3. Simon Goldenberg (co-chair)
First meeting 19/07/17
Advisory board and/ or consultancy and/ or speaker fees: Astellas, MSD, Pfizer.

Second meeting 04/10/17; third meeting 19/10/17: no change.

No action required.

B.4. Ailsa Hart
First meeting 19/07/17
Advisory board and/ or consultancy and/ or speaker fees: AbbVie, Atlantic, Bristol-Myers Squibb, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. Global steering committee for Genentech.

Second meeting 04/10/17; third meeting 19/10/17: no change.

No action required.

No declared conflict of interests for the other participants.
Additional Appendices

Appendix C. Clinical evidence tables

C.1. Reviewed case series of FMT for recurrent or refractory CDI
<table>
<thead>
<tr>
<th>Paper</th>
<th>Study and patient characteristics</th>
<th>Donor characteristics</th>
<th>FMT characteristics</th>
<th>Outcomes</th>
<th>Adverse events</th>
<th>CRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aas et al, Clinical Infectious Diseases, 2003</td>
<td>Case series.</td>
<td>Donors were 15 family members, and 3 clinical volunteers.</td>
<td>Amount of stool per transplant / administered to patients: 30g stool in 50-70ml normal saline; only 25ml of total administered to patient.</td>
<td>Overall cure within stated follow up period: 83.3% (n=15/18). Cure with one infusion alone: 83.3% (n=15/18). Total follow-up period: 90 days.</td>
<td>Minor GI adverse events: Nil stated. Minor non-GI adverse events: Nil stated. Serious adverse events: Nil stated. Deaths: x2 - one related to ESRF, one related to COPD.</td>
<td>Selection/ eligibility reported: Yes. Consecutively recruited: Yes. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: No - 89%.</td>
</tr>
<tr>
<td></td>
<td>Number of patients: 18.</td>
<td>Working in healthcare: Yes - for 3 donors.</td>
<td>Diluent used to prepare: Normal saline. Diluent used to store if frozen: N/A – fresh.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female: male 13:5.</td>
<td>Donor demographics: Not defined.</td>
<td>Preparation methods: Homogenised in domestic blender, then coffee filter.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age (mean): 73+/9 (range 53-88) years.</td>
<td>Donor screening: Questionnaire not explicitly stated.</td>
<td>Time from preparation to transplant (fresh): 6 hours. Time period for storage (frozen): N/A.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbidities: x1 patient with Crohn's colitis, x1 with leukaemia.</td>
<td>Travel and antibiotic exclusion period: No antibiotics for 6 months prior; nil stated regarding travel.</td>
<td>Route administered: Upper GI: all nasogastric (18); lower GI: nil; capsules: nil.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDI features: Recurrent (at least 2 x laboratory-confirmed CDI after initial antibiotic treatment).</td>
<td>Screening blood tests: Hepatitis A, B and C, HIV-1/2, syphilis.</td>
<td>Number of infusions: Single infusion for all patients.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-FMT antibiotics: Metronidazole +/- vancomycin (not defined).</td>
<td>PPI: 20mg omeprazole on day prior to FMT and day of FMT.</td>
<td>Antimotility: Not described.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prokinetics: Not described.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of patients: 18. Female: male 13:5. Age (mean): 73+/9 (range 53-88) years. Comorbidities: x1 patient with Crohn's colitis, x1 with leukaemia. CDI features: Recurrent (at least 2 x laboratory-confirmed CDI after initial antibiotic treatment). CDI diagnosis confirmation: Cytotoxin A and B positivity. Pre-FMT antibiotics: Metronidazole +/- vancomycin (not defined).
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Time before CDI treatment was stopped before FMT: Continued until day of FMT.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Agrawal et al, *Journal of Clinical Gastroenterology, 2016*

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Donors were identified by the patient or - if not available - provided by the physician.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 146.</td>
<td>Working in healthcare: Not stated.</td>
</tr>
<tr>
<td>Female: male: 100: 46.</td>
<td>Donor demographics: No antibiotics for last three months. Excluded if significant GI disease, metabolic syndrome, chronic illness, immunocompromise, recent travel, and/or high risk lifestyle in last three months.</td>
</tr>
<tr>
<td>Age(mean): 78.6 (range 65-97) years.</td>
<td>Donor screening: Questionnaire - excluded if significant GI disease, metabolic syndrome, chronic illness, immunocompromise, recent travel, and/or high risk lifestyle in last three months.</td>
</tr>
<tr>
<td>Comorbidities: Immunosupression in 15 patients (x3 Crohn’s, x2 UC, x1 renal transplant)</td>
<td>Travel and antibiotic exclusion period: Exclusion if travel to an area of high incidence of infectious diarrhoea, and/or antibiotics within last three months.</td>
</tr>
<tr>
<td>CDI features: 89 with recurrent CDI.</td>
<td>Number of infusions: 1 routinely; 2nd infusion given with vancomycin so data unusable to be extracted.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: As per ACG guidelines.</td>
<td>Bowel purgative: PEG on day prior to FMT.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: All had prior metronidazole, vancomycin and/or fidaxomicin.</td>
<td>Antimotility: Loperamide on day of FMT.</td>
</tr>
<tr>
<td></td>
<td>Prokinetics: Not stated.</td>
</tr>
<tr>
<td></td>
<td>Time before CDI treatment was stopped</td>
</tr>
<tr>
<td></td>
<td>Amount of stool per transplant / administered to patients: 60-100g of fresh stool.</td>
</tr>
<tr>
<td></td>
<td>Diluent used to prepare: Normal saline, upper GI: 75-200ml; lower GI: 250-400ml; enema: 150-200ml.</td>
</tr>
<tr>
<td></td>
<td>Diluent used to store if frozen: N/A – fresh.</td>
</tr>
<tr>
<td></td>
<td>Preparation methods: Handstirred and blender, sifted through gauze.</td>
</tr>
<tr>
<td></td>
<td>Time from preparation to transplant (fresh): Not stated.</td>
</tr>
<tr>
<td></td>
<td>Time period for storage (frozen): N/A.</td>
</tr>
<tr>
<td></td>
<td>Route administered: upper GI (16); lower GI (130); capsules: nil.</td>
</tr>
<tr>
<td></td>
<td>Number of infusions: 1 routinely; 2nd infusion given with vancomycin so data unusable to be extracted.</td>
</tr>
<tr>
<td></td>
<td>Bowel purgative: PEG on day prior to FMT.</td>
</tr>
<tr>
<td></td>
<td>PPI: Not stated.</td>
</tr>
<tr>
<td></td>
<td>Antimotility: Loperamide on day of FMT.</td>
</tr>
<tr>
<td></td>
<td>Prokinetics: Not stated.</td>
</tr>
<tr>
<td></td>
<td>Time before CDI treatment was stopped</td>
</tr>
<tr>
<td></td>
<td>Overall cure within stated follow-up period: 83% (n=121/146).</td>
</tr>
<tr>
<td></td>
<td>Cure with one infusion alone: 83% (n=121/146).</td>
</tr>
<tr>
<td></td>
<td>Total follow up period: mean follow up was 12.3 months (range 1-48 months).</td>
</tr>
<tr>
<td></td>
<td>Minor GI adverse events: Nil stated.</td>
</tr>
<tr>
<td></td>
<td>Minor non-GI adverse events: Nil stated.</td>
</tr>
<tr>
<td></td>
<td>Serious adverse events: x2 microscopic colitis, x1 Sjögren’s, x1 scalp follicular lymphoma, x1 contact dermatitis and idiopathic Bence-Jones gammaglobulinaemia. In addition, x1 SCC, x1 ileus (died two weeks after ileus), x1 colonic perforation secondary to CMV colitis and subsequent death after 1 year. Patients developing cancers had underlying risk factors.</td>
</tr>
<tr>
<td></td>
<td>Deaths: x10 (x4 decompensated CCF, x3 malignancies, x1 dementia, x1...</td>
</tr>
</tbody>
</table>
and parasites, *Giardia*,
*Cryptosporidium*, *Isospora*, *H. pylori*, *Rotavirus*.

before FMT: Between 3 days prior to FMT and one day prior to FMT.

stroke, x1 pneumonia); deaths between 19 days to 7 months post-FMT.
Additional Appendices

Alrabaa et al, Transplant Infectious Diseases, 2017

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 13.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 8:5.</td>
<td></td>
</tr>
<tr>
<td>Age (median): 69 (range 59-74) years.</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: Yes - x4 OLT, x1 kidney/ liver transplant, x1 lung transplant, x1 HIV+ with CD4 count of 453. x1 immunocompromised patients with IBS, x1 immunocompetent patient with IBS; no IBD patients.</td>
<td></td>
</tr>
<tr>
<td>CDI features: Not clear if recurrent or refractory. Mean of 4 previous episodes of CDI prior to FMT.</td>
<td></td>
</tr>
<tr>
<td>CDI diagnosis confirmation: PCR.</td>
<td></td>
</tr>
<tr>
<td>Pre-FMT antibiotics: All patients had previously had oral vancomycin, x7 prev metronidazole (either with or without vancomycin). x5 received fidaxomicin</td>
<td></td>
</tr>
<tr>
<td>Donors were unrelated.</td>
<td></td>
</tr>
<tr>
<td>Working in healthcare: Nox</td>
<td></td>
</tr>
<tr>
<td>Donor demographics: As per OpenBiome protocolx</td>
<td></td>
</tr>
<tr>
<td>Donor screening: Questionnaire - as per OpenBiome protocolx</td>
<td></td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: As per OpenBiome protocolx</td>
<td></td>
</tr>
<tr>
<td>Screening bloods: FBC, hepatitis A, B and C, LFTs, HIV, HTLV-1/-2, syphilis.</td>
<td></td>
</tr>
<tr>
<td>Screening stools: C. difficile toxin, MC&amp;S, ova, cysts and parasites, H.pylori stool antigen.</td>
<td></td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: 12.5g of stool in 28.5g of product.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to prepare: normal saline - diluted to approx 100-150ml to administer.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to store if frozen: Not clear.</td>
<td></td>
</tr>
<tr>
<td>Preparation methods: As per OpenBiome protocol.</td>
<td></td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): N/A.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): As per OpenBiome protocol - not described in paper.</td>
<td></td>
</tr>
<tr>
<td>Route administered: Upper GI (nasoduodenal): 13; lower GI: 0; capsules: nil.</td>
<td></td>
</tr>
<tr>
<td>Number of infusions: One routinely, but retreated if relapsed after primary outcome. However - one renal transplant patient received 2 doses of FMT on consecutive days (with successful outcome).</td>
<td></td>
</tr>
<tr>
<td>Bowel purgative: Bowel preparation used - GoLytely (PEG).</td>
<td></td>
</tr>
<tr>
<td>PPI: 40mg pantoprazole night before and morning of procedure.</td>
<td></td>
</tr>
<tr>
<td>Overall cure within stated follow up period: 84.6% (n=11/13) at eight weeks post-FMT.</td>
<td></td>
</tr>
<tr>
<td>Cure with one infusion alone: 100% (n=13/13) at 5 days.</td>
<td></td>
</tr>
<tr>
<td>Total follow up period: Follow up up to 8 weeks described.</td>
<td></td>
</tr>
<tr>
<td>Minor GI adverse events: Several patients transient cramps and/ or diarrhoea.</td>
<td></td>
</tr>
<tr>
<td>Minor non-GI adverse events: Nil noted.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events: x1 patient had episode of CMV reactivation at the time of FMT - thought unrelated. X1 patient had episode of mild transplant rejection two months after FMT - thought unrelated.</td>
<td></td>
</tr>
<tr>
<td>Deaths: None.</td>
<td></td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
<td></td>
</tr>
<tr>
<td>Consecutively recruited: Not clearly described.</td>
<td></td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
<td></td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
<td></td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
<td></td>
</tr>
</tbody>
</table>
Additional Appendices

<table>
<thead>
<tr>
<th>with or after oral vancomycin.</th>
<th>Antimotility: Loperamide 4mg 1 hour post FMT.</th>
<th>Prokinetics: Not described.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time before CDI treatment was stopped before FMT: See last box.</td>
<td></td>
</tr>
</tbody>
</table>
## Additional Appendices

**Brandt et al, American Journal of Gastroenterology, 2012**

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Amount of stool per transplant / administered to patients: 6 tablespoons of stool up to entire donation; 300-700ml of transplant administered.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 77.</td>
<td>Diluent used to prepare: Normal saline.</td>
</tr>
<tr>
<td>Female: male: 56: 21.</td>
<td>Diluent used to store if frozen: N/A – fresh.</td>
</tr>
<tr>
<td>Age (mean): 65+/-17 (range 22-87) years.</td>
<td>Preparation methods: Hand blender used to prep.</td>
</tr>
<tr>
<td>Comorbidities: Not stated.</td>
<td>Time from preparation to transplant (fresh): Within 8 hours.</td>
</tr>
<tr>
<td>CDI features: All recurrent/ refractory.</td>
<td>Time period for storage (frozen): N/A.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Not clear.</td>
<td>Route administered: Upper GI: 0; lower GI: all 77 colonoscopic.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: 62 patients had had prior metronidazole, 76 vancomycin (25 tapered vancomycin), 17 rifaximin.</td>
<td>Number of infusions: 77 patients had one (patients that had second not included because given with concurrent vancomycin).</td>
</tr>
<tr>
<td>Screening blood tests: HIV-1, HIV-2, hepatitis A, B and C, Syphilis.</td>
<td>Bowel purgative: All patients given prep but no details.</td>
</tr>
<tr>
<td>Screening stool tests: <em>Clostridium difficile toxin</em> (if unavailable then EIA), MC&amp;S, <em>Giardia, Cryptosporidium</em>, ova, cysts and parasites, <em>H.pylori</em>, Acid Fast stain for <em>Cyclospora, Isospora</em>.</td>
<td>PPI: Not described.</td>
</tr>
<tr>
<td>Overall cure within stated follow up period: N/A.</td>
<td>Antimotility: Not described.</td>
</tr>
<tr>
<td>Minor GI adverse events: Not stated.</td>
<td>Prokinetics: Not described.</td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not stated.</td>
<td>Time before CDI treatment was stopped</td>
</tr>
<tr>
<td>Deaths: x7 deaths (cause unknown in one case, x1 metastatic colorectal cancer (present from pre-FMT), x1 metastatic ovarian cancer, x1 pneumonia (non-enteric organism), x1 MI, x1 stroke, x1 sepsis five months after FMT.</td>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: Not clear.</td>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Loss to follow up explained: Reported but not explained.</td>
<td>At least 90% followed up: No - only 77%.</td>
</tr>
</tbody>
</table>
Additional Appendices

before FMT: 3 days.
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 42.</th>
<th>Overall cure within stated follow up period: 71% (n=30/42).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 23: 19.</td>
<td>Female: male: 23: 19.</td>
<td>Cure with one infusion alone: 71% (n=30/42) - remission in 94% (n=16/17) otherwise healthy children, 54% (n=7/13) (54%) with IBD, 75% (n=9/12) medically complex. Success in 71% of children when via NGT, and 67% via gastrostomy (non-significant).</td>
</tr>
<tr>
<td>Age (median): 9 (range 1 -18) years.</td>
<td>Age (median): 9 (range 1 -18) years.</td>
<td>Total follow up period: 5 patients with initial failure opted for 2nd and 2 cured, so total success of 76% (n=32/42).</td>
</tr>
<tr>
<td>Comorbidities: 31% had IBD (x4 Crohn’s, x9 UC); 29% ‘medically complex’, including oncological, metabolic, cardiopulmonary or neurological diagnoses.</td>
<td>Comorbidities: 31% had IBD (x4 Crohn’s, x9 UC); 29% ‘medically complex’, including oncological, metabolic, cardiopulmonary or neurological diagnoses.</td>
<td>Minor GI adverse events: 6/47 FMT administrations accompanied by vomiting within 24hrs; self-resolved.</td>
</tr>
<tr>
<td>CDI diagnosis: Diarrhoea, haematochezia and/ or crampy abdominal pain in combination with positive C. difficile PCR.</td>
<td>CDI diagnosis: Diarrhoea, haematochezia and/ or crampy abdominal pain in combination with positive C. difficile PCR.</td>
<td>Minor non-GI adverse events: Nil reported.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Not stated.</td>
<td>Pre-FMT antibiotics: Not stated.</td>
<td>Serious adverse events: Nil reported.</td>
</tr>
</tbody>
</table>

| Donor: OpenBiome-supplied FMT. | Diluent used to prepare: As per OpenBiome protocol |
| Working in healthcare: No. | Diluent used to store if frozen: As per OpenBiome protocol |
| Donor demographics: Not stated. | Preparation methods: As per OpenBiome protocol |
| Donor screening: Questionnaire: As per OpenBiome protocol. | Time from preparation to transplant (fresh): None given fresh |
| Travel and antibiotic exclusion period: As per OpenBiome protocol. | Time period for storage (frozen): N/A |
| Screening bloods: As per OpenBiome protocol. | Route administered: Upper GI: 41, nasogastric administration (some children used pre-existing gastrostomy); lower GI: 0; capsules: 1 (1 x 30 capsules). |
| Screening stools: As per OpenBiome protocol. | Number of infusions: 1 routinely |
| Bowel purgative: Not stated | PPI: Rantidine for 24hrs prior to FMT |
| Antimotility: N/A | Prokinetics: N/A |
| Time before CDI treatment was stopped | Time before CDI treatment was stopped |

| Amount of stool per transplant / administered to patients: 30ml OpenBiome aliquot/capsule, although not defined re stool quantity. |
| Consecutively recruited: Yes. | Consecutively recruited: Yes. |
| Loss to follow up explained: Yes. | Loss to follow up explained: Yes. |
| At least 90% followed up: Yes. | At least 90% followed up: Yes. |
before FMT: 48 hours, after minimum of 5 days of vancomycin.
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Donors were age 18 - 50, no medications, BMI 18.5 – 25.</th>
<th>Amount of stool per transplant / administered to patients: 41g of stool on average.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 35.</td>
<td>Working in healthcare: Not stated.</td>
<td>Diluent used to prepare: Normal saline.</td>
</tr>
<tr>
<td>Age (mean): 43 (range 8 - 93) years.</td>
<td>Donor screening: Questionnaire - adapted from US blood bank.</td>
<td>Preparation methods: Ambient air.</td>
</tr>
<tr>
<td>Comorbidities: IBD in all, 8 on corticosteroids, 3 on Immunomodulators, 11 on biologics.</td>
<td>Travel and antibiotic exclusion period: Excluded if antibiotic within past six months.</td>
<td>Time from preparation to transplant (fresh): N/A; given fresh.</td>
</tr>
<tr>
<td>CDI features: Recurrent - at least 2 episodes.</td>
<td>Screening blood tests: FBC, U&amp;E, LFTs, CRP, ANA, hepatitis A, B and C, HBV, HIV-1/-2, syphilis.</td>
<td>Time period for storage (frozen): Up to 156 days.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Not stated.</td>
<td>Screening stool tests: Faecal occult blood, rotavirus, bacterial pathogens, ova, cysts and parasites, Acid fast stain for Giardia and Cryptosporidium, C difficile, H. pylori.</td>
<td>Route administered: Upper GI: 5 via nasogastric tube; lower GI: 3 via colonoscopy; capsule: 27 patients.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Not stated.</td>
<td>Overall cure within stated follow up period: N/A.</td>
<td>Number of infusions: Not stated.</td>
</tr>
<tr>
<td></td>
<td>PPI: 7 on PPI not as premedications.</td>
<td>Total follow up period: At least 2 months (range 2 to 6 months).</td>
</tr>
<tr>
<td></td>
<td>Antimotility: Not described.</td>
<td>Serious adverse events: two required surgery (diverting colostomy and total proctectomy), two developed perianal disease with no prior history of it.</td>
</tr>
<tr>
<td></td>
<td>Prokinetics: Not described.</td>
<td>Deaths: Ni.</td>
</tr>
<tr>
<td></td>
<td>Time before CDI treatment was stopped before FMT: 2 days prior to FMT.</td>
<td>Minor GI adverse events: Not specified.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minor non-GI adverse events: Not specified.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Selection/ eligibility reported: No.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consecutively recruited: No.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss to follow up explained: No.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At least 90% followed up: No.</td>
</tr>
</tbody>
</table>
Additional Appendices

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Amount of stool per transplant / administered to patients: 60g stool average (35-75g), 250ml total once mixed with saline (100 - 300ml range).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 22.</td>
<td>Diluent used to prepare: Normal saline.</td>
</tr>
<tr>
<td>Female: male: 9: 13.</td>
<td>Diluent used to store if frozen: Not stated.</td>
</tr>
<tr>
<td>Age (median): Median 71.5 (range 16-92) years.</td>
<td>Preparation methods: Some fresh, some frozen.</td>
</tr>
<tr>
<td>Comorbidities: x1 IBD (colonoscopic group), x2 patients on chemotherapy, unclear why.</td>
<td>Time from preparation to transplant (fresh): Not stated.</td>
</tr>
<tr>
<td>CDI features: Recurrent or refractory.</td>
<td>Time period for storage (frozen): No details.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Diarrhoea and toxin testing.</td>
<td>Route administered: Upper GI: nasoduodenal in 10; lower GI: colonoscopic in 12.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: 19 patients given previous metronidazole, 9 vancomycin (with 13 both together).</td>
<td>Number of infusions: 1 FMT.</td>
</tr>
<tr>
<td>Screening bloods: No details.</td>
<td>Bowel purgative: 3l of PEG if colonoscopic administration.</td>
</tr>
<tr>
<td>Screening stools: No details.</td>
<td>PPI: PPI if upper GI administration.</td>
</tr>
<tr>
<td>Donors were 13 unrelated, 9 related.</td>
<td>Antimotility: Not described.</td>
</tr>
<tr>
<td>Working in healthcare: Yes - for unrelated.</td>
<td>Prokinetics: Metoclopramide just prior to upper GI administration.</td>
</tr>
<tr>
<td>Donor screening: Questionnaire - no details.</td>
<td>Time before CDI treatment was stopped</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded if antibiotics within past six months.</td>
<td>Overall cure within stated follow up period: 72.7% (n=16/22) at 2 months.</td>
</tr>
<tr>
<td>Screening bloods: No details.</td>
<td>Cure with one infusion alone: 72.7% (n=16/22) (5/10 upper GI (out of 7 analysed), 91.7% (n=11/12) for lower GI (out of 11 analysed)).</td>
</tr>
<tr>
<td>Screening stools: No details.</td>
<td>Total follow up period: Results reported at two months, but followed up to six months (7 months in the upper GI arm and 5 in the lower GI arm followed up to 6 months).</td>
</tr>
<tr>
<td>Donor screening: Questionnaire - no details.</td>
<td>Minor GI adverse events: x5 transient constipation/ abdominal discomfort.</td>
</tr>
<tr>
<td>Donor screening: Questionnaire - no details.</td>
<td>Minor non-GI adverse events: Not stated.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded if antibiotics within past six months.</td>
<td>Serious adverse events: See deaths.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded if antibiotics within past six months.</td>
<td>Deaths: x7 (x1 due to CDI, x1 chronic resp disease, x1 related to dialysis, x2 pneumonia, x1 sepsis at ten days post-FMT (aspiration of stool; had been gastroscopic administration), x1 died at home ?cause).</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded if antibiotics within past six months.</td>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded if antibiotics within past six months.</td>
<td>Consecutively recruited: Yes.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded if antibiotics within past six months.</td>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded if antibiotics within past six months.</td>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded if antibiotics within past six months.</td>
<td>At least 90% followed up: Yes.</td>
</tr>
</tbody>
</table>
### Additional Appendices

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th>before FMT: 12-24hrs.</th>
<th></th>
<th></th>
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</tr>
</thead>
</table>

| Case series. | Donors were 4 healthy volunteers. |
| Number of patients: 20. | Working in healthcare: No. |
| Female: male: not stated. | Donor demographics: No details. |
| Age (median): 69 years. | Donor screening: Questionnaire adapted from US blood bank. |
| Comorbidities: Not stated. | Travel and antibiotic exclusion period: Excluded if travel to diarrhoea-endemic areas within 6 months and/or used antibiotics for 3 months. |
| Pre-FMT antibiotics: Conventional therapy with metronidazole, vancomycin and/or fidaxomicin had failed in all. | Amount of stool per transplant / administered to patients: Not stated. |
| Diluent used to prepare: Normal saline. | Diluent used to store if frozen: 10% glycerol. |
| Preparation methods: Anaerobically prepared. | Time from preparation to transplant (fresh): all frozen. |
| Time period for storage (frozen): 16 patients had stool stored for < 2 months. 4 patients had stool stored > 2 months. | Route administered: Upper GI: 1; lower GI: 19; capsule: nil. |
| Number of infusions: 17 patients had 1, 3 patients had 2. | Bowel purgative: Not reported. |
| PPI: Not reported. | Antimotility: Not reported. |
| Prokinetics: Not reported. | Time before CDI treatment was stopped before FMT: Not reported. |

| Overall cure within stated follow up period: 85% (*n*=17/20). | Minor GI adverse events: None. |
| Cure with one infusion alone: 85% (*n*=17/20). | Minor non-GI adverse events: None. |
| Total follow up period: Minimum 3 months (but up to 14 months). | Serious adverse events: None. |
| Deaths: None. | Loss to follow up explained: Yes. |

| Selection/ eligibility reported: Yes. | Consecutively recruited: Yes. |
| Prospectively recruited: No. | At least 90% followed up: Yes. |
## Case series.

- **Number of patients:** 23.
- **Female:** male: 14: 9.
- **Age (median):** 66 years (range 25-99) years (including 8 additional patients treated with ‘bacteriotherapy’).
- **Comorbidities:** 3 with diabetes mellitus, 1 with microscopic colitis.
- **CDI features:** All recurrent.
- **CDI diagnosis confirmation:** Culture and/or toxin EIA.
- **Pre-FMT antibiotics:** Metronidazole and/or vancomycin used in all patients beforehand.

### Donors

- **Donors were spouses or close relative.**
- **Donor working in healthcare:** No.
- **Donor demographics:** Not stated.
- **Donor screening:** Questionnaire – asked regarding current and previous GI diagnoses/ symptoms.
- **Travel and antibiotic exclusion period:** Definitely an antibiotic use restriction but not clearly stated.
- **Screening blood tests:** HIV-1 and -2, hepatitis C virus, and hepatitis B surface antigen.
- **Screening stool tests:** *Salmonella, Shigella, Campylobacter, enterohemolytic Escherichia coli, and Clostridium difficile.*
- **Amount of stool per transplant / administered to patients:** 50g in 500mls.
- **Diluent used to prepare:** Normal saline.
- **Diluent used to store if frozen:** N/A - fresh.
- **Preparation methods:** Anaerobically prepared.
- **Time from preparation to transplant (fresh):** Not stated.
- **Time period for storage (frozen):** N/A.
- **Route administered:** Upper GI: nil; lower GI: 23 (enema/ rectal catheter); capsules: nil.
- **Number of infusions:** 22 patients received 1 FMT, 1 patient received 2 FMTs.
- **Bowel purgative:** Not stated.
- **PPI:** Not stated.
- **Antimotility:** Not stated.
- **Prokinetics:** Not stated.
- **Time before CDI treatment was stopped before FMT:** Not stated.

### Overall cure within stated follow up period:

- 65% (n=15/23).
- Cure with one infusion alone: 65% (n=15/23).

### Total follow up period:

- Median follow up of 18 months (range 0-201 months).

### Minor GI adverse events: None.

### Minor non-GI adverse events: None.

### Serious adverse events: None.

### Deaths: None.

### Selection/eligibility reported: Yes.

### Consecutively recruited: Yes.

### Prospectively recruited: No.

### Loss to follow up explained: Yes.

### At least 90% followed up: Yes.
### Additional Appendices

<table>
<thead>
<tr>
<th>Case series</th>
<th>Donors were patient-directed donor or unrelated healthy volunteers.</th>
<th>Amount of stool per transplant / administered to patients: lower GI: 25-50ml; upper GI: 250-500ml.</th>
<th>Overall cure within stated follow up period: 90% (n=60/67) within 3 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 67</td>
<td>Donors working in healthcare: not stated.</td>
<td>Diluent used to prepare: Preservative-free normal saline or 4% milk.</td>
<td>Cure with one infusion alone: 79% (n=53/67).</td>
</tr>
<tr>
<td>Comorbidities: x5 PSC, x4 liver transplant, x3 end stage liver disease, concurrent IBD in all (x35 Crohn’s, x31 UC, x1 indeterminate colitis).</td>
<td>Travel and antibiotic exclusion period: Excluded as donor if travel within last 6 months where diarrheal illnesses are endemic or risk of travelers diarrhea is high, and/or use of antibiotics within 3 months.</td>
<td>Time from preparation to transplant (fresh): Certainly within 24 hours, and preferably within 6 hours.</td>
<td>Minor non-GI adverse events: x4 pneumonia.</td>
</tr>
<tr>
<td>CDI features: recurrent or refractory.</td>
<td>Screening blood tests: HIV -1 &amp; -2, hepatitis A, B and C, syphilis.</td>
<td>Time period for storage (frozen): N/A.</td>
<td>Serious adverse events: x1 colectomy for refractory IBD, x7 hospitalised, x2 CDI recurrence, x2 IBD exacerbation, x1 small bowel obstruction, x1 CMV colitis.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: metronidazole in 47 patients, vancomycin in 63, vancomycin taper in 38 patients, fidaxomicin in 7, rifaxamin in 7.</td>
<td>Bowel purgative: Standard bowel preparation, but not specified.</td>
<td>Number of infusions: 53 patients received one infusion, 14 received 2 infusions.</td>
<td>Selection/eligibility reported: Yes.</td>
</tr>
<tr>
<td>Minor GI adverse events: x1 IBD flare, managed as outpatient.</td>
<td>PPI: If upper GI administration, PPI on the evening before and morning of the procedure.</td>
<td>Bowel purgative: Standard bowel preparation, but not specified.</td>
<td>Consecutively recruited: No.</td>
</tr>
<tr>
<td>Serious adverse events: x1 colectomy for refractory IBD, x7 hospitalised, x2 CDI recurrence, x2 IBD exacerbation, x1 small bowel obstruction, x1 CMV colitis.</td>
<td>Deaths: none.</td>
<td>Minor GI adverse events: x1 IBD flare, managed as outpatient.</td>
<td>Loss to follow up explained: N/A.</td>
</tr>
<tr>
<td>At least 90% followed up: N/A.</td>
<td>Minor non-GI adverse events: x4 pneumonia.</td>
<td>Serious adverse events: x1 colectomy for refractory IBD, x7 hospitalised, x2 CDI recurrence, x2 IBD exacerbation, x1 small bowel obstruction, x1 CMV colitis.</td>
<td>At least 90% followed up: N/A.</td>
</tr>
</tbody>
</table>
Additional Appendices

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antimotility: Loperamide optional for lower GI administration.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prokinetics: Not stated.</td>
<td></td>
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<tr>
<td></td>
<td>Time before CDI treatment was stopped before FMT: 24-48 hrs.</td>
<td></td>
</tr>
<tr>
<td>Case series.</td>
<td>Amount of stool per transplant / administered to patients: Not specified.</td>
<td></td>
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<tr>
<td>---</td>
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<td></td>
</tr>
<tr>
<td>Number of patients: 328.</td>
<td>Diluent used to prepare: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Female: male: 241: 87.</td>
<td>Diluent used to store if frozen: Both fresh and frozen, but specific details not given.</td>
<td></td>
</tr>
<tr>
<td>Age (mean/ standard deviation): 61.4 (+/-19.3) years.</td>
<td>Preparation methods: Dependent upon individual centre.</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: 77 immunocompromised (x3 CVID, x3 selective IgA deficiency, x71 immunosuppressants (20 for solid organ transplant, 29 for IBD, 6 for rheumatoid arthritis, 2 for SLE, 1 for pemphigoid, 1 for chronic obstructive airway disease, 1 for psoriasis)), x11 chemotherapy for malignancy, x63 IBD (25 UC, 33 Crohn’s), x118 diverticulosis.</td>
<td>Time from preparation to transplant (fresh): Dependent upon individual centre.</td>
<td></td>
</tr>
<tr>
<td>CDI features: Recurrent disease in 87.2% and severe or severe-complicated in 12.8%.</td>
<td>Time period for storage (frozen): Dependent upon individual centre.</td>
<td></td>
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<tr>
<td>CDI diagnosis confirmation: Positive stool C difficile toxin or</td>
<td>Route administered: Not specified (‘predominantly colonoscopy’).</td>
<td></td>
</tr>
<tr>
<td>Donors were 130 (40%) patient-directed donors, and 198 universal (60%).</td>
<td>Number of infusions: Dependent upon individual centre.</td>
<td></td>
</tr>
<tr>
<td>Donor working in healthcare: Not stated.</td>
<td>Bowel purgative: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Donor demographics: Not stated.</td>
<td>PPI: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Depended upon individual centre.</td>
<td>Prokinetics: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Screening blood tests: Depended upon individual centre.</td>
<td>Time before CDI treatment was stopped before FMT: Dependent upon each centre.</td>
<td></td>
</tr>
<tr>
<td>Screening stool test: Depended upon individual centre.</td>
<td>Overall cure within stated follow up period: 1 month 81.4% (n=267/328).</td>
<td></td>
</tr>
<tr>
<td>Minor GI adverse events: Not specified.</td>
<td>Cure with one infusion alone: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not specified.</td>
<td>Total follow up period: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events: Not specified.</td>
<td>Deaths: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
<td>Consecutively recruited: No.</td>
<td></td>
</tr>
<tr>
<td>Consecutively recruited: No.</td>
<td>Prospectively recruited: No.</td>
<td></td>
</tr>
<tr>
<td>Loss to follow up explained: N/A.</td>
<td>At least 90% followed up: N/A.</td>
<td></td>
</tr>
</tbody>
</table>
### Additional Appendices

<table>
<thead>
<tr>
<th>PCR.</th>
<th>Pre-FMT antibiotics: vancomycin.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Fischer et al, Gut Microbes, 2017</td>
<td></td>
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<tr>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>Case series.</td>
<td></td>
</tr>
<tr>
<td>Number of patients: 57.</td>
<td></td>
</tr>
<tr>
<td>Female: male: 34: 23.</td>
<td></td>
</tr>
<tr>
<td>Age (median): Median 72 (range 25-99) years.</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: x7 toxic megacolon, x12 acute kidney injury (x3 needing dialysis), x10 with hypovolaemic/ septic shock, x7 mental status changes, x4 on mechanical ventilation. x10 patients had inflammatory bowel disease (x5 with Crohn’s and x5 with ulcerative colitis) and x10 patients were on immunosuppressive medications.</td>
<td></td>
</tr>
<tr>
<td>CDI features: Severe, recurrent and severe-complicated.</td>
<td></td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Positive stool C.difficile PCR.</td>
<td></td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Included vancomycin,</td>
<td></td>
</tr>
<tr>
<td>Donors were screened patient-selected donors for first 29 patients, whilst next 28 from OpenBiome stool bank.</td>
<td></td>
</tr>
<tr>
<td>Donors working in healthcare: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Donor demographics: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Donor screening: Questionnaire – for patient-selected donors, this was as for Bakken et al, Clin Gastroenterol Hepatol, 2011; for OpenBiome, as per OpenBiome protocol.</td>
<td></td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: For patient-selected donors, this was as for Bakken et al, Clin Gastroenterol Hepatol, 2011; for OpenBiome, as per OpenBiome protocol.</td>
<td></td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): 6 hours.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): As per OpenBiome protocols.</td>
<td></td>
</tr>
<tr>
<td>Route administered Upper GI: nil; lower GI: 57 via colonoscopy or sigmoidoscopy.</td>
<td></td>
</tr>
<tr>
<td>Number of infusions: 32 patients: x1, 20 patients x2, 5 patients x3, 1 patient x4,1 patient x5. Pre-planned protocol for serial FMTs +/- vancomycin, as described in Fischer et al, Alim Pharm Ther, 2015.</td>
<td></td>
</tr>
<tr>
<td>Bowel purgative: Not stated.</td>
<td></td>
</tr>
<tr>
<td>PPI: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: As per Fischer et al, Alim Pharm Ther, 2015 or OpenBiome.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to prepare: As per Fischer et al, Alim Pharm Ther, 2015 or OpenBiome.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to store if frozen: As per Fischer et al, Alim Pharm Ther, 2015 or OpenBiome.</td>
<td></td>
</tr>
<tr>
<td>Overall cure within stated follow up period: 91% (n=52/57), i.e. 100% severe CDI (n=19/19), and 87% (n=33/38).</td>
<td></td>
</tr>
<tr>
<td>Cure with one infusion alone: 52.6% (n=30/57).</td>
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<tr>
<td>Total follow up period: Up to 6 months.</td>
<td></td>
</tr>
<tr>
<td>Minor GI adverse events: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Deaths: x7 unrelated deaths, x4 CDI-related deaths.</td>
<td></td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
<td></td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
<td></td>
</tr>
<tr>
<td>Prospectively recruited: Yes.</td>
<td></td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
<td></td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
<td></td>
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<tr>
<td>Additional Appendices</td>
<td></td>
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<tr>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>fidaxomicin, rectal, vancomycin, intravenous metronidazole.</td>
<td>for OpenBiome, as per OpenBiome protocol.</td>
</tr>
<tr>
<td>Fischer et al, Alimentary Pharmacology and Therapeutics, 2015</td>
<td></td>
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<tr>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Case series.</strong> Number of patients: 29.</td>
<td></td>
</tr>
<tr>
<td>Female: male: 17: 12.</td>
<td></td>
</tr>
<tr>
<td>Age (mean/standard deviation): Overall, mean 65.2 (+/-17.9)</td>
<td></td>
</tr>
<tr>
<td>years (range 25-92 years); mean 60.8 (range 26-87) years;</td>
<td></td>
</tr>
<tr>
<td>mean 67.6 (range 60-78) years in severe-complicated.</td>
<td></td>
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<tr>
<td>Comorbidities: x3 Crohn's, x2 UC, x1 hypogammaglobulinaemia,</td>
<td></td>
</tr>
<tr>
<td>x1 ESKD, x1 ESLD, x1 renal transplant, x1 liver transplant,</td>
<td></td>
</tr>
<tr>
<td>x4 on immunosuppressive meds. 12/19 of pts treated in ITU</td>
<td></td>
</tr>
<tr>
<td>the time with following complications: x5 patients with</td>
<td></td>
</tr>
<tr>
<td>toxic megacolon (caecal diam &gt;12cm or rectosigmoid&gt;6.5cm</td>
<td></td>
</tr>
<tr>
<td>diameter); x7 AKI and hypovolaemic/septic shock, x4 of which</td>
<td></td>
</tr>
<tr>
<td>required vasopressors, x3 with change in mental status, x2</td>
<td></td>
</tr>
<tr>
<td>patients ventilated. x22 with</td>
<td></td>
</tr>
<tr>
<td>Donors were either patient selected-donor, or universal</td>
<td></td>
</tr>
<tr>
<td>donors. If patient-directed, same donor used for</td>
<td></td>
</tr>
<tr>
<td>subsequent FMTs if required. 44 FMTs in all - patient-selected</td>
<td></td>
</tr>
<tr>
<td>for 16 FMTs, universal donor for 28 FMTs.</td>
<td></td>
</tr>
<tr>
<td>Donors working in healthcare: Not described.</td>
<td></td>
</tr>
<tr>
<td>Donor demographics: Not clear.</td>
<td></td>
</tr>
<tr>
<td>Donor screening: Questionnaire: As per Bakken et al, Clin</td>
<td></td>
</tr>
<tr>
<td>Gastroenterol Hepatol, 2011.</td>
<td></td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: As per Bakken et al,</td>
<td></td>
</tr>
<tr>
<td>Screening blood tests: As per Bakken et al, Clin Gastroenter</td>
<td></td>
</tr>
<tr>
<td>ol Hepatol, 2011.</td>
<td></td>
</tr>
<tr>
<td>Screening stool tests: As per Bakken et al, Clin Gastroenter</td>
<td></td>
</tr>
<tr>
<td>ol Hepatol, 2011.</td>
<td></td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients:</td>
<td></td>
</tr>
<tr>
<td>50-200g of stool.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to prepare: 300ml of saline.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to store if frozen: N/A – all fresh.</td>
<td></td>
</tr>
<tr>
<td>Preparation methods: No additional details.</td>
<td></td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Six hours.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A.</td>
<td></td>
</tr>
<tr>
<td>Route administered: Upper GI: nil; lower GI: flexible</td>
<td></td>
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<tr>
<td>sigmoidoscopy or colonoscopy either proximal or distal to</td>
<td></td>
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<tr>
<td>the splenic flexure at the discretion of the endoscopist. In</td>
<td></td>
</tr>
<tr>
<td>practice – proximal to the splenic flexure in 18 FMTs, distal</td>
<td></td>
</tr>
<tr>
<td>to 26.</td>
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<tr>
<td>Number of infusions: As many as per protocol until end point.</td>
<td></td>
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<tr>
<td>16 x 1 FMT (7 severe, 9 complicated), 11 x 2nd FMT (3 severe,</td>
<td></td>
</tr>
<tr>
<td>8 compl), 2 x 3rd FMT (0 severe, 2 complicated).</td>
<td></td>
</tr>
<tr>
<td>N.B. Oral vancomycin (125 mg every 6 hours) was resumed 24-48</td>
<td></td>
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<tr>
<td>hours after FMT for a minimum of 5 days if there were</td>
<td></td>
</tr>
<tr>
<td>pseudomembranes present at colonoscopy. For patients who did</td>
<td></td>
</tr>
<tr>
<td>not have pseudomembranes, oral vancomycin was initiated.</td>
<td></td>
</tr>
<tr>
<td>Overall cure within stated follow up period: By 3 months, 62%</td>
<td></td>
</tr>
<tr>
<td>(n=18/29) in remission.</td>
<td></td>
</tr>
<tr>
<td>Cure with one infusion alone: 70% (n=7/10) in severe arm; 47%</td>
<td></td>
</tr>
<tr>
<td>(n=9/19) in severe-complicated arm.</td>
<td></td>
</tr>
<tr>
<td>Total follow up period: Up to 3 months.</td>
<td></td>
</tr>
<tr>
<td>Minor GI adverse events: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events: Nil.</td>
<td></td>
</tr>
<tr>
<td>Deaths: x2 deaths by 1 month; x1 death from sepsis within</td>
<td></td>
</tr>
<tr>
<td>24 hours of FMT; death following colectomy after 3x failed</td>
<td></td>
</tr>
<tr>
<td>FMT in patient who was six weeks post-OLT. By 3 months – x2</td>
<td></td>
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<tr>
<td>further deaths from CDI recurrence, x1 death from cirrhosis,</td>
<td></td>
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<tr>
<td>x1 death from heart failure, x1 death from respiratory</td>
<td></td>
</tr>
<tr>
<td>failure, x1 death from aspiration.</td>
<td></td>
</tr>
<tr>
<td>Selection/eligibility recruited: Yes.</td>
<td></td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
<td></td>
</tr>
<tr>
<td>Prospectively recruited: Yes.</td>
<td></td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
<td></td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
<td></td>
</tr>
</tbody>
</table>
pseudomembranes at first FMT.

CDI features: 9 patients with first episode of CDI; all others with previous episodes.

CDI diagnosis confirmation: Diarrhoea (at least 3 loose stools/day) and positive toxin.

Pre-FMT antibiotics: Not stated.

improve by days 6–7, the vancomycin was stopped, and bowel prep was administered if no ileus was present. The next day (day 7–8), a repeat FMT, from the same donor as the first FMT if patient-directed, was performed by sigmoidoscopy or colonoscopy. If pseudomembranes were present, oral vancomycin was resumed for an additional 5 days. If no pseudomembranes were detected, antibiotics were not resumed following the repeat FMT.

Bowel purgative: Split dose 4l Golytely if no ileus/obstruction.

PPI: Not described.

Antimotility: Not described.

Prokinetics: Not described.

Time before CDI treatment was stopped before FMT: 12-24hr prior to FMT.
| Case series.          |  |  |  |  |  |  |
|----------------------|  |  |  |  |  |  |
| Number of patients: 40. |  |  |  |  |  |  |
| Female: male: 21: 19. |  |  |  |  |  |  |
| Age (mean): Mean age 75 (range 53-94) years. |  |  |  |  |  |  |
| Comorbidities: x1 Wegener’s, x1 AML. Repeated courses of antibiotics, not formally described. |  |  |  |  |  |  |
| CDI features: Not described. |  |  |  |  |  |  |
| CDI diagnosis confirmation: Diarrhoea and + C difficile toxin (testing for A and B). |  |  |  |  |  |  |
| Travel and antibiotic exclusion period: Not stated. |  |  |  |  |  |  |
| Screening bloods: Hepatitis A, B and C, HIV. |  |  |  |  |  |  |
| Pre-FMT antibiotics: All patients had had at least two courses of oral metronidazole (500mg three times daily) or vancomycin (125mg po four times daily). |  |  |  |  |  |  |

| Amount of stool per transplant / administered to patients: 50-100g. |  |  |  |  |  |  |
| Diluent used to prepare: 250ml sterile normal saline. |  |  |  |  |  |  |
| Diluent used to store if frozen: All fresh. |  |  |  |  |  |  |
| Preparation methods: Stool placed on gauze pad and strained; flushed with saline; drawn up into syringes ready for administration. |  |  |  |  |  |  |
| Time from preparation to transplant (fresh): Same day. |  |  |  |  |  |  |
| Time period for storage (frozen): N/A. |  |  |  |  |  |  |
| Route administered: Upper GI: OGD with delivery in distal duodenum; 38; lower GI: Colonoscopy; 2. |  |  |  |  |  |  |
| Number of infusions: One at baseline; follow up if ‘did not respond’ although not specifically defined. |  |  |  |  |  |  |
| Bowel purgative: Not mentioned, even for colonoscopy. |  |  |  |  |  |  |
| PPI: Not stated. |  |  |  |  |  |  |
| Antimotility: Not stated. |  |  |  |  |  |  |
| Prokinetics: Not stated. |  |  |  |  |  |  |
| Time before CDI treatment was stopped |  |  |  |  |  |  |

| Overall cure within stated follow up period: 835 (n=33/40). |  |  |  |  |  |  |
| Cure with one infusion alone: 73% (n=29/ 40) (28 in duodenum, 1 in colon). |  |  |  |  |  |  |
| Total follow up period: Up to 80 days. |  |  |  |  |  |  |

| Minor GI adverse events: Not stated. |  |  |  |  |  |  |
| Minor non-GI adverse events: Not stated. |  |  |  |  |  |  |
| Serious adverse events: Not stated. |  |  |  |  |  |  |
| Deaths: 5 deaths within 3 weeks - 2 months post-FMT but none attributable to FMT. x2 deaths attributed to ‘frailty’, x1 advanced Wegener’s, x1 AML/ antibiotics, one patients with advanced cardiovascular disease who had fulminant colitis, underwent colectomy, but died. |  |  |  |  |  |  |

| Selection/ eligibility reported: Yes. |  |  |  |  |  |  |
| Consecutively recruited: Yes. |  |  |  |  |  |  |
| Prospectively recruited: No. |  |  |  |  |  |  |
| Loss to follow up explained: Yes. |  |  |  |  |  |  |
| At least 90% followed up: Yes. |  |  |  |  |  |  |
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</tbody>
</table>
Additional Appendices

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 29.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 6: 23.</td>
<td></td>
</tr>
<tr>
<td>Age (mean/ standard deviation): 80.1 (+/-6.49) years (13 patients 70-79, 14 patients 80-89, 2 patients &gt; 90 years).</td>
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<tr>
<td>Comorbidities: x8 patients with diabetes mellitus.</td>
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<tr>
<td>CDI features: No specific details - purely symptoms &gt; 6 months, failed at least 3 antibiotic regimens.</td>
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</tr>
<tr>
<td>CDI diagnosis confirmation: At least three unformed stools in 24 hour and positive stool C difficile test by toxin (by ELISA) or toxin gene B (by PCR). All patients here defined RCDI by symptoms &gt;6 months and at least x3 failed antibiotics.</td>
<td></td>
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<tr>
<td>Pre-FMT antibiotics: Not indicated.</td>
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<tr>
<td>Donors were patient-selected family or friends.</td>
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<tr>
<td>Donors working in healthcare: No.</td>
<td></td>
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<tr>
<td>Donor demographics: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Donor screening: Questionnaire – peptic ulcer disease/GORD, IBS, IBD, polyps, malignancy, antibiotic use/ hospitalisation within past 3 months.</td>
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<tr>
<td>Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within the past three months.</td>
<td></td>
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<tr>
<td>Screening bloods: HIV, HTLV-I/-II, syphilis enzyme immunoassay, hepatitis A immunoglobulin M, hepatitis B surface antigen, hepatitis C antibody, and Helicobacter pylori antibody.</td>
<td></td>
</tr>
<tr>
<td>Screening stools: MC&amp;S/ ova, cysts and parasites x3, Cryptosporidium, Microspora, C difficile toxin.</td>
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<tr>
<td>Amount of stool per transplant / administered to patients: 450cc - 270cc via colonoscopy AND 180cc into jejunum via enteroscopy.</td>
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<tr>
<td>Diluent used to prepare: Saline - whole stool sample (&gt;30g) mixed with 50-70ml of sterile saline, made up to 5 x 90cc aliquots.</td>
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<tr>
<td>Diluent used to store if frozen: Fresh.</td>
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<tr>
<td>Preparation methods: Stool mixed with saline, homogenised in blender for &lt;4 minutes, filtered x2 with coffee filter paper.</td>
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<tr>
<td>Time from preparation to transplant (fresh): Within 6 hours.</td>
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<tr>
<td>Time period for storage (frozen): N/A.</td>
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<tr>
<td>Route administered: Enteroscopy into jejunum AND colonoscopy in all 29 patients.</td>
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<tr>
<td>Number of infusions: 1 FMT per patient (combined upper and lower GI administration).</td>
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<tr>
<td>Bowel purgative: Not described.</td>
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<tr>
<td>PPI: 20mg omeprazole evening before/ morning of procedure.</td>
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<tr>
<td>Antimotility: Not described.</td>
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<tr>
<td>Overall cure within stated follow up period: 100% (n=29/29).</td>
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<tr>
<td>Cure with one infusion alone: 100% (n=29/29).</td>
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<tr>
<td>Total follow up period: Reported 25.37 +/- 12.8 months follow-up (range 8-50 months).</td>
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<tr>
<td>In addition - researchers report 60% weight gain, 40% stable weight, 75% improved 'failure to thrive' (defined as decrease of weight &gt;10% from baseline, with no improvement despite medical treatment of CDI and nutritional treatment).</td>
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<tr>
<td>Minor GI adverse events: Bloating 10% (n=3/29).</td>
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<tr>
<td>Minor non-GI adverse events: Fever 7% (n=2/29) (transient for one day).</td>
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<tr>
<td>Serious adverse events: None.</td>
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<tr>
<td>Deaths: None.</td>
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<tr>
<td>Selection/ eligibility reported: Yes.</td>
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<tr>
<td>Consecutively recruited: Yes.</td>
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<tr>
<td>Prospectively recruited: No.</td>
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<tr>
<td>Loss to follow up explained: N/A.</td>
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<tr>
<td>At least 90% followed up: Yes.</td>
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Additional Appendices

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<thead>
<tr>
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<th>Prokinetics: Not described.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time before CDI treatment was stopped before FMT: &gt;12 hours.</td>
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</table>
### Hagel et al, Deutsches Arzteblatt International, 2016

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 133.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 86: 47.</td>
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<tr>
<td>Age (median): Median 75 (IQR 59.5 - 81.5) years.</td>
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<tr>
<td>Comorbidities: x3 chemotherapy, x19 immunosuppressants, x5 solid organ transplant, x1 allogeneic stem cell transplant, x43 GI comorbidities (no details).</td>
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<tr>
<td>CDI features: Median of 3 recurrences (IQR 1-4); no specific details re recurrent vs refractory confirmation.</td>
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<tr>
<td>Pre-FMT antibiotics: x4 metronidazole only, x13 vancomycin only, x2 fidaxomicin only, x61 metronidazole/ vancomycin, x8 vancomycin/ fidaxomicin, x34 metronidazole/ vancomycin/ fidaxomicin, x11</td>
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<tr>
<td>Donors working in healthcare: not stated</td>
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<tr>
<td>Donor demographics: Not stated.</td>
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<tr>
<td>Donor screening: Questionnaire - not stated.</td>
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<tr>
<td>Travel and antibiotic exclusion period: Not stated.</td>
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<tr>
<td>Screening blood tests.: Rapid plasma reagin and fluorescent <em>Treponemal</em> antibody-absorbed.</td>
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<tr>
<td>Screening stool tests: Not stated.</td>
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<tr>
<td>Amount of stool per transplant / administered to patients: Not stated.</td>
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<tr>
<td>Diluent used to prepare: Not stated.</td>
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<tr>
<td>Diluent used to store if frozen: Yes, in some cases - no details given.</td>
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<tr>
<td>Preparation methods: Not stated.</td>
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<tr>
<td>Time from preparation to transplant (fresh): Not stated.</td>
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<tr>
<td>Time period for storage (frozen): Not stated.</td>
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<tr>
<td>Route administered: Upper GI: 4 OGD, 40 enteroscopy, 19 nasoenteric tube; lower GI: 55 'endoscopic' (no further details); capsule: 13. x2 combination of jejunal and colonoscopic FMT.</td>
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<tr>
<td>Number of infusions: 1 FMT.</td>
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<tr>
<td>Bowel purgative: Yes - 117 (no details given).</td>
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<tr>
<td>PPI: Yes - 31 (no details given).</td>
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<tr>
<td>Antimotility: Yes - 31 (no details given).</td>
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<tr>
<td>Prokinetics: Not stated.</td>
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<tr>
<td>Time before CDI treatment was stopped before FMT: Not stated.</td>
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<tr>
<td>Pre-FMT antibiotics: x4 metronidazole only, x13 vancomycin only, x2 fidaxomicin only, x61 metronidazole/ vancomycin, x8 vancomycin/ fidaxomicin, x34 metronidazole/ vancomycin/ fidaxomicin, x11</td>
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<tr>
<td>Amount of stool per transplant / administered to patients: Not stated.</td>
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<tr>
<td>Diluent used to prepare: Not stated.</td>
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<tr>
<td>Diluent used to store if frozen: Yes, in some cases - no details given.</td>
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<tr>
<td>Preparation methods: Not stated.</td>
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<td>Time period for storage (frozen): Not stated.</td>
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<td>Route administered: Upper GI: 4 OGD, 40 enteroscopy, 19 nasoenteric tube; lower GI: 55 'endoscopic' (no further details); capsule: 13. x2 combination of jejunal and colonoscopic FMT.</td>
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<td>Number of infusions: 1 FMT.</td>
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<tr>
<td>Bowel purgative: Yes - 117 (no details given).</td>
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<td>PPI: Yes - 31 (no details given).</td>
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<tr>
<td>Antimotility: Yes - 31 (no details given).</td>
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<tr>
<td>Prokinetics: Not stated.</td>
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<tr>
<td>Time before CDI treatment was stopped before FMT: Not stated.</td>
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<tr>
<td>Overall cure within stated follow up period: Primary cure on day 30 and 90 was achieved in 84.2% (n=101/120) and 78.3% (n=72/92).</td>
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<tr>
<td>Cure with one infusion alone: No diarrhoea at 30 days in 84.2% (n=101/120); no diarrhoea at 90 days in 78.3% (n=72/92).</td>
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<tr>
<td>Total follow up period: Median follow up 141 days (IQR 50-353 days).</td>
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<tr>
<td>Minor GI adverse events: x5 nausea, x3 abdominal pain, 2 belching, x2 vomiting, x2 'food intolerance', x1 IBS.</td>
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<tr>
<td>Minor non-GI adverse events: x3 fever, x2 throat discomfort.</td>
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<tr>
<td>Serious adverse events: x1 aspiration pneumonia, x1 haemorrhage (during endoscopy - no details), x1 loss of tooth, x1 polyneuropathy, x1 weight gain &gt; 10kg in 12 months post-FMT.</td>
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</table>
| Deaths: x7 died during follow up, x2 within 90 days of FMT. In x6 cases, definitely not related to CDI (in one patient, recurrence of CDI one week after FMT contributed to her death (but
Additional Appendices

| unknown. |  |  | stroke described as primary cause of death). |
**Case series.**

**Number of patients:** 43.

**Female: male:** 31: 12.

**Age (mean/ standard deviation):** Mean 59 (+/- 21) years.

**Comorbidities:** x14 IBD patients.

**CDI features:** Recurrent.

**CDI diagnosis confirmation:** Toxin positive with at least two subsequent recurrences.

**Pre-FMT antibiotics:** All had vancomycin, 17 patients had addition of vancomycin and 2 weeks of rifaximin (one of these 17 had 4 weeks of rifaximin); 3 patients took 2-4 weeks of nitazoxanide.

**Donors were standard donors for 33 FMTs, and individual donors for 10 FMTs.**

**Donors working in healthcare:** Not stated.

**Donor demographics:** Not stated.

**Donor screening:** Questionnaire before recruitment, the donors were required to submit available medical records and have a separate medical history interview away from the recipient patient. The history included assessment of infectious risk, including identification of known risk factors for HIV and hepatitis, current communicable diseases, and recent travel to areas of the world with a higher prevalence of diarrheal illnesses.

**Travel and antibiotic exclusion period:** Excluded as donors if recent travel to areas where high prevalence of diarrheal illness (not specified), and/or antibiotic use within the past six months.

**Screening blood tests:** HIV,

**Amount of stool per transplant / administered to patients:** 50g.

**Diluent used to prepare:** 250ml sterile, non-bacteriostatic normal saline.

**Diluent used to store if frozen:** 10% glycerol.

**Preparation methods:** Stool from individual donors was passed through stainless steel tea strainers; stool from universal donors was transported on ice to the lab, and processed within 2 hours. Material was weighed and homogenised in commercial blender under nitrogen gas. Slurry then passed through 2.0, 1.0, 0.5 and 0.25mm stainless steel lab sieves. The resulting material was then centrifuged at 6000 x g for 15 minutes and resuspended to one-half the original volume in normal saline.

**Time from preparation to transplant (fresh):** 1-2 hours.

**Time period for storage (frozen):** 1-8 weeks.

**Route administered:** Upper GI: nil; lower GI: colonoscopy (with majority into terminal ileum or caecum, with a small proportion into other colonic areas) in all 43; capsules: nil.

**Number of infusions:** 1x FMT in 37
Additional Appendices

| Screening stool tests: *Clostridium difficile* toxin B PCR, MC&S, ova, cysts and parasites, *Giardia, Cryptosporidium, Helicobacter pylori* antigen. | patients, 2x FMT in 6 patients. | Bowel purgative: Yes - GoLYTELY or Moviprep. | PPI: Not described. | Antimotility: Not described. | Prokinetics: Not described. | Time before CDI treatment was stopped before FMT: 2 days. |
Additional Appendices

<table>
<thead>
<tr>
<th>Hefazi et al, Mayo Clinic Proceedings, 2017</th>
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<tbody>
<tr>
<td>Case series.</td>
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<tr>
<td>Number of patients: 23.</td>
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<tr>
<td>Age (median): 66 (range 23-88) years.</td>
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<tr>
<td>Comorbidities: x13 patients had haematological malignancy (x4 diffuse large B cell lymphoma, x2 Hodgkin’s lymphoma, x1 chronic myeloid leukaemia, x1 follicular lymphoma, x1 stage IV cutaneous T cell lymphoma, x1 B cell acute lymphocytic leukaemia, x1 hairy cell leukaemia, x1 chronic lymphocytic leukaemia, x1 severe aplastic anaemia); x1 with active disease at time of FMT, x2 with recent chemotherapy use, x2 with neutropenia within 12 weeks prior to FMT. x10 patients with solid organ malignancy (x4 breast, x2 anal, x1 colon, x1 pancreatic, x1 tonsillar, x1 non-small</td>
</tr>
<tr>
<td>Donors: Fresh stool from family/ friends in 10 patients, frozen stool from standard donors in 13 patients.</td>
</tr>
<tr>
<td>Donor working in healthcare: Not stated.</td>
</tr>
<tr>
<td>Donor demographics: Not stated.</td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: ~50g.</td>
</tr>
<tr>
<td>Diluent used to prepare: 250ml normal saline.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: Not stated.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Not stated.</td>
</tr>
<tr>
<td>Time period for storage (frozen): Not stated.</td>
</tr>
<tr>
<td>Route administered: Upper GI: nil; lower GI: All 23 patients received FMT via colonoscopy into caecum.</td>
</tr>
<tr>
<td>Number of infusions: 1 FMT.</td>
</tr>
<tr>
<td>Bowel purgative: Not stated.</td>
</tr>
<tr>
<td>PPI: Not stated.</td>
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<tr>
<td>Antimotility: Not stated.</td>
</tr>
<tr>
<td>Prokinetics: Not stated.</td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: 24 hours.</td>
</tr>
<tr>
<td>Overall cure within stated follow up period: 92% (n=11/12) of haematological malignancy patients (other patient died), and 80% (n=8/10) solid malignancy patients.</td>
</tr>
<tr>
<td>Cure with one infusion alone: 86% (n=19/22) by primary outcome criteria.</td>
</tr>
<tr>
<td>Total follow up period: x1 CLL patient recurred at 22 months post-FMT in context of ibrutinib and coamoxiclav; successfully treated with 10 days of metronidazole. x1 tonsillar cancer patient had CDI recurrence at 14 months after exposure to cefalexin; successfully treated with 10 days of</td>
</tr>
<tr>
<td>Minor non-GI adverse events: None.</td>
</tr>
<tr>
<td>Serious adverse events: None.</td>
</tr>
<tr>
<td>Deaths: x1 death after cardiac arrest of Hodgkin’s lymphoma patient at day 5 (multiple medical comorbidities thought likely cause, not FMT); x2 deaths at &gt; 60 days related to the underlying malignancy progressing.</td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
</tr>
</tbody>
</table>
cell lung, x5 with metastasis at time of FMT, x3 recent chemotherapy use, x1 with recent neutropenia. Other comorbidities include x1 COPD, x1 ESKD on haemodialysis, x1 graft versus host disease (on immunosuppression), x1 granulomatosis with polyangiitis (Wegener’s) on immunosuppression, x1 hypogammaglobulinaemia on intravenous immunoglobulin, x1 inflammatory arthritis on corticosteroids.

CDI features: All recurrent.

CDI diagnosis confirmation: Not explicitly defined, but definitions of recurrent, severe and complicated CDI as per American College of Gastroenterology.

Pre-FMT antibiotics: All given additional vancomycin until 24hrs

vancomycin then 10 days of fidaxomicin. N.B. In all - x10 more chemotherapy courses and x8 more antibiotic courses after FMT.
prior to FMT. Median of 2.5 standard treatment courses per patient (defined as at least 10 days of metronidazole, vancomycin or fidaxomicin), x1 previous vancomycin taper, and x4 total treatment courses for CDI).
**Case series.**

**Number of patients:** 19.

**Female: male:** 13: 6.

**Age (mean):** 61 (range 26-92) years.

**Comorbidities:** x3 IBS, x2 diabetes mellitus, x1 diverticulitis, x1 lymphoma, x1 acute myeloid leukaemia, x1 renal cancer, x1 chronic renal failure.

**CDI features:** Refractory and recurrent (2 or more episodes).

**CDI diagnosis confirmation:** Not stated.

**Pr - FMT antibiotics:** metronidazole, vancomycin +/or fidaxomicin.

**Donors were 3 unrelated participants.**

**Donors working in healthcare:** Not stated.

**Donor demographics:** Excluded if BMI>25, diabetes mellitus, psychiatric history, IBD, or IBS.

**Donor screening:** Questionnaire - standard questionnaire, with details as above.

**Travel and antibiotic exclusion period:** Excluded if travel outside the USA within 30 days prior to donation, and/or use of antibiotics within the past 6 months.

**Screening blood tests:** HIV, hepatitis A, B, C, *Treponema* / syphilis, and HTLV-1.

**Screening stool tests:** *Clostridium difficile* toxin B, *Salmonella*, *Shigella*, *Campylobacter*, *E. coli*, *Yersinia*, *Vibrio*, *Aeromonas*, *Plesiomonas*.

| Amount of stool per transplant / administered to patients: 2.3g. | Overall cure within stated follow up period: 68% (n=13/19). |
| Diluent used to prepare: 350ml in 0.9% normal saline. | Cure with one infusion alone: 68% (n=13/19) at 90 days. |
| Diluent used to store if frozen: 15% glycerol. | Total follow up period: Primary outcome assessed at 90 days, whilst secondary outcome assessed at 6 weeks after this. |
| Preparation methods: Strict environmental control <6 hours after defaecation. All sterile, wet weight of stool was homogenised in 350ml 0.9% normal saline and aliquoted; samples were then centrifuged at 200 x g for 10 mins. Supernatant was decanted and centrifuged at 4600 x g for 15 minutes. supernatant removed and pellet re-suspended in 0.9% normal saline with glycerol. The typical concentration was 0.5g/ml. The resulting FMT slurry was put in 5-10ml syringes and frozen at -80°C. | Minor GI adverse events: x5 abdominal pain 5 (x4 self-resolved; x1 required opiates and was hospitalised). |
| Time from preparation to transplant (fresh): N/A. | Minor non-GI adverse events: None. |
| Time period for storage (frozen): 1-3 weeks at -80°C; prior to use, syringes were transferred to -20°C and used within six weeks. | Serious adverse events: None. |
| Route administered: Nil upper or lower GI; all capsules. Aliquots of 0.4 mL of FMT slurry were dispensed into Size 1 acid-resistant hypromellose capsules, | Deaths: x1 died from respiratory failure after failing FMT treatment. |

**Selection / eligibility reported:** Yes.

**Consecutively recruited:** Not clear.

**Prospectively recruited:** No.

**Loss to follow up explained:** No.

**At least 90% followed up:** Yes.
subsequently placed within Size 0 acid-resistant hypromellose capsules and then nested within Size 00 gelatin Caps. Capsules were administered immediately upon filling and capping.

Number of infusions: One course was 8-12 capsules (one only took 6).

Bowel purgative: Not described.

PPI: Yes - evening and morning of procedure.

Antimotility: Not described.

Prokinetics: Yes - encouraged to drink 4 ounces of Kefir fermented milk product twice a day, and also given a list of prebiotics to consume for 3 days.

Time before CDI treatment was stopped before FMT: On day prior to FMT.
### Clinical Microbiology and Infection, 2017

**Ianiro et al.**

**Case series.**
Number of patients: 64.
Female:male: 39: 25.
Age (mean): Mean 74 years.
Comorbidities: Not reported.
CDI features: Recurrent CDI - all patients had 3 recurrences on average range (range 2-6).
CDI diagnosis confirmation: Defined using ESCMID guidelines.
Pre-FMT antibiotics: All patients had had prior metronidazole, vancomycin and/or fidaxomicin.
Donors were unrelated for 36 FMTs, and related for 28 FMTs.
Donor working in healthcare: No.
Donor demographics: Not specified.
Travel and antibiotic exclusion period: As per Cammarota et al, *Alim Pharm Ther*, 2015.
Amount of stool per transplant / administered to patients: not reported.
Diluent used to prepare: 500ml of 0.9% saline.
Diluent used to store if frozen: N/A – fresh.
Preparation methods: After dilution, the solution was blended and supernatant strained and poured into sterile container.
Time from preparation to transplant (fresh): 6 hours.
Time period for storage (frozen): Not specified.
Route administered: Upper GI: nil; lower GI: all 64 given FMT via colonoscopy; capsules: nil.
Number of infusions: 44 patients had x1 FMT, 20 patients had >1 FMT (undefined).
Bowel purgative: 4l macrogol on last 1-2 days of antibiotics treatment.
PPI: Not specified.
Antimotility: Not specified.
Prokinetics: Not specified.
Overall cure within stated follow up period: 975 (n=62/64) at 8 weeks.
Cure with one infusion alone: 69% (n=44/64).
Total follow up period: 8 weeks.
Minor GI adverse events: Not specified.
Minor non-GI adverse events: Not specified.
Serious adverse events: Not specified.
Deaths: Not specified.
Selection/ eligibility reported: Yes.
Consecutively recruited: Yes.
Prospectively recruited: No.
Loss to follow up explained: Yes.
At least 90% followed up: Yes.
Additional Appendices

Time before CDI treatment was stopped before FMT: FMT given on last 1 or two days of CDI treatment.
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 27.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male 13: 14.</td>
<td></td>
</tr>
<tr>
<td>Age (mean): 69.4 (range 26-87) years.</td>
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<tr>
<td>Comorbidities: Not specified.</td>
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<tr>
<td>CDI features: Recurrent and refractory.</td>
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<tr>
<td>CDI diagnosis confirmation: (1) Laboratory-confirmed C difficile toxin using EIA with no other cause for diarrhea; (2) refractory CDI (defined as ongoing diarrhea despite antimicrobial treatment) or recurrent CDI (defined as symptom resolution for at least 2 days after discontinuation of treatment with recurrence of diarrhea).</td>
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<tr>
<td>Pre-FMT antibiotics: All had at least prior metronidazole; 19 had subsequent vancomycin monotherapy. 8 had</td>
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<tr>
<td>Donors were two healthy volunteers.</td>
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<tr>
<td>Donors working in healthcare: Not specified.</td>
<td></td>
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<tr>
<td>Donor demographics: Not specified.</td>
<td></td>
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<tr>
<td>Donor screening: Questionnaire - not specified.</td>
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</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded if used antibiotics within last 6 months.</td>
<td></td>
</tr>
<tr>
<td>Screening blood tests: Hepatitis B surface antigen, hepatitis C antibody, Helicobacter pylori and syphilis serologic markers, HIV types -1 and -2, and HTLV types -I and -II.</td>
<td></td>
</tr>
<tr>
<td>Screening stool tests: Stool was processed for enteric bacterial pathogens, C difficile toxin, and ova and parasites.</td>
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</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: 150g of stool.</td>
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<tr>
<td>Diluent used to prepare: 300mls sterile water.</td>
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<tr>
<td>Diluent used to store if frozen: N/A.</td>
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<tr>
<td>Preparation methods: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Not specified.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A – fresh.</td>
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<tr>
<td>Route administered: Upper GI: nil; lower GI: 27 via retention enema.</td>
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<tr>
<td>Number of infusions: 1 enema in 22 patients, 2 enemas in 5 patients.</td>
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</tr>
<tr>
<td>Bowel purgative: Not specified.</td>
<td></td>
</tr>
<tr>
<td>PPI: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Antimotility: Not specified.</td>
<td></td>
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<tr>
<td>Prokinetics: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: At least 24 hours before.</td>
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<tr>
<td>Overall cure within stated follow up period: 81% (n=22/27).</td>
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</tr>
<tr>
<td>Cure with one infusion alone: 81% (n=22/27).</td>
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<tr>
<td>Total follow up period: Mean follow-up of 427.3 days after transplant.</td>
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<tr>
<td>Minor GI adverse events: Not specified.</td>
<td></td>
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<tr>
<td>Minor non-GI adverse events: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events: Not specified.</td>
<td></td>
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<tr>
<td>Deaths: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
<td></td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
<td></td>
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<tr>
<td>Prospectively recruited: No.</td>
<td></td>
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<tr>
<td>Loss to follow up explained: Yes.</td>
<td></td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
<td></td>
</tr>
</tbody>
</table>
Additional Appendices

| combination metronidazole and vancomycin therapy. |  |  |  |
Case series.
Number of patients: 26.
Female: male: 24:2
Age (mean): 59 years.
Comorbidities: Not stated.
CDI features: Recurrent. Mean duration of diagnosis of CDI prior to FMT of 12.6 (range 4 to 84) months.
CDI diagnosis confirmation: Not stated.
Pre-FMT antibiotics: All had previous treatment with metronidazole, and repeated tapering courses of vancomycin. 19 had failed at least one course of rifaximin. Some patients had prior *Saccharomyces boulardii* or *Lactobacillus GG*. Pre-FMT, all had 2 weeks of metronidazole or vancomycin, discontinued 2-3 days before FMT.

Donors were family members in 25 cases, and friend in 1 case. Donor working in healthcare: No. Donor demographics: Not specified. Donor screening: Questionnaire – asked regarding known exposure to HIV within 12 months, high-risk sexual behaviours, use of illicit drugs, tattoo within 6 months, incarceration within 12 months, risk factors for Creutzfeldt-Jakob disease, GI comorbidities, recent ingestion of allergen, systemic autoimmunity, chronic pain syndromes. Travel and antibiotic exclusion period: No antibiotics for preceding 90 days. Screening blood tests: blood for hepatitis A, B and C, HIV-1&-2, *Treponema pallidum*. Screening stool tests: Stool for culture for bacteria, stain for ova and parasites, *C difficile* toxin A and B.

Amount of stool per transplant / administered to patients: "6:8 tablespoons of donor stool". Diluent used to prepare: 1 litre of sterile water passed through gauze. Aliquoted in 60ml syringes. Diluent used to store if frozen: N/A – fresh. Preparation methods: As above. Time from preparation to transplant (fresh): 6 hours prior to transplant. Time period for storage (frozen): N/A. Route administered: Upper GI: nil; lower GI: all 26 via colonoscopy; capsules: nil. Number of infusions: not explicitly stated but implies single infusion for all patients. Bowel purgative: PEG bowel prep night before transplant. PPI: Not stated. Antimotility: Not stated. Prokinetics: Not stated. Time before CDI treatment was stopped before FMT: 2-3 days.

### Case series.
- **Number of patients:** 80.
  - Female: male: 42: 38.
- **Age (mean):** N.B. 75 adults, and 5 children.
  - Mean age of adults: 53 (range 20-88) years; mean age of paediatric patients: 10.9 (range 6.5–16) years.
- **Comorbidities:**
  - x36 IBD,
  - x19 solid organ transplant,
  - x3 HIV/AIDS,
  - x7 cancer,
  - x4 rheumatoid arthritis,
  - x1 adrenal insufficiency,
  - x6 cirrhosis,
  - x1 ESKD,
  - x1 panhypopituitarism,
  - x1 end-stage COPD,
  - x1 ESKD with allograft failure,
  - x1 Sjögren.
- **CDI features:** Both refractory and recurrent patients included as well as severe/complicated disease.
- **CDI diagnosis:** Not clearly specified.
- **Pre-FMT antibiotics:**

### Donors working in healthcare:
- Not specified.

### Donor demographics:
- Not specified.

### Donor screening:
- Questionnaire: Varied by centre.
- Travel and antibiotic exclusion period: Varied by centre.
- Screening blood tests: Varied by centre.
- Screening stool tests: Varied by centre.
- Bowel purgative: Varied by centre.
- PPI: Varied by centre.
- Antimotility: Varied by centre.
- Prokinetics: Varied by centre.
- Time before CDI treatment was stopped before FMT: Varied by centre.

### Amount of stool per transplant / administered to patients:
- Varied by centre.

### Diluent used to prepare:
- Varied by centre.

### Diluent used to store if frozen:
- Varied by centre.

### Preparation methods:
- Varied by centre.

### Time from preparation to transplant (fresh):
- Varied by centre.

### Time period for storage (frozen):
- Varied by centre.

### Route administered:
- Not specified.

### Number of infusions:
- 85% (n=68/80) had single FMT, 15% (n=12/80) had > 1 FMT.

### Overall cure within stated follow up period:
- 89% (n=71/80) within a minimum of 12 weeks.

### Cure with one infusion alone:
- 78% (n=62/80).

### Total follow up period:
- 12 weeks post-FMT.

### Minor GI adverse events:
- x3 self-limiting diarrhoea,
- x3 bloating and abdominal discomfort,
- x1 Crohn’s flare,
- x1 nausea,
- x1 minor mucosal tear at colonoscopy.

### Minor non-GI adverse events:
- x1 fever,
- x1 hip pain,
- x1 pertussis.

### Serious adverse events:
- x10 hospitalization (x1 for fever, encephalopathy and pancytopenia; x1 abdo pain post FMT, x3 IBD flares (x2 Crohn’s, x1 UC), x1 stroke, x1 colectomy, x1 fall and sustained hip fracture, x1 influenza B and diarrhea, x1 catheter infection.

### Deaths:
- x2 deaths (x1 pneumonia and x1 aspiration after...
### Additional Appendices

<p>| Vancomycin 67 (84%), fidaxomicin 23 (29%), rifaximin 13 (16%), metronidazole 55 (69%). |  |  | sedation for colonoscopic FMT). |</p>
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 272.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 189: 83.</td>
<td></td>
</tr>
<tr>
<td>Age (mean/median/standard deviation): Mean 57.2 (+/- 19.2) years; median 59.0 (range 16-100) years.</td>
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<tr>
<td>Comorbidities: x10 dialysis, x22 established Crohn’s, x21 established UC, x15 lymphocytic colitis, x5 diagnosed with Crohn’s during colonoscopy for FMT, x1 diagnosed UC during colonoscopy for FMT, x14 newly-diagnosed lymphocytic colitis. x13 reclassified in terms of IBD. x8 solid organ recipients, x30 patients without IBD were taking biologics (anti-TNF, rituximab), immunomodulators (methotrexate, purine analogues), and/or corticosteroids.</td>
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</tr>
<tr>
<td>CDI features: All patients had at least two</td>
<td></td>
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<tr>
<td>Donors working in healthcare: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Screening blood tests: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to prepare: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to store if frozen: As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (fresh): As per Hamilton et al, Am J Gastroenterol, 2012.</td>
<td></td>
</tr>
<tr>
<td>Route administered: Upper GI: nil; lower GI: colonoscopy (272); capsule: nil.</td>
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<tr>
<td>Number of infusions: One routinely, more than one if required - specific criteria not defined.</td>
<td></td>
</tr>
<tr>
<td>Bowel purgative: Yes - all had purgative on day prior to procedure (as per Hamilton et al, Am J Gastroenterol, 2012).</td>
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</tr>
<tr>
<td>Overall cure within stated follow up period: 74% (n=32/43) in IBD patients and 92.2% (n=211/229) in non-IBD patients.</td>
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<tr>
<td>Cure with one infusion alone: 74% (n=32/43) in IBD patients and 92.2% (n=211/229) in non-IBD patients.</td>
<td></td>
</tr>
<tr>
<td>Total follow up period: Up to 6 years.</td>
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</tr>
<tr>
<td>Minor GI adverse events: Not specified.</td>
<td></td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not specified.</td>
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<tr>
<td>Serious adverse events: 25.6% (n=11/43) of IBD patients diagnosed with FMT-related flare. x2 patients hospitalised with IBD flare within two months of FMT.</td>
<td></td>
</tr>
<tr>
<td>Clearance of CDI by FMT generally associated with improved control of IBD over the long term. x6 patients struggled with IBD despite optimisation of immunosuppressive treatment, x3 of whom underwent colectomies.</td>
<td></td>
</tr>
<tr>
<td>Deaths: Nil.</td>
<td></td>
</tr>
<tr>
<td>Selection/ eligibility criteria: Yes.</td>
<td></td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
<td></td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
<td></td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
<td></td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
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</tr>
</tbody>
</table>
spontaneous relapses of CDI following initial episode, defined as recurrence within three months of discontinuation of anti-CDI antibiotics treatment in conjunction with diarrheal symptoms.

CDI diagnosis confirmation: Positive stool testing within two months of FMT - not clearly defined.

Pre-FMT antibiotics: x206 patients had had prior metronidazole, x270 vancomycin, x69 fidaxomicin, x71 rifaximin, x104 probiotics.

PPI: Not described.

Antimotility: Not described.

Prokinetics: Not described.

Time before CDI treatment was stopped before FMT: 2 days.
**Case series.**

Number of patients: 61.
Female: male: 40:21.
Age (mean): 84 (range 66-101) years.
Comorbidities: Not specified.
CDI features: Some patients refractory/recurrent; some during first CDI.
CDI diagnosis confirmation: PCR that detects toxin and B genes, and toxin C gene deletion that characterises O27.
Pre-FMT antibiotics: Patients divided into 'tardive transplant' (i.e. only after x3 antibiotic failures) or 'early transplant' (during first week of infection during first treatment, accompanied by antibiotics). Antibiotics were for non-severe disease: metronidazole.

<table>
<thead>
<tr>
<th>Amount of stool per transplant / administered to patients: &gt;30g.</th>
<th>Overall cure within stated follow up period: Global death rate of 19% (n=3/16) in early transplant arm (day 20, day 37, day 166). 67% (n=2/3) died in arm of those treated by tardive transplant (day 28, day 54). None of these patients died with evidence of CDI. Cure with one infusion alone: 33% (n=1/3) treated by tardive FMT dead at day 31; 4.2% (n=1/16) treated by early FMT dead at day 31. Total follow up period: No details on absolute length of follow-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent used to prepare: Whole stool mixed with 400ml normal saline, homogenised for 10 minutes.</td>
<td>Minor GI adverse events: x24 diarrhea (resolved day 1 after FMT), x1 nausea. Minor non-GI adverse events: Not specified. Deaths: 3/16 in early transplant arm (vs 29/45 treated by abx only or tardive transplant). No sign of CDI at time of death (days 20, 37, 166).</td>
</tr>
<tr>
<td>Diluent used to store if frozen: N/A – fresh.</td>
<td>Selection/ eligibility reported: Yes. Consecutively recruited: No - not stated. Prospectively recruited: No. Loss to follow up explained: Yes. At least 90% followed up: Yes.</td>
</tr>
<tr>
<td>Preparation methods: 10 minutes of homogenisation in blender, filtered, put into a syringe at room temperature.</td>
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<tr>
<td>Time from preparation to transplant (fresh): &lt;6 hours.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A.</td>
<td></td>
</tr>
<tr>
<td>Route administered: Upper GI: Via nasogastric tube in 61 patients; nil lower GI or capsules.</td>
<td></td>
</tr>
<tr>
<td>Number of infusions: In early FMT arm - one FMT routine; but offered 2nd FMT if relapse.</td>
<td></td>
</tr>
<tr>
<td>Screening blood tests: HIV, hepatitis A, B, C, E, active CMV, active EBV, Treponema pallidum, HTLV.</td>
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</tr>
<tr>
<td>Bowel purgative: 4l Klean Prep/ two glasses of Fast Prep day before FMT.</td>
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<tr>
<td>PPI: No - but used 200ml 1.4% bicarbonate 15 minutes before FMT. Antimotility: Not specified. Prokinetics: Not specified.</td>
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<tr>
<td>Time before CDI treatment was stopped before FMT: Not specified.</td>
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<tr>
<td>orally three times a day for 14 days, then vancomycin 125mg four times a day for 14 days, then fidaxomicin 200mg twice a day for 10 days; for severe disease (defined as AKI, paralytic ileus, or peritoneal fluid), used vancomycin and metronidazole for primary infection, then fidaxomicin if relapse/failure.</td>
<td></td>
</tr>
</tbody>
</table>
Lee et al, European Journal of Clinical Microbiology and Infectious Diseases, 2014

Case series.
Number of patients: 94
Female: male: 53: 41.
Age (mean): Mean 71.8 (range 24-95) years.
Comorbidities: x3 IBD, x3 post-renal transplant.
CDI features: Some patients refractory (defined as ongoing diarrhea despite treatment with at least 5 days of oral vancomycin, 125mg four times daily), or recurrent (symptom resolution for at least two days after the discontinuation of treatment with recurrence of diarrhoea.
CDI diagnosis confirmation: Toxin positive by enzyme immunoassay or polymerase chain reaction.
Pre-FMT antibiotics: Average of 2.1 previous anti-CDI antibiotic

Donors were volunteers.
Donor working in healthcare: Not specified
Donor demographics: Not specified.
Donor screening: Questionnaire - describes use of questionnaire but no details given - "similar to the Full Length Donor History Questionnaire documents (US Food and Drug administration, DHQ version 1.3, May 2008"
Travel and antibiotic exclusion period: Not specified.
Screening stools: Ova, cysts and parasites, MC&S, C difficile toxin, norovirus, adenovirus, rotavirus.

Amount of stool per transplant / administered to patients: Not specified.
Diluent used to prepare: 300ml water.
Diluent used to store if frozen: N/A – fresh.
Preparation methods: Homogenisation of stool in water using a disposable spatula.
Time from preparation to transplant (fresh): Not specified.
Route administered: Upper GI: nil; lower GI: retention enema in all 94 patients; nil capsules.
Number of infusions: No fixed number - as many as required to achieve remission. No clear definition of non-response.
Bowel purgative: Not specified.
PPI: Not specified.
Antimotility: Not specified.
Prokinetics: Not specified.
Time before CDI treatment was stopped before FMT: Not specified.

Overall cure within stated follow up period: At 6 months – 87% (n=81/94) in remission after FMT.
Cure with one infusion alone: 47.9% (n=45/94) with single FMT in remission at 6 months.
Total follow up period: 24 months.

Minor GI adverse events: "10% experienced transient constipation and excess flatulence post-FMT".
Minor non-GI adverse events: None described.
Serious adverse events: None described.
Deaths: 75% (n=6/8) patients not responding to FMT died (not clear when). All "over 70 years of age", with multiple underlying significant comorbidities and passed away due to critical illnesses; none had deaths attributable to FMT or directly due to CDI.

Selection/ eligibility reported: Yes.
Consecutively recruited: Yes.
Prospectively recruited: No.
Loss to follow up explained: Yes.
At least 90% followed up: Yes.
| courses (range 1-4), specifically: x74 metronidazole courses (79.3%), x71 vancomycin (75%), x14 vancomycin taper (15.2%), x3 probiotic monotreatment (0.03%), x16 concomitant metronidazole/vancomycin (17.4%). |   |   |   |
Case series.
Number of patients: 15.
Female: male: 14: 1.
Age (median): 81.5 (range 68-95) years.
Comorbidities: no haematological or IBD.
CDI features: Relapsing defined as recurrence of loose stool following successful antibiotic treatment in a patient with previous toxin positive CDI.
CDI diagnosis confirmation: Not specified.
Pre-FMT antibiotics: All had had previous metronidazole and vancomycin; x3 patients tapering vancomycin and intravenous Immunoglobulin.

<table>
<thead>
<tr>
<th>MacConnachie et al, QJM, 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional Appendices</td>
</tr>
</tbody>
</table>

| Amount of stool per transplant administered to patients: 30g. |
| Diluent used to prepare: 0.9% normal saline. |
| Diluent used to store if frozen: N/A – fresh. |
| Preparation methods: Stool sample prepared in less than 6 hours; add 50-70ml of normal saline, homogenise with handheld stool blender, gradually advance speed, continue for 2-4 mins until smooth, filter suspension in coffee filter paper. |
| Time from preparation to transplant (fresh): 6 hours. |
| Time period for storage (frozen): Not applicable. |
| Route administered: Upper GI: All 15 patients received FMT via nasogastric tube; lower GI and capsules: nil. |
| Number of infusions: 1 FMT per patient routinely, repeat if required. |
| Bowel purgative: Not given. |
| PPI: Omeprazole 20mg eve before and on morning. |
| Antimotility: Not given. |

Overall cure within stated follow up period: 84% (n=15/18) “resolution”.
Cure with one infusion alone: 884% (n=15/18) “resolution”.
Total follow-up period: 90 days.

Minor GI adverse events: x1 diarrhoea.
Minor non-GI adverse events: Nil.
Serious adverse events: Nil.
Deaths: x2 (not felt related to FMT).

Selection/ eligibility reported: Yes.
Consecutively recruited: Yes.
Prospectively recruited: No.
Loss to follow up explained: Yes.
At least 90% followed up: Yes.
<p>| | | Prokinetics: Not given. Time before CDI treatment was stopped before FMT. Stopped on the evening before FMT. | | | |
| Case series. | Donors: 61 donors were close relatives/other household members; in 9 cases, healthy volunteers. |
| Number of patients: 70. | Donors working in healthcare: Not specified. |
| Age (mean): Mean 73 (range 22-90) years. | Donor screening: Questionnaire - &quot;No antibiotics and no intestinal symptoms within 6 months&quot;. |
| Comorbidities: No IBD, one adenocarcinoma of colon diagnosed during colonoscopy for FMT. | Travel and antibiotic exclusion period: Excluded as donor if any antibiotic use within past six months; no details of travel restrictions. |
| CDI features: Recurrent, mean of 3.5 previous episodes of CDI pre-FMT (range 1-12). | Screening blood tests: Hepatitis B surface antigen, Hepatitis C antibody, HIV-1/2, Treponema pallidum plasma reagin test; total blood count, C-reactive protein, creatinine, liver enzymes. |
| CDI diagnosis confirmation: Positive culture and toxin. | Screening stool tests: C difficile culture/tox A/B; MC&amp;S, ova cysts and parasites. |
| Pre-FMT antibiotics: Mixture of metronidazole, vancomycin, rifaximin - no patient-level data. | Amount of stool per transplant / administered to patients: 20-30ml stool. |
| Diluent used to prepare: 100-200ml water; 100ml of suspension administered to caecum. |
| Diluent used to store if frozen: N/A – all fresh. |
| Time from preparation to transplant (fresh): 6 hours. |
| Time period for storage (frozen): N/A. |
| Route administered: Upper GI: nil; lower GI: colonoscopy (70); capsules: nil. |
| Number of infusions: 1 FMT. |
| Bowel purgative: 4l PEG (Colonsteril). |
| PPI: Not specified. |
| Antimotility: Not specified. |
| Prokinetics: Not specified. |
| Time before CDI treatment was stopped: Average of 36 hours. |
| Overall cure within stated follow up period: 94% (n=66/70) (100% (n=34/34) of those with non-027, 89% (n=32/36) with 027) within 12 weeks. |
| Cure with one infusion alone: 94% (n=66/70) (100% (n=34/34) of those with non-027, 89% (n=32/36) with 027) within 12 weeks. |
| Total follow up period: One year. |
| Minor GI adverse events: Not specified. |
| Minor non-GI adverse events: Not specified. |
| Serious adverse events: Not specified. |
| Deaths: 4 patients infected with 027 did not respond to FMT and died within 3 months. 10 other patients died of 'unrelated illnesses' during one year of follow-up. |
| Selection/eligibility reported: Yes. |
| Consecutively recruited: Not clear. |
| Prospectively recruited: No. |
| Loss to follow up explained: Yes. |
| At least 90% followed up: Yes. |</p>
<table>
<thead>
<tr>
<th>Case series.</th>
<th>Male: 76.</th>
<th>Overall cure within stated follow up period: 88% ($n=176/201$) over 90 days.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 201.</td>
<td>Female: 125.</td>
<td>Cure with one infusion alone: 73.1% ($n=147/201$).</td>
</tr>
<tr>
<td>Age (mean/ standard deviation): Mean age 66.6 (+/- 18.3) years.</td>
<td>Donors working in healthcare: not specified.</td>
<td>Total follow-up period: Each patient for 90 days.</td>
</tr>
<tr>
<td>Comorbidities: x37 cancer, x30 immunosuppressed, x26 CKD. Immunosuppressed defined as chemotherapy within 1 year of FMT, HIV with CD4 &lt; 200, or prednisolone use greater than or equal to 20mg for more than 1 month.)</td>
<td>Donor demographics: not specified.</td>
<td>Minor GI adverse events: Not specified.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Positive toxin or polymerase chain reaction.</td>
<td>Travel and antibiotic exclusion period: Not specified.</td>
<td>Deaths: 18 deaths in cohort but no clear timeframe, and not clear if any related to FMT. Described as mortality rate of 6.25% in response group, 28% in failure rate.</td>
</tr>
<tr>
<td>Diluent used to prepare: Not specified.</td>
<td>Donors working in healthcare: not specified.</td>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: Not specified.</td>
<td>Donor demographics: not specified.</td>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td>Time period for storage (frozen): Not specified.</td>
<td>Route administered: Upper GI: nasogastric tube x 76, PEG x5; lower GI: x45 enema, x75 colon; capsules: nil.</td>
<td></td>
</tr>
</tbody>
</table>
Additional Appendices

stated as anti-CDI treatment.
<table>
<thead>
<tr>
<th>Meighani et al, Digestive Diseases and Sciences, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case series.</strong></td>
</tr>
<tr>
<td>Number of patients: 201.</td>
</tr>
<tr>
<td>Female: male: 124: 77.</td>
</tr>
<tr>
<td>Age (mean/ standard deviation): Mean 68.79 (+/-16.78) years for x181 non-IBD patients, mean 46.9 (+/-19.97) for the x20 IBD patients.</td>
</tr>
<tr>
<td>Comorbidities: 13/20 IBD patients were immunosuppressed (no further details); no further specific details about immunosuppression.</td>
</tr>
<tr>
<td>CDI features: Recurrent CDI in 13/20 of IBD patients, primary refractory in 7/20. 1.90 (+/- 1.02) CDI infections in past three months for IBD patients, 1.79 (+/1.17) CDI infections in past three months for non-IBD patients.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: GDH first, then toxin A and B; PCR used if discordance.</td>
</tr>
<tr>
<td>Donors were typically family members, but small number of unrelated universal donors. Amongst IBD cohort - 6 patients had family members as donor, universal donor in other 14.</td>
</tr>
<tr>
<td>Donor working in healthcare: Not defined.</td>
</tr>
<tr>
<td>Donor demographics: Not defined.</td>
</tr>
<tr>
<td>Donor screening: Questionnaire - not defined.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Not defined.</td>
</tr>
<tr>
<td>Screening blood tests: Not defined.</td>
</tr>
<tr>
<td>Screening stool tests: Not defined.</td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: Not defined.</td>
</tr>
<tr>
<td>Diluent used to prepare: Not defined.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: Not defined.</td>
</tr>
<tr>
<td>Preparation methods: Not defined.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Not defined.</td>
</tr>
<tr>
<td>Time period for storage (frozen): Not defined.</td>
</tr>
<tr>
<td>Route administered: Upper GI: 5 nasogastric (IBD patients only; not described re non-IBD patients) lower GI: 13 colonoscopy (IBD patients only; not described in non-IBD patients); 2 retention enema (IBD patients only; not described re non-IBD patients) (15).</td>
</tr>
<tr>
<td>Number of infusions: Any relapse beyond 90 days was defined as 'new infection'. However, not made clear if patients given more than one FMT.</td>
</tr>
<tr>
<td>Bowel purgative: Not described.</td>
</tr>
<tr>
<td>PPI: Not described.</td>
</tr>
<tr>
<td>Antimotility: Not described.</td>
</tr>
<tr>
<td>Prokinetics: Not described.</td>
</tr>
<tr>
<td>Overall cure within stated follow up period: As per primary outcome - difficult to give more specific information than already given.</td>
</tr>
<tr>
<td>Cure with one infusion alone: 87.3% (n=158/181) in non-IBD, 75% (15/20) in IBD; but 17.15 (n=31/181) non-IBD relapse within 90 days/ 13.9% (n=25/180) beyond 90 days, and 25% (n=5/20) IBD relapse within 90 days/ 20% (n=4/20) beyond 90 days. 3/5 failures in IBD arm had newly-diagnosed IBD, other had severe active disease.</td>
</tr>
<tr>
<td>Minor GI adverse events: None.</td>
</tr>
<tr>
<td>Minor non-GI adverse events: None.</td>
</tr>
<tr>
<td>Serious adverse events: None.</td>
</tr>
<tr>
<td>Deaths: None.</td>
</tr>
<tr>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
</tr>
</tbody>
</table>
Pre-FMT antibiotics: Not defined for non-IBD; for IBD, 15 vancomycin alone, 5 vancomycin and oral metronidazole.

Time before CDI treatment was stopped before FMT: No specific details.
### Additional Appendices

**Patel et al, Mayo Clinic Proceedings, 2013**

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Number of patients: 31.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male: 17: 14.</td>
<td></td>
</tr>
<tr>
<td>Age (mean/ standard deviation): Mean 61.26 (+/- 19.34) years.</td>
<td></td>
</tr>
<tr>
<td>Comorbidities: x5 diverticulosis, x5 IBS, x3 UC, x1 Crohn's, x1 gastroparesis, x1 colonal fistula, x3 prev sigmoid surgery for diverticulitis, x2 subtotal colectomy with ileosigmoid anastomosis, x1 left hemicolecotomy with colostomy, x3 long term corticosteroids, x2 hypogammaglobulinaem ia, x1 OLT, x1 renal transplant, x1 long term methotrexate.</td>
<td></td>
</tr>
<tr>
<td>CDI features: Recurrent - mean +/- SD number of confirmed relapses before FMT of 4 +/- 1.4 (range 2-7) episodes.</td>
<td></td>
</tr>
<tr>
<td>CDI diagnosis confirmation: At least 3x unformed stools/ day, at</td>
<td></td>
</tr>
<tr>
<td>Donors were healthy family/ contacts of recipients - 14 spouses, 9 children, 5 siblings, 3 parents, 1 niece, 1 friend.</td>
<td></td>
</tr>
<tr>
<td>Working in healthcare: Not stated.</td>
<td></td>
</tr>
<tr>
<td>Donor demographics: No stated age/ BMI limits.</td>
<td></td>
</tr>
<tr>
<td>Donor screening: Questionnaire - exclude if: chronic GI disease, active peptic ulcer disease, GORD requiring daily PPI, IBS, IB, history of colon polyps/ cancer, antibiotics or hospitalisation in past three months.</td>
<td></td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: No stated travel restrictions; excluded as donor if antibiotic use within past 3 months.</td>
<td></td>
</tr>
<tr>
<td>Screening blood tests: hepatitis A IgM, HBsAg, HBC IgG/M, hepatitis C antibody, HIV-1/2 antibody, HTLV-1/2 antibody, RPR/ syphilis EIA.</td>
<td></td>
</tr>
<tr>
<td>Screening stool tests: MC&amp;S, ova, cysts and parasites, <em>Cryptosporidium</em> antigen, <em>Microsporidia</em> smear, <em>C difficile</em></td>
<td></td>
</tr>
<tr>
<td>Amount of stool per transplant / administered to patients: Whole stool - median transplanted weight of 115g (range 18-397g).</td>
<td></td>
</tr>
<tr>
<td>Diluent used to prepare: Normal saline - &quot;added in 100ml increments until mixture suitable for instillation through working channel of colonoscope&quot;.</td>
<td></td>
</tr>
<tr>
<td>Median volume of FMT 360 (range 180-900) ml.</td>
<td></td>
</tr>
<tr>
<td>Diluent used to store if frozen: N/A – fresh.</td>
<td></td>
</tr>
<tr>
<td>Preparation methods: Blender/ pitcher.</td>
<td></td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): Six hours; kept at room temperature until processing.</td>
<td></td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A.</td>
<td></td>
</tr>
<tr>
<td>Route administered: Upper GI: nil; lower GI: colonoscopy (31); capsule: nil.</td>
<td></td>
</tr>
<tr>
<td>Number of infusions: One initially.</td>
<td></td>
</tr>
<tr>
<td>Bowl purgative: Yes - PEG day before FMT.</td>
<td></td>
</tr>
<tr>
<td>PPI: Not described.</td>
<td></td>
</tr>
<tr>
<td>Antimotility: 4mg loperamide either pre- or immediately after colonoscopy.</td>
<td></td>
</tr>
<tr>
<td>Overall cure within stated follow up period: At 3 months – 91.3% (n=21/23) said diarrhoea no longer present; at 1 year, 100% (n=6/6) reported maintained improvement or resolution.</td>
<td></td>
</tr>
<tr>
<td>Minor GI adverse events: Not described.</td>
<td></td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not described.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events: Micro perforation - caused by biopsy of an area of presumed ischaemic small bowel injury during the FMT procedure; managed conservatively.</td>
<td></td>
</tr>
<tr>
<td>Deaths: x1 death at three months - directly related to recently diagnosed metastatic pancreatic cancer, not related to FMT .</td>
<td></td>
</tr>
</tbody>
</table>

---

**Selection/ eligibility reported: Yes.**

**Consecutively recruited: Yes, implied that were.**

**Prospectively recruited: No.**

**Loss to follow up explained: Yes.**

**At least 90% followed up: Yes - at least as far as primary outcome.**
<p>| least 2 x toxin positive episodes previously to participate. Pre-FMT antibiotics: All 31 previous methotrexate, all 31 previous vancomycin, 6 previous fidaxomicin, 10 previous rifaximin, 23 prior probiotic. | toxin (PCR or EIA). | Prokinetics: Not described. Time before CDI treatment was stopped before FMT: Antibiotics continued until 4 hours before prep (i.e. stopped day prior to FMT). |</p>
<table>
<thead>
<tr>
<th>Pathak <em>et al.</em>, Clinical &amp; Experimental Gastroenterology, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case series.</strong></td>
</tr>
<tr>
<td>Number of patients: 12.</td>
</tr>
<tr>
<td>Female: male: 8: 4.</td>
</tr>
<tr>
<td>Age (mean): Mean 71.9 (range 37 – 90) years.</td>
</tr>
<tr>
<td>Comorbidities: x1 UC, 1 renal transplant, x1 left colon adenocarcinoma and diverticulitis; x1 ruptured appendix; x2 ventilator-dependent.</td>
</tr>
<tr>
<td>CDI features: Recurrent; full details not given. Two of the patients had had recurrent CDI treated with FMT ‘many years ago’.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Not specifically defined.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: All vancomycin, 8 patients fidaxamicin, 4 patients methotrexate.</td>
</tr>
<tr>
<td>Donors were preferably family/first degree relatives; family used in all cases here.</td>
</tr>
<tr>
<td>Working in healthcare: Not specifically addressed.</td>
</tr>
<tr>
<td>Donor demographics: Not given.</td>
</tr>
<tr>
<td>Donor screening: Questionnaire - exposure to HIV, hepatitis, STDs; high risk sexual behaviour; drug use, tattoos/piercings, imprisonment, other high risk behaviour; known current communicable disease; GI morbidities including IBD or GI malignancy; antibiotic use within 90 days.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): 6 hours.</td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A.</td>
</tr>
<tr>
<td>Route administered: Upper GI: nasoduodenal tube (1; as a second FMT); lower GI: colonoscopy (12).</td>
</tr>
<tr>
<td>Number of infusions: 1 FMT initially.</td>
</tr>
<tr>
<td>Bowel purgative: PEG the night before FMT.</td>
</tr>
<tr>
<td>PPI: Not described.</td>
</tr>
<tr>
<td>Antimotility: 2 tablets diphenoxylate/atropine post-FMT.</td>
</tr>
<tr>
<td>Prokinetics: Not described.</td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: 24 hours.</td>
</tr>
<tr>
<td>Overall cure within stated follow-up period: 91.7% (n=11/12).</td>
</tr>
<tr>
<td>Cure with one infusion alone: 91.7% (n=11/12).</td>
</tr>
<tr>
<td>Total follow up period: 2-26 months.</td>
</tr>
<tr>
<td>Minor GI adverse events: Not stated.</td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not stated.</td>
</tr>
<tr>
<td>Deaths: x1 death. Patient with perforated appendix developed rCDI didn't respond to six months of anti-CDI treatment, went to ITU. Donor was husband - no screening, and no response to colonoscopic FMT. For 2nd FMT, used healthy volunteer donor FMT via nasoduodenal tube - responded. Urinary tract infection at nursing home few months later – antibiotic treatment precipitated further CDI. Further sepsis, returned to ITU -</td>
</tr>
<tr>
<td><strong>Preparation methods:</strong> No specific details.</td>
</tr>
<tr>
<td><strong>selection/eligibility reported:</strong> Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: Yes, implied that were.</td>
</tr>
<tr>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
</tr>
<tr>
<td>At least 90% followed up: Yes.</td>
</tr>
</tbody>
</table>

Additional Appendices
declined treatment, then died, four months after initial FMT.
<table>
<thead>
<tr>
<th><strong>Case series.</strong></th>
<th><strong>Donors were 4 family members, 14 partners, and 1 housemate.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients:</strong> 19.</td>
<td><strong>Donors working in healthcare:</strong> Excluded.</td>
</tr>
<tr>
<td><strong>Female: male:</strong> 17: 2.</td>
<td><strong>Donor demographics:</strong> Donor screening: Questionnaire — included current or recent diarrhoeal illness, sexual behaviour.</td>
</tr>
<tr>
<td><strong>Age (mean): Mean age 49 years.</strong></td>
<td><strong>Travel and antibiotic exclusion period: Excluded if 'recent antibiotic use'; not further defined.</strong></td>
</tr>
<tr>
<td><strong>Comorbidities: Not described.</strong></td>
<td><strong>Screening blood tests:</strong> HIV, hepatitis A, B and C, and <em>Treponema</em> serology.</td>
</tr>
<tr>
<td><strong>CDI features:</strong> Recurrent CDI.</td>
<td><strong>Screening stool tests:</strong> <em>C. difficile</em>, bacterial culture, ova, cysts and parasites, <em>Giardia</em>, <em>Cryptosporidium</em>.</td>
</tr>
<tr>
<td><strong>CDI diagnosis confirmation:</strong> Positive <em>C. difficile</em> toxin and consistently recurring symptoms over a span of six months.</td>
<td><strong>Number of infusions:</strong> One routinely, with one patient having a second FMT.</td>
</tr>
<tr>
<td><strong>Pre-FMT antibiotics:</strong> Not given in detail - all at least three courses of conventional anti-CDI antibiotics, including pulsed and tapered vancomycin.</td>
<td><strong>Bowel purgative:</strong> PEG.</td>
</tr>
<tr>
<td></td>
<td><strong>PPI:</strong> Not described.</td>
</tr>
<tr>
<td></td>
<td><strong>Antimotility:</strong> Loperamide post-FMT.</td>
</tr>
<tr>
<td></td>
<td><strong>Prokinetics:</strong> Not described.</td>
</tr>
<tr>
<td></td>
<td><strong>Time before CDI treatment was stopped before FMT:</strong> 1-3 days.</td>
</tr>
<tr>
<td></td>
<td><strong>Time before CDI treatment was stopped before FMT:</strong> 1-3 days.</td>
</tr>
<tr>
<td></td>
<td><strong>Overall cure within stated follow up period:</strong> 100% (<em>n</em>=20/20).</td>
</tr>
<tr>
<td></td>
<td><strong>Cure with one infusion alone:</strong> 95% (<em>n</em>=19/20).</td>
</tr>
<tr>
<td></td>
<td><strong>Total follow-up period:</strong> 6 months to 5 years.</td>
</tr>
<tr>
<td></td>
<td><strong>Minor GI adverse events:</strong> Nil reported.</td>
</tr>
<tr>
<td></td>
<td><strong>Minor non-GI adverse events:</strong> Nil reported.</td>
</tr>
<tr>
<td></td>
<td><strong>Serious adverse events:</strong> Nil reported.</td>
</tr>
<tr>
<td></td>
<td><strong>Deaths:</strong> Nil reported.</td>
</tr>
<tr>
<td></td>
<td><strong>Selection/ eligibility reported:</strong> Yes.</td>
</tr>
<tr>
<td></td>
<td><strong>Consecutively recruited:</strong> Yes.</td>
</tr>
<tr>
<td></td>
<td><strong>Prospectively recruited:</strong> No.</td>
</tr>
<tr>
<td></td>
<td><strong>Loss to follow up explained:</strong> Yes – variable follow-up.</td>
</tr>
<tr>
<td></td>
<td><strong>At least 90% followed up:</strong> Yes.</td>
</tr>
</tbody>
</table>
### Rubin et al, Anaerobe, 2013

<table>
<thead>
<tr>
<th>Case series.</th>
<th>Donors were healthy people from the same household as the patient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients: 75.</td>
<td>Donors working in healthcare: Not stated.</td>
</tr>
<tr>
<td>Comorbidities: x10 diabetes mellitus, x8 malignancy, x7 corticosteroids in prior three months.</td>
<td>Travel and antibiotic exclusion period: As per Aas et al, Clin Infect Dis, 2003.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Oral metronidazole or vancomycin alone or in combination for initial FMT in all cases; not clear exact breakdown/use for recurrences.</td>
<td>Number of infusions: One routinely.</td>
</tr>
<tr>
<td>Amount of stool per transplant/administered to patients: 30g of stool.</td>
<td>Bowel purgative: Not described.</td>
</tr>
<tr>
<td>Diluent used to prepare: Saline - As per Aas et al, Clin Infect Dis, 2003. 25ml of stool/saline mixture per FMT.</td>
<td>PPI: Evening prior to/morning of procedure - no further details.</td>
</tr>
<tr>
<td>Diluent used to store if frozen: N/A-fresh.</td>
<td>Antimotility: Not described.</td>
</tr>
<tr>
<td>Time from preparation to transplant (fresh): As per Aas et al, Clin Infect Dis, 2003.</td>
<td>Overall cure within stated follow up period: 78.7% (n=59/75).</td>
</tr>
<tr>
<td>Time period for storage (frozen): N/A-fresh.</td>
<td>Cure with one infusion alone: 78.7% (n=59/75).</td>
</tr>
<tr>
<td>Route administered: Upper GI: 64 nasogastric, 4 PEG, 7 OGD (75 administrations to 74 patients); lower GI: nil; capsule: nil.</td>
<td>Total follow up period: Up to 60 days.</td>
</tr>
<tr>
<td>Number of infusions: One routinely.</td>
<td>Deaths: No - up to 60 days.</td>
</tr>
<tr>
<td>Bowel purgative: Not described.</td>
<td>Minor GI adverse events: Nil.</td>
</tr>
<tr>
<td>PPI: Evening prior to/morning of procedure - no further details.</td>
<td>Minor non-GI adverse events: Nil.</td>
</tr>
<tr>
<td>Antimotility: Not described.</td>
<td>Serious adverse events: Nil.</td>
</tr>
<tr>
<td>Prokinetics: Not described.</td>
<td>Selection/eligibility reported: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
<td>Prospectively recruited: No.</td>
</tr>
<tr>
<td>Loss to follow up explained: Yes.</td>
<td>At least 90% followed up: Yes.</td>
</tr>
</tbody>
</table>
Time before CDI treatment was stopped before FMT: Stopped on the day prior to procedure.
<table>
<thead>
<tr>
<th>Additional Appendices</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case series.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Number of patients:</strong> 49.</td>
<td></td>
</tr>
<tr>
<td><strong>Female:</strong> 34: <strong>Male:</strong> 15.</td>
<td></td>
</tr>
<tr>
<td><strong>Age (mean):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Fresh:</strong> 52 (range 22-81) years; <strong>Frozen:</strong> 61 (range 20-88) years.</td>
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</tr>
<tr>
<td><strong>Comorbidities:</strong> Not described in significant details.</td>
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<tr>
<td><strong>CDI features:</strong> Recurrent - mean 4.6 (range 2-12) relapses in fresh; mean 4.9 (range 1-6) relapses in frozen.</td>
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<tr>
<td><strong>CDI diagnosis confirmation:</strong> &quot;Positive culture and toxin&quot;.</td>
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<tr>
<td><strong>Pre-FMT antibiotics:</strong> Describes using vancomycin with all, but no specific details.</td>
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<tr>
<td><strong>Donors:</strong> 15 fresh FMTs with individual donors, 11 fresh FMTs with universal donors; and 23 frozen FMTs with universal donor.</td>
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<tr>
<td><strong>Donor working in healthcare:</strong> Not stated.</td>
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<tr>
<td><strong>Donor demographics:</strong> No clear age or BMI limits.</td>
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<tr>
<td><strong>Donor screening:</strong> Questionnaire - &quot;No antibiotics in past six months and no intestinal symptoms&quot;.</td>
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<tr>
<td><strong>Travel and antibiotic exclusion period:</strong> Excluded as donors if had used antibiotics in past six months.</td>
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<tr>
<td><strong>Screening bloods:</strong> Total blood count, CRP, creatinine, LFTs, hepatitis B and C, HIV-1/-1, <em>Treponema</em>.</td>
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<tr>
<td><strong>Screening stools:</strong> <em>C difficile</em> culture and toxin A/B test, MC&amp;S, ova, cysts and parasites.</td>
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<tr>
<td><strong>Amount of stool per transplant/administered to patients:</strong> Fresh - approximately 30g of stool.</td>
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<tr>
<td><strong>Diluent used to prepare:</strong> Fresh - approximately 150ml of tap water.</td>
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<tr>
<td><strong>Diluent used to store if frozen:</strong> Frozen - 30g of stool added to 150ml N/saline and then glycerol.</td>
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<tr>
<td><strong>Preparation methods:</strong> As described.</td>
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<tr>
<td><strong>Time from preparation to transplant (fresh):</strong> Fresh - less than 6 hours between delivery and administration; less than 15 minutes between making FMT and delivery.</td>
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<tr>
<td><strong>Time period for storage (frozen):</strong> Up to 16 weeks; thawed over 4-5 hours at room temp or in 37°C water bath.</td>
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<tr>
<td><strong>Route administered:</strong> Upper GI: nil; lower GI: colonoscopy (49); capsules: nil.</td>
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<tr>
<td><strong>Number of infusions:</strong> One FMT routinely.</td>
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<tr>
<td><strong>Bowel purgative:</strong> 4l Colonsteril PEG/ 2l MoviPrep.</td>
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<tr>
<td><strong>PPI:</strong> Not described.</td>
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<tr>
<td><strong>Antimotility:</strong> Not described.</td>
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<tr>
<td><strong>Prokinetics:</strong> Not described.</td>
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<tr>
<td><strong>Overall cure within stated follow up period:</strong> Fresh: 96% (n=25/26); frozen: 96% (n=22/23).</td>
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<tr>
<td><strong>Total follow up period:</strong> 12 weeks.</td>
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<tr>
<td><strong>Minor GI adverse events:</strong> N/A.</td>
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<tr>
<td><strong>Minor non-GI adverse events:</strong> Mild transient fever in x2 patients with frozen FMT.</td>
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<tr>
<td><strong>Serious adverse events:</strong> N/A.</td>
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<tr>
<td><strong>Deaths:</strong> x1 fresh faeces patient died within one year of FMT - not related; x2 frozen patients had relapse within one year, both treated with further antibiotics – x1 died of recurrent CDI, x1 died of arterial thrombosis.</td>
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<tr>
<td><strong>Selection/eligibility reported:</strong> Yes.</td>
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<tr>
<td><strong>Consecutively recruited:</strong> Yes.</td>
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<tr>
<td><strong>Prospectively recruited:</strong> No.</td>
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<tr>
<td><strong>Loss to follow up explained:</strong> Yes.</td>
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<tr>
<td><strong>At least 90% followed up:</strong> Yes.</td>
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*Satokari et al, Alimentary Pharmacology and Therapeutics, 2015*
### Time before CDI treatment was stopped before FMT: Stopped at an average of 36 hours prior to administration.

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Description</th>
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</table>
## Case series

- **Number of patients:** 12
- **Female:** 9  
  **Male:** 3  
- **Age (mean):** Mean 66 (range 30 - 86) years
- **Comorbidities:** 9 with diverticulosis (with 2 of these having diverticulitis as index infection)  
- **CDI features:** 1 patient with first CDI, 2 with 2nd, 5 with 3rd, 1 with 4th, 1 with 5th, 1 with 6th, 1 with 8th
- **CDI diagnosis confirmation:** Toxin testing for either toxin A or B, or assessment of both via EIA
- **Donors:** Spouses/partners in 8 patients; for other 4 patients, donors were one son, two daughters, and one granddaughter
- **Donors working in healthcare:** No
- **Donor demographics:** No details
- **Donor screening:** Questionnaire - no details
- **Travel and antibiotic exclusion period:** No details given
- **Screening bloods:** Hepatitis B and C, HIV
- **Screening stools:** *C. difficile* toxin, enteric pathogens, ova, cysts and parasites - at treating clinician’s discretion
- **Pre-FMT antibiotics:** 12 had oral metronidazole, 3 had intravenous metronidazole, 12 had oral vancomycin, 4 x rifaximin, no mention of fidaxomicin
- **Number of infusions:** Single
- **Bowel purgative:** All colonoscopic, but no specific details given
- **PPI:** Not described
- **Antimotility:** Not described
- **Prokinetics:** Not described
- **Time CDI treatment was stopped before overall cure within stated follow up period:** 100% (n=12/12)
- **Total follow up period:** 3 weeks to 8 years - no details on relation to individual patients
- **Minor GI adverse events:** Nil described
- **Minor non-GI adverse events:** Nil described
- **Serious adverse events:** Nil described
- **Deaths:** Nil described
- **Selection/eligibility reported:** Yes
- **Consecutively recruited:** Yes
- **Prospectively recruited:** No
- **Loss to follow up explained:** No
- **At least 90% followed up:** Yes
## Additional Appendices

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<th>FMT: 3 days.</th>
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</table>
### Youngster et al, JAMA, 2014

<table>
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<tr>
<th>Propective case series.</th>
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</thead>
<tbody>
<tr>
<td>Number of patients: 20.</td>
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<tr>
<td>Female: male: 9: 11.</td>
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<tr>
<td>Age (median): Median 64.5 (range 11-89) years.</td>
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<tr>
<td>Comorbidities: Specific comorbidities not described.</td>
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<tr>
<td>CDI features: Included patients with both recurrent or refractory CDI.</td>
</tr>
<tr>
<td>CDI diagnosis confirmation: Toxin and ELISA, PCR if toxin negative but ELISA is positive or indeterminate.</td>
</tr>
<tr>
<td>Pre-FMT antibiotics: Failed vancomycin taper and/or fidaxomicin.</td>
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</tbody>
</table>

| Donors were unrelated adult volunteers. |
| Donor working in healthcare: Not stated. |
| Donor demographics: Age range 18-50 years, BMI 18.5-25. |
| Donor screening: Questionnaire - American Association of Blood Banks donor questionnaire. |
| Travel and antibiotic exclusion period: Excluded as potential donors if used antibiotics within preceding 6 months. |
| Screening blood tests: Antibodies to hepatitis A, B, and C; HIV; and *Treponema pallidum* within 2 weeks of donations. |
| Screening stool tests: "Enteric pathogens". |

| Amount of stool per transplant/ administered to patients: 30 capsules (single treatment) - total 48g of stool. |
| Diluent used to prepare: saline in 1/10th volume of stool. |
| Diluent used to store if frozen: 10% glycerol. |
| Preparation methods: Faecal matter solution was pipetted into size 0 capsules (650 μL), which were closed and then secondarily sealed in size 00 capsules. Capsules were stored frozen at ~80°C until use. |
| Time from preparation to transplant (fresh): N/A. |
| Time period for storage (frozen): Mean 113 days (30-252 days). |
| Route administered: All courses were 30 oral capsules. |
| Number of treatments: 1 course (given as 15 capsules on 2 consecutive days). If failed, retreated at a mean of 7 days. |
| Bowel purgative: Not described. |
| PPI: Not described. |
| Antimotility: Not described. |

| Overall cure within stated follow up period: 90% (n=18/20). |
| Minor GI adverse events: Transient abdominal cramping and bloating in 6 patients (30%) that resolved in 72 hours. |
| Minor non-GI adverse events: Not described. |
| Serious adverse events: x1 hospitalised with a documented relapse of severe CDI after taking 15 capsules, but had successful treatment after receiving the remaining 15 capsules. No other severe adverse events (grade 2 or above). |
| Deaths: none. |

| Selection/ eligibility reported: Yes. |
| Consecutively recruited: Yes. |
| Prospectively recruited: Yes. |
| Loss to follow up explained: Yes. |
| At least 90% followed up: Yes. |
## Additional Appendices

<table>
<thead>
<tr>
<th>Time before CDI treatment was stopped before FMT: 48 hours prior to FMT.</th>
<th>Prokinetics: Not described.</th>
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</thead>
</table>

Prokinetics: Not described.

Time before CDI treatment was stopped before FMT: 48 hours prior to FMT.
Donors were healthy volunteers.
Donors working in healthcare: Not mentioned.
Donor demographics: 18-50 years of age, on no medications, with a ‘normal body mass index’.
Donor screening: Questionnaire - initial screening using the American Association of Blood Banks donor questionnaire for exposure to infectious agents.
Travel and antibiotic exclusion period: Excluded as donor if antibiotic use within 6 months.
Screening bloods: Blood was screened for antibodies to hepatitis A, B, and C; HIV; and Treponema pallidum within 2 weeks of donations.
Screening stool test: Donor faeces were screened for enteric bacterial pathogens including rotavirus, Listeria monocytogenes, Vibrio cholerae, Escherichia coli O157, ova and parasites (including general microscopy, acid-fast staining, and/or antigen testing
Amount of stool per transplant / administered to patients: 30 capsules derived from a mean of 48g of faeces.
Diluent used to prepare: Normal saline.
Diluent used to store if frozen: 10% glycerol.
Preparation methods: Homogenised using a commercial blender then passed through sieves in ambient air.
Time from preparation to transplant (fresh): N/A.
Time period for storage (frozen): Study of capsule-formulated FMT. Faecal slurry was double-encapsulated in hypromellose capsules (Capsugel, Cambridge, MA) and stored at –80 °C for up to 6 months pending use.
Route administered: All received 30 capsules as a ‘dose’.
Number of infusions: 1 course of capsules in 147 patients, 2 courses in 26 patients and 3 course in 4 patients.
Bowel purgative: not mentioned.
PPI: not mentioned.
Antimotility: not mentioned.

<table>
<thead>
<tr>
<th>Donor characteristics</th>
<th>Case series.</th>
<th>Number of patients: 180.</th>
<th>Female: male: Not stated.</th>
<th>Age (median): Median 64 (range 7–95) years.</th>
<th>Comorbidities: Not described.</th>
<th>CDI features: Three or more mild-to-moderate episodes of CDI or two episodes requiring hospitalisation.</th>
<th>CDI diagnosis confirmation: Not specifically described.</th>
<th>Pre-FMT antibiotics: Not described.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cure within stated follow up period: 91% (n=164/180)</td>
<td>Cure with one infusion alone: 82% (n=147/180)</td>
<td>Total follow up period: 8 weeks for primary response.</td>
<td>Minor GI adverse events: x5 vomiting, x112 diarrhoea, x45 nausea/ bloating, x40 abdominal pain.</td>
<td>Minor non-GI adverse events: x3 fever, x54 fatigue, malaise, and headache, x12 other complaints.</td>
<td>Serious adverse events: Related serious (x1 fever, x2 new UC, x6 hospitalisations for CDI/ diarrhoea).</td>
<td>Unrelated serious adverse events: x26 hospitalisations, x14 deaths.</td>
<td>Deaths: x14 (unrelated).</td>
<td>Selection/eligibility reported: Yes.</td>
</tr>
</tbody>
</table>
### Additional Appendices

| for *Giardia, Cryptosporidium, Isospora, and Microsporidia*, *C. difficile*, and *Helicobacter pylori* antigen. | Prokinetics: not mentioned.  
Time before CDI treatment was stopped before FMT: 24–48 hours prior. |
<table>
<thead>
<tr>
<th>Zainah et al, Digestive Diseases and Sciences, 2014</th>
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</thead>
<tbody>
<tr>
<td>Case series.</td>
</tr>
<tr>
<td>Number of patients: 14.</td>
</tr>
<tr>
<td>Female: male: 9:5.</td>
</tr>
<tr>
<td>Age (mean +/-range)*: 73.4 (+/-11.9) years.</td>
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<tr>
<td>Comorbidities: x4 patients with cancer, x1 OLT patient.</td>
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<tr>
<td>CDI features: 8 patients had prev CDI episodes (2-5 episodes prior).</td>
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<tr>
<td>CDI diagnosis: Diarrhoea (at least 3 unformed stool/d for 2 consecutive days) + positive C difficile EIA and/or PCR. All patients here severe by definition - defined here as age &gt;60 years, albumin &lt;2.5mg/dl, temp at least 38.3°C, WBC &gt; 15 within 48 hour of CDI diagnosis; or at least one of the following: pseudomembranes, treatment in intensive care.</td>
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<tr>
<td>Donors: 12 patients received FMT from related donor (7 spouse, 5 children); the other two used unrelated donors.</td>
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<tr>
<td>Donors working in healthcare: Not stated.</td>
</tr>
<tr>
<td>Donor demographics: Not stated.</td>
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<tr>
<td>Donor screening: Questionnaire - not described.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: No details.</td>
</tr>
<tr>
<td>Screening blood tests: HIV-1/-2, hepatitis A IgM, hepatitis B serology, hepatitis C antibody, syphilis (RPR and FTA-ABS).</td>
</tr>
<tr>
<td>Screening stools: C difficile toxin by PCR, stool ova, cysts and parasites.</td>
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<tr>
<td>Amount of stool per transplant/ administered to patients: 30-50g.</td>
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<tr>
<td>Diluent used to prepare: Warm tap water.</td>
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<tr>
<td>Diluent used to store if frozen: N/A.</td>
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<tr>
<td>Preparation methods: Homogenised mixture, then filtered through gauze; 120-180ml of suspension if through nasogastric tube, 300-500ml if through colonoscopy.</td>
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<tr>
<td>Time from preparation to transplant (fresh): &quot;Same day&quot;.</td>
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<tr>
<td>Time period for storage (frozen): N/A.</td>
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<tr>
<td>Route administered: Upper GI: Nasogastric administration in all but one patient (13 patients); lower GI: colonoscopic administration in one patient (1 patient).</td>
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<tr>
<td>Number of infusions: One routinely; repeated if no response at 48-72hr.</td>
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<tr>
<td>Bowel purgative: No details.</td>
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<tr>
<td>PPI: Yes, pre nasogastric administration - no details given.</td>
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<tr>
<td>Antimotility: Not described.</td>
</tr>
<tr>
<td>Prokinetics: Not described.</td>
</tr>
<tr>
<td>Overall cure within stated follow up period: 79% (n=11/14) by seven days.</td>
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<tr>
<td>Cure with one infusion alone: 71% (n=10/14).</td>
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<tr>
<td>Total follow up period: Up to 100 days.</td>
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<tr>
<td>Minor GI adverse events: Not described.</td>
</tr>
<tr>
<td>Minor non-GI adverse events: Not described.</td>
</tr>
<tr>
<td>Serious adverse events: Not described.</td>
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<tr>
<td>Deaths: x1 within 7 days of FMT - but died of their malignancy.</td>
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<tr>
<td>Selection/ eligibility reported: Yes.</td>
</tr>
<tr>
<td>Consecutively recruited: Yes.</td>
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<tr>
<td>Prospectively recruited: No.</td>
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<tr>
<td>Loss to follow up explained: Yes.</td>
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<tr>
<td>At least 90% followed up: Yes.</td>
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</table>
## Additional Appendices

<table>
<thead>
<tr>
<th>Pre-FMT antibiotics: 14 patients prior vancomycin, 12 prior metronidazole too.</th>
<th>Time before CDI treatment was stopped before FMT: 24 hours.</th>
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C.2. Reviewed randomised studies of FMT for recurrent or refractory CDI
<table>
<thead>
<tr>
<th>Paper</th>
<th>Study and patient characteristics</th>
<th>Donor characteristics</th>
<th>FMT characteristics</th>
<th>Outcomes</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td>Camacho-Ortiz et al, PLoS ONE, 2017</td>
<td>Intervention: FMT (pooled from three donors). Number of patients: 9. Female: male: 3: 4 (data only presented for 7 patients). Age: Mean of 39.7 (+/- 24.8) years. Comparator: Vancomycin (250mg every 6 hours for 10-14 days). Number of patients: 10. Female: Male: 3: 6 (data only presented for 9 patients). Age (mean/median): Mean of 46.7 (+/- 15.8) years. Comorbidities: In FMT arm – x1 abdominal abscess, x1 Child B cirrhotic, x1 pulmonary TB; in vancomycin arm – x2 haemodialysis patients, x1 meningeal TB, x1 ‘abscessed squamous cell carcinoma’. CDI features: All first episode of CDI, occurring at least 48hrs after admission. CDI diagnosis confirmation: &gt;3 bowel movements during the previous 24 hours, Bristol scale &gt; 5, positive C. difficile EIA or PCR. Pre-FMT antibiotics: no antibiotics within FMT arm; patients in vancomycin arm received 250mg</td>
<td>Donors working in healthcare: Not stated. Donor demographics: &gt;18 years, non-pregnant, BMI 20-25kg/m² Donor screening: On questionnaire, rejected potential donors who in the past three months had had use of PPI, use of antibiotics, use of immunosuppressives, hospitalisation and/or diarrhoea. Also excluded if high risk sexual behaviour, first degree relative with diabetes mellitus, abdominal surgery, and any GI disease/cancer. Travel and antibiotic exclusion period: Excluded if antibiotics within the past 3 months. Screening blood tests: Normal full blood count and liver enzymes essential for inclusion. Also screened for HAV, HBV, HCV, HIV, CMV, EBV, Trypanosoma, Brucella, Treponema pallidum. Screening stool tests: Included parasites, enteropathogenic bacteria, rotavirus.</td>
<td>Amount of stool per transplant: 45ml of pooled donor stool (from three donors), at ~0.19g/ml. Diluent used to prepare: 0.9% saline. Diluent used to store if frozen: 15% v/v glycerol. Preparation methods: Stool from donors pooled, mixed, resuspended in saline, filtered to remove particles &gt; 330μm. Time from preparation to transplant (fresh): N/A. Time period for storage (frozen): Not stated.</td>
<td>Treatment arm: FMT Overall cure rate: 71.4% (n=5/7) (after 2 x FMT) Cure with one infusion alone: 57.1% (n=4/7). Treatment arm: Vancomycin Overall cure rate: 88.9% (n=8/9) (not clear if failed patient received FMT subsequently, as is described in protocol).</td>
<td>Minor GI adverse events: Nil stated. Minor non-GI adverse events: Nil stated. Serious adverse events: Nil stated. Deaths: Nil.</td>
</tr>
<tr>
<td>Time before CDI treatment was stopped before FMT: Nil given.</td>
<td>Prokinetics: Not stated.</td>
<td>Antimotility: Not stated.</td>
<td>PPI: Not stated.</td>
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<tr>
<td>Total follow up period: up to one year.</td>
<td>Cochrane Collaboration risk of bias assessment: uncertain risk of bias.</td>
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<tr>
<td>every 6hrs for 10-14 days.</td>
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</table>
### Cammarota et al, Alimentary Pharmacology and Therapeutics, 2015

| Intervention: FMT. | Number of patients: 20.  
Female: Male: 12: 8.  
Age (mean/median): Mean 71 (range 29-89) years.  
Comparador: Vancomycin (125mg four times daily for 10 days, follow by a pulse regimen (125-500mg/day every 2-3 days, for at least three weeks).  
Number of patients: 19.  
Female: Male: 11: 8.  
Age (mean/median): Mean 75 (range 49-93) years.  
Comorbidities: No significant difference of Charlson comorbidity index between groups.  
CDI features: All recurrent. 7/20 in FMT arm with pseudomembranous colitis.  
CDI diagnosis confirmation: Diarrhoea and CDT positive within 10 weeks of previous antibiotic treatment.  
Pre-FMT antibiotics: All had had vancomycin or metronidazole. 19/20 of FMT arm and 16/20 of vancomycin arm had had previous vancomycin taper.  
Total follow up period: 10 weeks. | Donors working in healthcare: no.  
Donor demographics: Less than 50 years of age, no antibiotics within past 6 months.  
Donor screening: Questionnaire - no antibiotics for last 6/12. Excluded if significant GI disease, metabolic syndrome, chronic illness, immunocompromise, recent travel, high risk lifestyle in last three months.  
Screening blood tests: Hepatitis A, B, and C, HIV, EBV, syphilis, *Stongyloides, Entamoeba histolytica*, FBC, LFTs, creatinine, CRP.  
Screening stool tests: *C. difficile* cult and toxin, enteric bacteria, ova, cysts and parasites, VRE, MRSA, Gram negative multi-drug resistant bacteria.  
Amount of stool per transplant / administered to patients: Not specified.  
Diluent used to prepare: Normal saline 500mls.  
Diluent used to store if frozen: N/A – fresh.  
Preparation methods: Blended and strained.  
Time from preparation to transplant (fresh): 6 hours.  
Time period for storage (frozen): N/A.  
Route administered: Upper GI nil; lower GI: colonic (20); capsule: nil.  
Number of infusions: 14 had 1 infusion, 4 had 2 infusions, 1 had 3 infusions and 1 had 4 infusions. Initial protocol was that if non-response to first FMT, then second FMT after one week; however, after first two patients, changed to all patients with pseudomembranous colitis receiving repeat FMT every 3 days until resolution of CDI.  
Bowel purgative: Macrogol.  
PPI: No. | Treatment arm: FMT  
Overall cure rate: 90% (n=18/20). Cure with one infusion alone: 65% (n=13/20); none of these were patients with pseudomembranous colitis. The 7 patients not cured with first FMT all had pseudomembranous colitis; of these, 5/7 cured with protocol of recurrent FMTs.  
Treatment arm: Vancomycin:  
Overall cure rate: Cure with one infusion alone: 26% (n=5/19). | Minor GI adverse events: x19 diarrhoea, x12 bloating (all resolved at 12 hours).  
Minor non-GI adverse events: None.  
Serious adverse events: None.  
Deaths: x2 from *C difficile*-related complications.
Prokinetics: No.  
Time before CDI treatment was stopped before FMT: Between five and two days prior to FMT. |  |  |
| Allegretti et al, Gastroenterology (abstract), 2016 |
|---|---|---|---|
| Intervention: Low dose FMT capsules (30 pills once).  
Number of patients: 10.  
Female: male: Not stated.  
Age (mean/median): Not stated.  
Comparator: High dose FMT capsules (30 pills daily on two consecutive days).  
Number of patients: 9.  
Female: male: Not stated.  
Age (mean/median): Not stated.  
Comorbidities: Not stated.  
CDI features: Not stated.  
CDI diagnosis confirmation: Not stated.  
Pre-FMT antibiotics: Not stated.  
Total follow up period: 8 weeks.  
Cochrane Collaboration risk of bias assessment: uncertain risk of bias.  
Donors were unrelated donors from universal stool bank (OpenBiome).  
Donors working in healthcare: No.  
Donor demographics: mean age 26, mean BMI 22.2.  
Donor screening: Questionnaire - as per OpenBiome protocol.  
Travel and antibiotic exclusion period: As per OpenBiome protocol.  
Screening bloods: As per OpenBiome protocol.  
Screening stools: As per OpenBiome protocol.  
Amount of stool per transplant / administered to patients: 30 pills a day for one day.  
Diluent used to prepare: Not stated.  
Diluent used to store if frozen: Stored at -80°C prior to use.  
Preparation methods: Capsules physically stable for 30 days at 25°C using an emulsion-based production protocol.  
Time from preparation to transplant (fresh): Not stated.  
Time period for storage (frozen): Not stated.  
Route administered: All capsule – as described above.  
Number of infusions: 30 tablets (over one day).  
Bowel purgative: Not stated.  
PPI: Not stated.  
Antimotility: Not stated.  
Prokinetics: Not stated.  
Time before CDI treatment was stopped before FMT: Not stated.  
Overall cure rate: 70% (n=7/10).  
Minor GI adverse events: None.  
Minor non-GI adverse events: None.  
Serious adverse events: None.  
Deaths: None. |
| Hota et al, *Clinical Infectious Diseases*, 2016 | **Intervention:** FMT.  
**Number of patients:** 16.  
**Female:** male: 11: 5.  
**Age (mean/ standard deviation):** Mean 75.7 +/- 14.5 years.  
**Comparator:** 6 week vancomycin taper.  
**Number of patients:** 12.  
**Female:** male: 8: 4.  
**Age (mean/ standard deviation):** Mean 69.6 +/- 14.2 years.  
**Comorbidities:** Not stated, but similar Charlson comorbidity index score between groups.  
**CDI features:** All recurrent.  
**CDI diagnosis confirmation:** Symptoms and toxin or PCR detection.  
**Pre-FMT antibiotics:** At least 1 course of vancomycin for a minimum of 10 days. The majority of patients in both arms had prior vancomycin tapers.  
**Total follow up period:** 120 days.  
**Cochrane Collaboration risk of bias assessment:** uncertain risk of bias.  
| **Donors working in healthcare:** Not stated.  
**Donor demographics:** ≥18yrs.  
**Donor screening:** Questionnaire - self-screening questionnaire of behaviours associated with risk for blood-borne pathogens.  
**Travel and antibiotic exclusion period:** Antibiotic use for at least two days in the preceding three months.  
**Screening blood tests:** Extensive screening comparable with previous studies.  
**Screening stool tests:** Extensive screening comparable with previous studies.  
| **Amount of stool per transplant / administered to patients:** 50g.  
**Diluent used to prepare:** 500mls normal saline.  
**Diluent used to store if frozen:** N/A – fresh.  
**Preparation methods:** Stomacher laboratory blender.  
**Time from preparation to transplant (fresh):** 48 hours.  
**Time period for storage (frozen):** N/A.  
**Route administered:** Upper GI: nil; lower GI: 16; capsule: nil.  
**Number of infusions:** All had 1 infusion.  
**Bowel purgative:** None.  
**PPI:** None.  
**Antimotility:** None.  
**Prokinetics:** None.  
**Time before CDI treatment was stopped before FMT:** Day prior to FMT.  
| **Minor GI adverse events:** abdominal pain, tenderness and bloating, equal in both groups.  
**Minor non-GI adverse events:** Nil.  
**Serious adverse events:** x1 developed anasarca from liver disease, x1 had perforated bowel from diverticulitis at 35 days post-FMT.  
**Deaths:** None.  

| **Treatment arm:** 6 week vancomycin taper.  
**Overall cure rate:** 58.3% (n=7/12).  
**Cure with one infusion alone:** 43.8% (n=7/16).  
| **Treatment arm:** FMT:  
**Overall cure rate:** 43.8% (n=7/16).  
**Cure with one infusion alone:** 43.8% (n=7/16). |
<table>
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<tbody>
<tr>
<td>Amount of stool per transplant / administered to patients: 50g. Diluent used to prepare: Normal saline. Diluent used to store if frozen: Implied use of glycerol for frozen product but not clearly stated. Preparation methods: mix stool with normal saline (1:10), aerobic conditions, use Stomacher to homogenise. Time from preparation to transplant (fresh): Within 2 hours of preparation. Time period for storage (frozen): Not specified. Route administered: All colonoscopically. Number of infusions: 1 Bowel purgative: PEG on night before FMT. PPI: No. Antimotility: 4mg loperamide 3 hours before. Prokinetics: No. Time before CDI treatment was</td>
</tr>
<tr>
<td>Minor GI adverse events: no differences in the three groups. Mild transient abdominal pain and diarrhoea in 86% of patients. x6 experienced fatigue and x4 had a headache. x2 gained weight. Minor non-GI adverse events: None stated. Serious adverse events: None. Deaths: None.</td>
</tr>
</tbody>
</table>
stopped before FMT: Not specified.
Kao et al, JAMA, 2017

Companion: Oral FMT capsules.
Number of patients: 57.
Age (median/standard deviation): 58.7 (+/- 18.5) years.

Companion: Colonoscopic FMT.
Number of patients: 59.
Female: male: 36: 13.
Age (median/standard deviation): 57.4 (+/- 19.1) years.

CDI features: All recurrent.

CDI diagnosis: Recurrence of diarrhea (>3 unformed bowel movements every 24 hours) within 8 weeks of completing a prior course of treatment, with either a positive C difficile toxin by glutamate dehydrogenase and C difficile toxins A/B (C diff QuikChek Complete; Techlab) or by detection of glutamate dehydrogenase and C difficile cytotoxin B gene (Cepheid), plus resolution of diarrhea for the current episode.

Pre-FMT antibiotics: Oral vancomycin (125mg twice daily) up to 24hrs before FMT.

Total follow-up period: 12 weeks.

Donors were unrelated volunteers.

Working in healthcare: Not stated.

Donor demographics: Not stated.


Travel and antibiotic exclusion period: As per Kelly et al, Gastroenterology, 2015.

Screening blood tests: As per Kelly et al, Gastroenterology, 2015.

Screening stool tests: As per Kelly et al, Gastroenterology, 2015.

Amount of stool per transplant / administered to patients: 80-100g.

Diluent used to prepare: Normal saline.

Diluent used to store if frozen: 100% glycerol.

Preparation methods: Mix stool with 200ml of normal saline, and filtered using a Stomacher to homogenise 180ml of faecal slurry.

Time from preparation to transplant (fresh): up to 2 months frozen, collected fresh within 12 hours.

Time period for storage (frozen): up to 2 months.

Route administered: lower GI: 59 (colonoscopy); capsule: 57.

Number of infusions: x1 of colonoscopy, or x40 capsules as one-off.

Bowel purgative: PEG on the night before.

PPI: No.

Prokinetics: Not stated.

Treatment arm: Oral FMT capsules: 96.2% (n=51/53) absence of CDI at 12 weeks.

Cure with one treatment alone: 96.2% (n=51/53).

Treatment arm: FMT via colonoscopy: 96.2% (n=50/52).

Cure with one infusion alone: 96.2% (n=50/52).

Minor GI adverse events: Capsule group: x1 nausea, x2 vomiting, x1 abdominal pain.

Colonoscopy group: x1 nausea, x1 vomiting, x1 fever, x5 abdominal pain.

Minor non-GI adverse events: 1 developed confusion in the colonoscopy group between time of screening and delivery of FMT. This was not communicated to team, and despite an uneventful FMT she died three days later from heart failure.

Serious adverse events: None.

Deaths: x1 in each group from cardiopulmonary disease (see above for colonoscopy). The other patient developed Staphylococcus epidermidis bacteraemia 10 weeks after capsule
Time before CDI treatment was stopped before FMT: 24 hours. Treatment and died from sepsis.
<table>
<thead>
<tr>
<th>Kelly et al, <em>Annals of Internal Medicine, 2016</em></th>
</tr>
</thead>
</table>
| **Intervention:** Donor FMT.  
**Number of patients:** 22.  
**Female:** male: 18: 4.  
**Age (mean/ standard deviation):** 48 (+/-16) years.  
**Comparator:** Autologous FMT.  
**Number of patients:** 24.  
**Female:** male: 19: 5.  
**Age (mean/ standard deviation):** 55 (+/-14) years.  
**Comorbidities:** Similar median Charlson comorbidity scores between groups.  
**CDI features:** Recurrent.  
**CDI diagnosis confirmation:** ≥3 unformed stools over 24 hours for 2 consecutive days, and either a positive stool test result for *C difficile* or pseudomembranes on colonoscopy.  
**Pre-FMT antibiotics:** All patients had had prolonged prior courses of vancomycin.  
**Total follow up period:** 8 week outcome follow up, 6 month safety follow-up.  
**Cochrane Collaboration risk of bias assessment:** low risk of bias.  
| **Donors working in healthcare:** Not stated.  
**Donor demographics:** Not stated.  
**Donor screening:** Questionnaire - potential donors also completed a modified AABB full-length donor history questionnaire, and those with risk factors for infectious agents were excluded.  
**Travel and antibiotic exclusion period:** Excluded as donor if antibiotics within preceeding 90 days.  
**Screening bloods:** Testing for HIV-1 and HIV-2 was performed within 2 weeks before donation for FMT. Other serologic testing was performed within 1 month before FMT and included testing for hepatitis A, B, and C viruses; also, testing for *Treponema pallidum*.  
**Screening stool tests:** polymerase chain reaction (PCR) testing for detection of *C difficile* toxin; culture for enteric pathogens (*Escherichia coli*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Listeria monocytogenes*, *Vibrio parahaemolyticus*, and *V cholerae*); testing for fecal *Giardia* and *Cryptosporidium* antigens; acid-fast stain for detection of *Cyclospora* and *Cyclospora.*  
| **Amount of stool per transplant / administered to patients:** Mean stool dose of 64 g (standard deviation of 25 g; range, 20 to 100g).  
**Diluent used to prepare:** 100g of stool in 500mls of normal saline.  
**Diluent used to store if frozen:** N/A.  
**Preparation methods:** Not reported.  
**Time from preparation to transplant (fresh):** 6 hours.  
**Time period for storage (frozen):** N/A.  
**Route administered:** Upper GI: nil; lower GI: all patients in both groups (colonoscopy); capsule: nil.  
**Number of infusions:** 1 infusion only.  
**Bowel purgative:** polyethylene glycol (PEG).  
**PPI:** No.  
**Antimotility:** Not described.  
**Prokinetics:** No.  
**Time before CDI treatment was stopped before FMT:** continued |
| **Minor GI adverse events:** Low rates of abdominal pain, bloating, nausea, vomiting, diarrhea, flatulence, anorexia, and constipation; these did not differ significantly between groups.  
**Minor non-GI adverse events:** None described.  
**Serious adverse events:** None described.  
**Deaths:** None.  
<p>|</p>
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<tr>
<th></th>
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<th>Isospora; ova and parasite testing; and enzyme immunoassay for detection of Rotavirus.</th>
<th>therapy until 2 to 3 days before the procedure.</th>
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<td>93</td>
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<tr>
<td>Intervention: Frozen FMT. Number of patients: 108. Female: male: 72: 36. Age (mean/ standard deviation): Mean age 73.0 (+/-16.4) years.</td>
<td>Donors were unrelated volunteers. Donors working in healthcare: Not specifically described. Donor demographics: Not defined. Donor screening: questionnaire – comparable to blood donor screening questionnaire. Travel and antibiotic exclusion period: Excluded as donor if travel (within the last 6 months) to areas of the world where diarrheal illnesses are endemic or risk of traveler’s diarrhea is high; also excluded if antibiotics within the preceeding 3 months. Screening blood tests: HIV-1 and -2, hepatitis A IgM, HbsAg, anti-HBc (both IgG and IgM), and anti-HBs, hepatitis C antibody, RPR and FTA-ABS. Screening stool tests: <em>Clostridium difficile</em> toxin B by PCR; if unavailable, then evaluation for toxins A and B by EIA; routine bacterial culture for enteric pathogens; faecal <em>Giardia</em> antigen; faecal <em>Cryptosporidium</em> antigen; Acid-fast stain for <em>Cyclospora,</em> Amount of stool per transplant / administered to patients: 100g of stool. Diluent used to prepare: 300mls of water. Diluent used to store if frozen: no solvents used for storage. Preparation methods: 100g of stool homogenised and mixed in 300mls of water. Time from preparation to transplant (fresh): If fresh, administered within 24hrs. Time period for storage (frozen): If frozen, kept for 30 days at -20°C. Route administered: Upper GI enema FMT for all patients in both groups; capsule: nil. Number of infusions in frozen arm: 57 patients had 1 infusion; 24 patients had 2 infusions; rest had &gt;2 infusions; in fresh arm: 56 patients had 1 infusion; 22 patients had 2 infusion; rest had &gt;2 infusions. Bowel purgative: Not described. PPI: Nil.</td>
<td>Minor GI adverse events: Transient diarrhoea (70%), abdominal cramps (10%), nausea (5%) in 24 hours post-FMT; constipation (20%) and flatulence (25%) in follow-up period. No difference between the two groups. Minor non-GI adverse events: None described. Serious adverse events: x12 patients required hospitalization because of illnesses unrelated to FMT. Deaths: x6 deaths in frozen and x13 deaths in fresh arm (all unrelated to FMT).</td>
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<td>Comparator: Fresh FMT. Number of patients: 111. Female: Male: 74: 37. Age (mean/ standard deviation): Mean age 72.5 (+/-16.2) years. Comorbidities: Not described. CDI features: All recurrent disease. CDI diagnosis confirmation: Toxin and PCR. Pre-FMT antibiotics: All had had prior metronidazole, vancomycin, or both in combination. Almost all patients had had prior vancomycin taper. Total follow up period: 13 weeks. Cochrane Collaboration risk of bias assessment: low risk of bias.</td>
<td>Treatment arm: Frozen: Overall cure rate: 90.7% (n=98/109). Cure with one infusion alone: 52.8% (n=57/108). Treatment arm: Fresh: Overall cure rate: 85.6% (n=95/111). Cure with one infusion alone: 50.5% (n=56/111).</td>
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<td>Lee et al, JAMA, 2016</td>
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<td><strong>Isospora</strong> and, if antigen testing unavailable, <strong>Cryptosporidium</strong>; ova, cysts and parasites.</td>
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</table>

Antimotility: Not described.

Prokinetics: Not described.

Time before CDI treatment was stopped before FMT: Discontinued 24 - 48 hours prior to FMT. |   |   |   |
<table>
<thead>
<tr>
<th>van Nood et al, New England Journal of Medicine, 2013</th>
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<tbody>
<tr>
<td>Donors were healthy volunteers. Donors working in healthcare: No. Donor demographics: &lt;60 years of age. Donor screening: questionnaire: questionnaire addressed risk factors for potentially transmissible diseases.</td>
</tr>
<tr>
<td>Travel and antibiotic exclusion period: Excluded as donor if travel to tropical area within past 3 months, or antibiotic use within the past two months. Screening blood tests: Blood was screened for HIV; human T-cell lymphotropic virus types 1 and 2; hepatitis A,B, and C; cytomegalovirus; Epstein-Barr virus; Treponema pallidum; Strongyloides stercoralis; and Entamoeba histolytica. Screening stool tests: Donor feces were screened for parasites, including Blastocystis hominis and Dientamoeba fragilis; C</td>
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<tr>
<td>Amount of stool per transplant / administered to patients: A mean (+/-standard deviation) of 1411g of faeces was infused. Diluent used to prepare: Faeces were diluted with 500mls of sterile saline, 0.9%. Diluent used to store if frozen: N/A. Preparation methods: The solution was stirred, and the supernatant strained and poured in a sterile bottle. Time from preparation to transplant (fresh): Mean time from defecation to infusion was 3.1+/1.9 hours. Time period for storage (frozen): N/A. Route administered: Upper GI: 16 (via nasoduodenal tube); lower GI: nil; capsule: nil. Number of infusions: 16 patients had 1 infusion; 3 who did not respond in this group had 2nd infusion. Bowel purgative: 4 litres of macrogol solution (Klean-Prep) on the last day of antibiotic treatment. PPI: Not stated.</td>
</tr>
<tr>
<td>Minor GI adverse events: 94% immediate diarrhoea, 31% abdominal pain with cramping, 19% belching - resolved within 3 hours. During follow-up, 3 patients had constipation (19%). Minor non-GI adverse events: Nil. Serious adverse events: Nil described. Deaths: None.</td>
</tr>
</tbody>
</table>
per day). Total follow up period: After first infusion at 10 weeks; follow-up was extended to 10 weeks after the second infusion. Cochrane Collaboration risk of bias assessment: low risk of bias.

difficile, and enteropathogenic bacteria.

Antimotility: Not stated.
Prokinetics: Not stated.
Time before CDI treatment was stopped before FMT: 24 hours.
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<td>Age (mean/ standard deviation):</td>
<td>50.4 (+/- 28.8) years.</td>
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</table>

**Comorbidities:** Not defined.

**CDI diagnosis confirmation:** Toxin; initial GDH enzyme-linked immunosorbent assay, followed by PCR only if the GDH test is positive or indeterminate.

**CDI features:** Relapsing or recurring (having at least 3 episodes of mild-to-moderate CDI or at least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity.

**CDI diagnosis confirmation:** Toxin; initial GDH enzyme-linked immunosorbent assay, followed by PCR only if the GDH test is positive or indeterminate.

**Pre-FMT antibiotics:** Treatment failures of a 6- to 8-week taper with vancomycin (95% of patients) with or without an alternative antibiotic, including fidaxomicin (70% of participants).

**Total follow up period:** 8 weeks follow-up for primary response.

<table>
<thead>
<tr>
<th>Donors were healthy volunteer non-pregnant adults.</th>
<th>Donors working in healthcare: No.</th>
</tr>
</thead>
</table>

**Donor demographics:** 18-50 years of age, on no medications, with a normal body mass index.

**Donor screening:** questionnaire - initial screening using the American Association of Blood Banks donor questionnaire for exposure to infectious agents.

**Donor screening:** questionnaire - initial screening using the American Association of Blood Banks donor questionnaire for exposure to infectious agents.

**Screening blood tests:** Blood was screened for antibodies to hepatitis A, B, and C; HIV; and *Treponema pallidum* within 2 weeks of donations.

**Screening stool tests:** Donor faeces were screened for enteric bacterial pathogens including rotavirus, *Listeria monocytogenes*, *Vibrio cholerae*, *Clostridium difficile*, *Salmonella*, *Shigella*.

<table>
<thead>
<tr>
<th>Amount of stool per transplant / amount of fluid administered to patients: 90mls of thawed FMT (41g).</th>
<th>Diluent used to prepare: Normal saline.</th>
</tr>
</thead>
</table>

**Diluent used to store if frozen: 10% glycerol.**

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<tr>
<th>Preparation methods:</th>
<th>Homogenised using a commercial blender then passed through sieves.</th>
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</table>

**Time from preparation to transplant (fresh): N/A.**

**Time period for storage (frozen):** Inocula were stored frozen for up to 156 days, range, 29-156 days.

<table>
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<tr>
<th>Route administered: Upper GI (nasogastric) 10; lower GI (colonoscopy): 10; capsule: nil.</th>
<th>Number of infusions: Colonoscopy: 8 patients - 1 infusion, 2 patients – 2 infusions; NG: 7 patients - 1 infusion; 3 patients – 2 infusions.</th>
</tr>
</thead>
</table>

**Number of infusions:** Colonoscopy: 8 patients – 1 infusion, 2 patients – 2 infusions; NG: 7 patients - 1 infusion; 3 patients – 2 infusions.

**Bowel purgative:** For colonic route - 4 liters of PEG solution.

**PPI:** 20mg of omeprazole orally for 48 hours prior to FMT.

**Antimotility:** single dose of oral

**Overall**: Colonoscopy: Overall cure rate: 100% (n=10/10). Cure with one infusion alone: 80% (n=8/10).

**Minor GI adverse events:** Mild abdominal discomfort and bloating in x4 patients (20%). X1 child treated colonoscopically had a transient fever of 38.8°C on day 2 that resolved spontaneously.

**Minor non-GI adverse events:** Nil described.

**Serious adverse events:** x1 new diagnosis of malignancy, x1 hospitalisation for Fournier gangrene (unrelated to FMT).

**Deaths:** x2 deaths (unrelated to FMT).
Cochrane Collaboration risk of bias assessment: uncertain risk of bias.

*cholerae, Escherichia coli O157, ova and parasites* (including general microscopy, acid-fast staining, and/or antigen testing for *Giardia, Cryptosporidium, Isospora, and Microsporidia*, *C difficile*, and *Helicobacter pylori* antigen).

Iloperamide prior to procedure.

Prokinetics: Nil.

Time before CDI treatment was stopped before FMT: Patients were required to discontinue all antibiotics at least 48 hours prior to the procedure.
C.3. Reviewed randomised studies of FMT for non-CDI indications
<table>
<thead>
<tr>
<th>Paper</th>
<th>Study and patient characteristics</th>
<th>Donor characteristics</th>
<th>FMT characteristics</th>
<th>Outcomes</th>
<th>Adverse events</th>
</tr>
</thead>
</table>
| Moayyedi et al, Gastroenterology, 2015 | Intervention: FMT. Number of patients: 38. Female: male 20: 18. Age (mean +/-range)*: 42.2 +/- 15.0 years. Comparator: Water enema. Number of patients: 37. Female: male: 11: 26. Age (mean +/-range)*: 35.8 +/- 12.1 years. Primary outcome: Remission at week 7, defined as full Mayo score < 3 and complete healing of mucosa at flexible sigmoidoscopy (endoscopic Mayo score: 0). Secondary outcome: Clinical response (at least 3 point reduction in Mayo score), change in Mayo, IBD Questionnaire scores, EQ-5D scores. | Donors were unrelated volunteers - six donors used. Plus - one patient in active treatment arm had spouse as donor (treatment failure). Working in healthcare: Not specifically stated. Donor demographics: 18-60 years. Donor screening: Questionnaire – yes. Travel and antibiotic exclusion period: Retesting of stool whenever donor travelled outside North America. Excluded as donor if antibiotics within past 3 months. Screening repeated regardless every 6 months. Screening blood tests: HIV, hepatitis A IgM, HBsAg, hepatitis C antibody, syphilis, HTLV-1/-2. Screening stool tests: MC&S, ova, cysts and parasites, C difficile toxin, VRE, MRSA. | Amount of stool per transplant / administered to patients: 8.3g of stool per enema Diluent used to prepare: 50g of stool mixed with 300ml of commercial bottled drinking water, then 50ml of mixture administered as enema. Diluent used to store if frozen: No glycerol. FMT administered either fresh, or stored at -20 degrees. 21 received frozen, 15 received fresh, 1 mixture of fresh and frozen. Preparation methods: Not anaerobic. Single donor per FMT. Time from preparation to transplant (fresh): Processing within 5hr of collection. Time period for storage (frozen): Not stated. Route administered and frequency: Upper GI: nil; lower GI: enema - weekly for 6 weeks. Aimed to retain for at least 20 mins (38); capsule: nil. Bowel purgative: No PEG. PPI: Not described. Antimotility: Not described. | Remission rates: 24% (n=9/38). Clinical response rates: 40% (n=15/38) had reduction in full Mayo score of at least 3 points. Quality of Life Assessment: Yes - IBDQ and EQ-5D not significantly different between groups. | FMT arm: Minor GI adverse events: Two patients developed patchy inflammation in the colon and also rectal abscess formation - resolved with antibiotics. Minor non-GI adverse events: None. Serious adverse events: x2 patients had diagnosis changed to Crohn's colitis, one was C difficile toxin positive at end of therapy. Deaths: None. Water enema arm: Remission rates: 5% (n=2/37) (p=0.03) Clinical response rates: 24% (n=9/37) had reduction in full Mayo score of at least 3 points (p=0.16). | Water enema arm: Minor GI adverse events: x1 patient developed patchy inflammation in the colon and also rectal abscess formation - resolved with antibiotics. Minor non-GI adverse events: None. Serious adverse events: x1 patient changed diagnosis from UC to Crohn's colitis; x1...
<table>
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<tr>
<th>Concomitant medications: Stable dose thiopurines, mesalamine, corticosteroids, and anti-TNF allowed as long as stable dose for at least 12 weeks (4 weeks for steroids).</th>
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<tbody>
<tr>
<td>Total follow-up period: Up to 12 months.</td>
</tr>
<tr>
<td>Cochrane Collaboration risk of bias assessment: low risk of bias.</td>
</tr>
<tr>
<td>Prokinetics: Not described.</td>
</tr>
<tr>
<td>admitted with hospital with active severe colitis and required colectomy.</td>
</tr>
<tr>
<td>Deaths: None.</td>
</tr>
</tbody>
</table>
| **Rossen et al, Gastroenterology, 2015** | **Intervention:** Donor faeces.  
Number of patients: 23.  
Female: male: 12: 11.  
Age (median, (range)): 40 (33-56) years.  
Comparator: Autologous faeces.  
Number of patients: 25.  
Female: male: 14:11.  
Age (median, (range)): 41 (30 – 48) years.  
**Primary outcome:** Clinical remission (defined as a SCCAI score ≤2) in combination with 1-point improvement on the combined Mayo endoscopic score of the sigmoid and rectum, as compared with baseline sigmoidoscopy, 12 weeks after the first treatment.  
**Secondary outcome:** Endpoints at 6 and 12 weeks were clinical response (defined as a reduction of 1.5 points on the Simple Clinical Colitis Activity Index (SCCAI)), a validated disease activity index tool in ulcerative colitis, clinical remission (defined as a SCCAI of ≤2), endoscopic response, change in median (Inflammatory Bowel Disease Questionnaire [IBDQ]) score from baseline to shortly after treatment (week 6), and adverse events.  
**Inclusion criteria:** enteric infection, use of biologics within 8 weeks or donors were healthy partners, relatives, or volunteers.  
**Working in healthcare:** Not stated  
**Donor demographics:** >18 yrs  
**Donor screening:** Questionnaire - Dutch Red Cross Questionnaire addressing risk factors for potential transmissible diseases used for screening of blood donors in The Netherlands.  
**Travel and antibiotic exclusion period:** Excluded as donor if antibiotics within 8 weeks.  
**Screening blood tests:** CMV (IgG + IgM), EBV (IgG + IgM), hepatitis A (total antibody), hepatitis B (HBsAg), hepatitis C (hepatic C virus antibody), HIV (1+2 antibodies/antigen), HTLV (I + II antibodies), Entamoeba (antibodies against *Entamoeba histolytica*).  
**Strongyloides (Strongyloides ELISA).**  
**Screening stools:** Multiplex PCR containing probes against enteral viruses (*rotavirus, norovirus, enterovirus parechovirus, sapovirus, adenovirus 40/41/52, astrovirus), FT + TFT II: PCR op *Giardia, SSYC, Clostridium* toxin  
**Amount of stool per transplant / administered to patients:** 120g  
**Diluent used to prepare:** Normal saline  
**Diluent used to store if frozen:** not stated  
**Preparation methods:** Not anaerobic  
**Time from preparation to transplant (fresh):** not stated  
**Time period for storage (frozen):** not stated  
**Route administered and frequency:** Upper GI: Nasoduodenal route. 2 infusions three weeks apart. Nil lower GI or capsule  
**Bowel purgative:** Macrogol before both infusions  
**PPI:** Not described  
**Antimotility:** Not described  
**Prokinetics:** Not described  
**Deaths:** Nil.  
**Minor GI adverse events:** 78.3% (n=18/23) of donor stool and 64% (n=16/25) of autologous stool experienced side effects post FMT: transient borborygmus, diarrhoea, vomiting, fever.  
**Minor non-GI adverse events:** None.  
**Serious adverse events:** 4 overall (small bowel perforation – secondary to Crohn’s), CMV infection, abdominal pain, cervical carcinoma.  
|
methotrexate within 4 weeks

Concomitant medications: stable doses of thiopurines, mesalamine, or corticosteroids 10 mg/day for the 8 weeks before inclusion.

Total follow-up period: 12 weeks.

Cochrane Collaboration risk of bias assessment: low risk of bias.
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<tr>
<td>21</td>
<td>Intervention: FMT. Number of patients: 41. Female: male 19: 22. Age (median, (range)): 35.6 (27.8-48.9) years. Comparator: Placebo-isotonic saline with added colourant odourant and glycerol cryoprotectant (concentration 10%). Number of patients: 40. Female: male 15: 25. Age (median, (range)): 35.4 (27.7-45.6) years. Primary outcome: Composite of steroid-free clinical remission and endoscopic remission or response at week 8, defined as a total Mayo score of 2 or less, with all Mayo subscores of 1 or less, and at least a 1 point reduction from baseline in the endoscopy subscore. Secondary outcome: Secondary outcomes were: steroid-free clinical remission (defined as combined Mayo subscores of 1 or less for rectal bleeding plus stool frequency); steroid-free clinical response (defined as either a decrease of 3 points or more on the Mayo score, a 50% or greater reduction from baseline in combined rectal bleeding plus stool frequency Mayo subscores, or both); steroid-free endoscopic remission. Donors were between 3-7 unrelated donors. Working in healthcare: No. Donor demographics: Not described. Donor screening: Questionnaire asked regarding: · Known HIV, hepatitis B or hepatitis C infection · Known exposure to HIV or viral hepatitis within the previous 12 months · High risk sexual behavior (e.g. sexual contact with anyone with HIV/AIDS or viral hepatitis, men who have sex with men, sex for drugs or money) · Use of illicit drugs · Tattoo or body piercing within the preceding 6 months · Incarceration or history of incarceration · Known current communicable disease (e.g. upper respiratory tract infection) · Risk factors for variant Creutzfeldt-Jakob disease · Travel within last 2 weeks to areas of the world where diarrhoal illnesses are endemic or risk of traveler’s diarrhea is high · History of or current inflammatory bowel disease (IBD) · History of or current irritable bowel disease (IBD) Amount of stool per transplant / administered to patients: 37.5g of blended stool to isotonic saline; volume of each infusion was 150ml. Diluent used to prepare: isotonic saline with 10% glycerol cryoprotectant. Diluent used to store if frozen: -80°C with glycerol cryoprotectant (concentration 10%). Preparation methods: Donors had to provide faeces within 4 hours of a bowel movement, which was inspected visually for suitability (formed stool, no blood or mucous). Donor stool homogenised for a given batch on each day in a biosafety cabinet in isotonic saline then filtered. Placebo infusions comprised isotonic saline; brown food colourant, odourant, and glycerol cryoprotectant (concentration 10%) was added to all study infusions (investigational and placebo). The volume of each infusion was 150 mL. Infusions were stored at −80°C until dispensation to patients at fortnightly study visits for home freezer storage at −20°C before daily administration. Donor FMT arm: Remission rates: 275 (n=11/41). Clinical response rates: 54% (n=22/41). Quality of Life Assessment: Not described. Placebo arm: Remission rates: 8% (n=3/40) (p=0.021). Clinical response rates: 23% (n=9/40) (p=0.04). Quality of Life Assessment: Not described. Donor FMT arm: Minor GI adverse events: abdominal pain x12 (29%), colitis x10 (24%), flatulultance x10 (24%), bloating x8 (20%), nausea x2 (5%), elevated ALT x2 (5%), vomiting x2 (5%), enterocolitis x1 (2%), diarrhea x1 (2%), reflux x1 (2%), haemorrhoids x1 (2%), elective surgical procedure x1 (2%). Minor non-GI adverse events: None. Serious adverse events: x2 (5%) - x1 clinical deterioration and colectomy, x1 needed intravenous intravenous steroids. Deaths: Nil. Placebo arm: Minor GI adverse events: abdominal pain x11 (28%), colitis x9 (23%), flatulence x8 (20%), bloating x11 (28%), nausea x5 (13%), vomiting x1 (3%), enterocolitis x3 (8%), anal fissure x1 (3%), faecal incontinence x1</td>
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response (defined as a Mayo endoscopy subscore of 1 or less, with a reduction of at least 1 point from baseline); steroid-free endoscopic remission (defined as a Mayo endoscopy subscore of 0); quality of life (assessed with the IBDQ); and safety (assessed by adverse events).

Inclusion criteria: 1. 18-75 years; 2. UC for >3 months; 3. UC of any extent except isolated proctitis <5cm; 4. currently active mild-moderate UC as measured by a Mayo score of 4-10, endoscopy score must be greater or equal to 1 and a physician global assessment score of less than or equal to 2; 5. Written consent.

Concomitant medications: Drugs permitted as long as the dose was stable preceding enrolment: oral 5-aminosalicylates (stable dose for 4 weeks); thiopurines and methotrexate (on medication for ≥90 days and dose stable for 4 weeks); and oral prednisolone (dose ≤20mg daily and stable for 2 weeks). During the study, patients remained on the same dose of 5-aminosalicylate, thiopurine, and methotrexate. For oral prednisolone, patients received a mandatory taper of up to 2-5 mg per week so that patients would be steroid-free by week 8.

Route administered and frequency:
Upper GI: 0; lower GI: 5 enemas per week following colonoscopic delivery -5 days on, two days off for 8 weeks (40 enemas per patient); capsule: 0.

Bowel purgative: Yes, but no details
PPI: Not described
Antimotility: Not described
Prokinetics: Not described

(3%), elevated ALT x2 (5%).
Minor non-GI adverse events: None.
Serious adverse events: x1 (3%) - admitted to hospital (no details why).
Deaths: Nil.
Cochrane Collaboration risk of bias assessment: low risk of bias.

Travel and antibiotic exclusion period: Excluded if travel within last 2 weeks to areas where diarrheal illnesses are endemic or risk of travelers diarrhea is high.

Screening blood tests: Complete blood count, electrolytes, urea and creatinine, LFTS, ESR, CRP, HIV-1 and -2, hepatitis A IgM, hepatitis B SaG, hepatitis B core antibody (IgM and IgG) and surface antibody, hepatitis c antibody, rapid plasma reagin and/or fluorescent treponemal antibody-absorbed, HTLV-1 and HTLV-2.

Screening stools: C difficile PCR, faecal MC&S with routine bacterial culture for enteric pathogens, Giardia antigen, Cryptosporidium antigen, faecal ova/cysts/parasites including Blastocystis hominis and Dientamoeba fragilis, and Norovirus.
<table>
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<th>Intervention: Donor FMT. Number of patients: 38. Female: male: Not stated. Age (mean/median): Not stated. Comparator: Control - autologous FMT in saline. Number of patients: 35. Female: male: Not stated. Age (mean/median): Not stated. Primary outcome: Steroid-free remission of UC, as defined by total Mayo of 2 or less with an endoscopic Mayo score of 1 or less at week 8. Secondary outcome: Clinical response (at least 3 point reduction in Mayo score), clinical remission (i.e. SCCAI of 2 or less), and safety. Inclusion criteria: UC - Mayo 3-10 with endoscopic subscore at least 2. Concomitant medications: Stable dose of immunomodulator, 5-ASA, biological, tapering prednisolone. Cochrane Collaboration risk of bias assessment: uncertain risk of bias.</th>
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<td>Donors were healthy volunteers. Working in healthcare: Not clear. Donor demographics: Not described. Donor screening: Questionnaire – yes but no details described. Screening blood tests: Yes but not described. Screening stool tests: Yes but not described.</td>
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<td>Amount of stool per transplant / administered to patients: 50g of stool for first FMT, 25g of stool in subsequent enemas. Diluent used to prepare: 65% saline. Diluent used to store if frozen: Yes - frozen with 10% glycerol. Preparation methods: Anaerobic prep, donor stool pooled from 3-4 donors. Time from preparation to transplant (fresh): N/A. Time period for storage (frozen): Not stated. Route administered and frequency: Upper GI: nil; lower GI: FMT via colonoscopy on day 0, followed by 2 enemas on day 7 (38); capsule: nil Bowel purgative: PEG before colonoscopy but not enema PPI: Not described Antimotility: Not described Prokinetics: Not described</td>
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<td>Donor FMT arm: Remission rates: 9% (n=3/35) in steroid-free remission at week 8. Clinical response rates: 20% (n=7/35) (p&lt;0.01). Quality of Life Assessment: Not described. Control - autologous FMT in saline arm. Minor GI adverse events: Nil. Minor non-GI adverse events: None. Serious adverse events: Worsening colitis in x2 placebo patients. x1 patient requiring colectomy, x1 pneumonia. Deaths: Nil.</td>
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</table>
**Intervention:** Donor FMT.  
Number of patients: 55.  
Female: male: 36: 19.  
Age (median, range): 44 (33-54) years.  

**Comparator:** Control - autologous FMT.  
Number of patients: 28.  
Female: male: 5: 9.  
Age (median, range): 45 (34-57) years.  

**Inclusion criteria:** 18-75 yrs of age, IBS with diarrhoea or mixed IBS according to Rome III criteria.  
Exclusion criteria: participants with severe cardiac disease, pulmonary disease, or kidney failure, non-IBS type abdominal pain, immunodeficiency or on immunomodulating agents.  

**Cochrane Collaboration risk of bias assessment:** low risk of bias  

**Primary outcome:** Symptom relief of more than 75 points assessed by IBS-SSS at 3 months after FMT.  

**Inclusion criteria:** 18-75 yrs of age, IBS with diarrhoea or mixed IBS according to Rome III criteria.  
Exclusion criteria: participants with severe cardiac disease, pulmonary disease, or kidney failure, non-IBS type abdominal pain, immunodeficiency or on immunomodulating agents.  

**Cochrane Collaboration risk of bias assessment:** low risk of bias  

**Donors were two volunteers screened at start and at 7 months post donation.**  

**Working in healthcare:** Not stated.  

**Donor demographics:** Not described.  

**Donor screening:** Questionnaire - new tattoos or piercings in the past 3 months; high-risk sexual behaviour; former imprisonment; or history of any of the following conditions: chronic diarrhoea, constipation, inflammatory bowel disease, IBS, colorectal polyps or cancer, immunosuppression, obesity, metabolic syndrome, atopic skin disease, or chronic fatigue.  

**Travel and antibiotic exclusion period:** Excluded if antibiotics within past three months.  

**Screening blood tests:** Glycated haemoglobin; and serology for HIV, *Treponema pallidum*, and hepatitis A, B, and C.  

**Screening stool tests:** *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, *Yersinia* spp, and toxin-producing *C difficile*; faecal tests for *Helicobacter pylori* antigen,  

**Amount of stool per transplant / administered to patients:** 50 to 80g of stool in 50mls.  

**Diluent used to prepare:** 200ml isotonic saline and 50mls of 85% glycerol.  

**Diluent used to store if frozen:** glycerol, only for autologous transplants.  

**Preparation methods:** Aerobic, stool from both donors was mixed together.  

**Time from preparation to transplant (fresh):** 7 hours.  

**Time period for storage (frozen):** 2-4 weeks.  

**Route administered and frequency:** upper GI: none; lower GI: single infusion of FMT via colonoscopy; nil capsule.  

**Bowel purgative:** Picoprep.  

**PPI:** Not described.  

**Antimotility:** Loperamide 8mg 2 hours before.  

**Prokinetics:** Not described.  

**Donor FMT arm:**  
Remission rates: 66% (n=36/55).  
Quality of Life Assessment: Not described.  

**Autologous FMT arm:**  
Remission rates: 43% (n=12/28) (p=0.49).  
Quality of Life Assessment: Not described.  

**Minor GI adverse events:**  
Self limiting intermittent abdominal pain x1, self limiting nausea and vertigo x1.  

**Minor non-GI adverse events:** Nil.  

**Serious adverse events:** Nil.  

**Deaths:** Nil.  

**Placebo arm:**  
Minor GI adverse events: Nil.  

**Minor non-GI adverse events:** Nil.  

**Serious adverse events:** Nil.  

**Deaths:** Nil.
viruses (norovirus, rotavirus, Sapovirus, adenovirus), and faecal calprotectin.
Intervention: Donor FMT. Number of patients: 10. Female: male: 0:10. Age (mean+/standard deviation): 64.5 +/- 5.1 years. Aetiology (HCV / alcohol / HCV+alcohol / NAFLD / others): 2/4/2/2/0.


Primary outcome: Proportion of participants with FMT-related serious adverse events (SAEs) at day 150, a composite endpoint of death, hospitalisations, emergency room visits or transmissible infections, as defined by the FDA.

Secondary outcomes: Changes in cognitive function at day 20, cirrhosis severity (MELD score, albumin), changes in liver function and white blood cell (WBC) count, development of all adverse events (AEs), and changes in microbiota composition and function in the FMT arm compared to standard of care arm.

Screening stool tests: 
- Clostridium difficile
- Toxin B and PCR
- Cyclospora
- and Isospora
- Examination, ova, cysts
- and parasites with Giardia Antigen
- EIA, Salmonella/ Shigella/ Campylobacter Culture, Shiga Toxin
- E. coli
- Culture and Vibrio Culture,
- Cryptosporidium
- Antigen
- HELICOBACTER PYPOLI
- Antigen
- EIA,
- Amount of stool per transplant / administered to patients: 37.5g of stool.
- Diluent used to prepare: 90mls glycerol saline buffer in total.
- Diluent used to store if frozen: glycerol.
- Preparation methods: Aerobic.
- Time from preparation to transplant (fresh): N/A - frozen.
- Time period for storage (frozen): not stated.
- Route administered and frequency: Upper GI: non; lower GI: Single infusion of FMT via enema.
- Bowel purgative: Picoprep.
- PPI: Not described.
- Antimotility: Loperamide 8mg 2 hrs before.
- Prokinetics: None.
- Others: Lactulose and rifaximin were continued for all patients throughout the trial. A 5-day broad-spectrum coverage regimen was used (metronidazole 500 mg orally three times daily, ciprofloxacin 500 mg orally twice-daily, and amoxicillin.

FMT arm:
- Patients with SAEs at day 150: 20% (n=2/10) (p=0.02).
- Total SAEs at day 150: 20% (n=2/10) (p=0.01).
- Patients with altered mental status by day 150: 0% (n=0/10) (p=0.03).
- Total HE episodes at day 150: 0% (n=0/10) (p=0.03).
- Stroop OffTime+OnTime change (day 0 and day 20): positive indicates improvement: 29.1 +/- 27.9 (p=0.04) (N.B. Stroop OffTime+OnTime is a validated tool for objectively assessing for hepatic encephalopathy using a smartphone app).
- PHES score change (day 0 and day 20); negative indicates improvement - 3.1 +/- 2.1 (p=0.01).
- MELD score change (day 0 and day 35): 0.1 +/- 2.0 (p=0.78).

Deaths: Nil.

Standard of care arm:
- Serious adverse events: x1 hospitalisation for acute kidney injury, and 1 was due to chest pain (all within 5 months post FMT).
- Standard of care arm:
- Patients with SAEs at day 150: 80% (n=8/10).

Deaths: Nil.
| Inclusion criteria: >/18 yrs outpatients with cirrhosis and recurrent hepatic encephalopathy (HE) defined as at least two documented overt HE episodes requiring therapy.

Exclusion criteria: MELD score >17, on oral or intravenous antimicrobial agents besides nonabsorbable rifaximin, allergies to pretreatment antibiotics, immunosuppressive medications, positive C. difficile test, pregnancy, active infection, those with active alcohol abuse, and unable to provide informed consent.

Cochrane Collaboration risk of bias assessment: low risk of bias. | Stool Norovirus EIA, Stool Rotavirus Antigen Detection, Adenovirus Antigen Detection, Gastroenteritis EIA, Vancomycin-resistant Enterococcus Culture, *Microsporidia* Exam. | 500 mg orally three times daily). All antibiotics were discontinued at least 12 hours before FMT. This regime was not used in patients randomised to standard of care arm. | Total SAEs at day 150: 11. Patients with altered mental status day 150: 50% (*n* =5/10).

Total HE eps day 150: 6 Stroop OffTime+OnTime change (day 0 and day 20): -43.5 +/- 95.7.

PHES score change (day 0 and day 20): 0.0 +/- 3.1.

MELD score change (day 0 and day 35): 0.2 +/- 2.7.

N.B. no significant difference in serum albumin, AST, ALT, WBC or haemoglobin counts between the two groups. |
Intervention: Donor FMT (one for six days in a row).
Number of patients: 30.
Female: male 19: 11.
Age (mean+/-SD): 53.1 +/- 10.2 years.
Comparator: Standard of care (education, behavioural strategies, oral laxaives; expressively told to avoid antibiotics). Macrogol permitted if no bowel movement for three days, and enema permitted if even this failed.
Number of patients: 30.
Female: male 21: 9.
Age (mean+/-SD): 55.4 +/- 12.1 years.
Primary outcome: At least three complete spontaneous bowel movements (CSBMs) per week during the 12 week follow-up.
Secondary outcomes: 1) Proportion of patients with average increase of at least 1 CSBM per week; 2) Number of CSBMs per week; 3) Colonic transit time (assessed via abdominal x-ray/ radiopaque markers); 4) subjective stool consistency; 5) Wexner constipation scale.
Inclusion criteria: ≥18 yrs outpatients with cirrhosis and recurrent hepatic encephalopathy (HE) defined as at least two

One universal donor used throughout (24 year old healthy university student).
Working in healthcare: No.
Donor demographics: As above.
Donor screening: Similar to FDA blood screening.
Screening blood tests: Full blood count, chemistry and iron profile, hepatitis A, B and C, HIV-1 and-2, CMV, EBV, HSV, VZV, and Treponema pallidium.
Screening stool tests: Yersinia spp, Salmonella spp, Shigella spp, Campylobacter jejuni, C difficile toxin, helminths, ova, parasites, and Helicobacter pylori.

Amount of stool per transplant / administered to patients: 100g of stool.
Diluent used to prepare: Either 500mls normal saline, or normal saline amended with glycerol to final concentration of 10%.
Diluent used to store if frozen: Glycerol.
Preparation methods: Not stated.
Time from preparation to transplant (fresh): 2 hours.
Time period for storage (frozen): 1-4 weeks.
Route administered and frequency: Upper GI: all via nasojejunal tube (originally placed endoscopically); lower GI: nil.
Bowel purgative: Not described.
PPI: Not described.
Antimotility: Not described.
Prokinetics: None.

Meeting primary outcome: 37% (n=11/30) (p=0.04).
Meeting second outcomes: At least one more CSBM per week: 53% (n=16/30) (p=0.009).
Number of CSBMs per week: 3.2+/-1.4.
Stool consistency score: 3.9+/-1.3.
Colonic transit time (hours): 58.5+/-9.8.
Wexner constipation score: 8.6+/-1.5.
Quality of Life Assessment: Not described.

Meeting primary outcome: 13% (n=4/30)
Meeting second outcomes: At least one more CSBM per week: 20% (n=6/30).
Number of CSBMs per week: 2.1+/-1.2.
Stool consistency score: 2.4+/-1.1.

FMT arm: 50 in total (1 x sedation contraindications, x22 endoscopy-related respiratory difficulty, x12 nausea, x5 abdominal pain, x4 diarrhoea, x4 flatulence, x2 transient fever).
Placebo arm: x4 in total (x0 sedation contraindications, x0 endoscopy-related respiratory difficulty, x0 nausea, x3 abdominal pain, x0 diarrhoea, x1 flatulence, x0 transient fever).
documented overt HE episodes requiring therapy.

Exclusion criteria: At least 18 years, BMI of 18-25 kg/m², and slow transit constipation defined as colonic transit time of >48hr, and symptoms unresponsive to dietary modification, enemas or biofeedback in the previous six months.

Cochrane Collaboration risk of bias assessment: low risk of bias.

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</table>
Intervention: Donor FMT

Number of patients: 9.
Female: male 0: 9.
Age (mean +/- SD): 47 +/- 4 years.

Comparator: Autologous FMT.
Number of patients: 9.
Female: male 0: 9.
Age (mean +/- SD): 53 +/- 3 years.

Primary outcome: Effect of lean donor gut microbiota infusion on insulin sensitivity after 6 weeks.

Secondary outcomes: Change in specific small- and large-gut microbiota as well as produced fecal short chain fatty acids.

Inclusion criteria: Male Caucasian obese subjects with characteristics of the metabolic syndrome, specifically with a body mass index > 30 kg/m^2, or waist circumference > 102 cm, and a fasting plasma glucose level > 5.6 mmol/L.

Exclusion criteria: History of cholecystectomy were excluded, as well as subjects who used any medication, probiotics, and/or antibiotics in the past 3 months.

Cochrane Collaboration risk of bias assessment: low risk of bias.

Donor FMT arm:
Median rate of glucose disappearance, Rd: from 26.2 to 45.3 μmol/kg/min; p<0.05).

Autologous FMT arm:
Median rate of glucose disappearance, Rd: from 18.9 to 19.5 μmol/kg/min).

Quality of Life Assessment:
Not described.

Secondary outcomes: No change in the total numbers of fecal bacteria (allogenic, from 10.8 +/- 0.2 to 11.0 +/- 0.4 vs autologous, from 11.6 +/- 0.6 to 11.3 +/- 0.4 log_{10} bacteria/g faeces, non significant [NS]). Fecal short-chain fatty acids decreased after allogenic gut microbiota infusion (median acetate from 49.5 to 37.6; p < 0.05; butyrate, from 14.1 to 8.9; p < 0.05; and propionate, from 18.2 to 16.3 mmol/kg feces; NS).

No adverse events.
| Kootte et al, *Cell Metabolism*, 2017 | Intervention: Donor FMT  
Number of patients: 26.  
Female: male 0: 26.  
Age (mean): 54 years.  
Comparator: Autologous FMT.  
Number of patients: 12.  
Female: male 0: 12.  
Age (mean): 54 years.  
Primary outcome: Change in intestinal microbiota composition upon FMT in relation to insulin sensitivity.  
Secondary outcomes: Post-prandial lipid, glucose excursions and plasma metabolites  
Inclusion criteria: All adult (age 21-69 years) Caucasian males, who had obesity (body mass index (BMI) > 30 kg/m²), fulfilled the National Cholesterol Education Program (NCEP)-criteria for metabolic syndrome, were treatment-naive and who where otherwise healthy.  
Exclusion criteria: History of recent weight loss, cardiovascular event, cholecystectomy and the use of any medication known to influence gut microbial composition in the last three months (including proton pump inhibitors, antibiotics and pre-/pro-/synbiotics) or treatments targeting metabolic diseases. | Lean healthy Caucasian males (body mass index < 25 kg/m²).  
Working in healthcare: Not stated.  
Donor demographics: As above.  
Donor screening: Questionnaires regarding diet and bowel habits, travel history, comorbidity including (family history of) diabetes mellitus, and lack of medication use.  
Screening blood tests: Human immunodeficiency virus; human T-lymphotropic virus; hepatitis A, B, and C; cytomegalovirus; Epstein–Barr virus; *Strongyloides*; lues and amoebiasis  
Screening stool tests: Pathogenic parasites (e.g., *Blastocystis hominis*, *Dientamoeba fragilis*, *Giardia lamblia*), bacteria (*Shigella*, *Campylobacter*, *Yersinia*, *Salmonella*, enteropathogenic *E. coli* and *Clostridium difficile*) or viruses (norovirus, rotavirus, astrovirus, adenovirus (40/41/52), entero-, parecho- and sapovirus).  
Amount of stool per transplant / administered to patients: Not stated.  
Diluent used to prepare: 500mls of normal saline.  
Diluent used to store if frozen: N/A.  
Preparation methods: Faeces was covered with sterile saline (500 ml 0.9% NaCl) to reduce exposure to oxygen, transferred to a blender, and mixed for 10 minutes. The homogenized solution then was filtered twice through a clean metal sieve.  
Time from preparation to transplant (fresh): Same day.  
Time period for storage (frozen): N/A.  
Route administered and frequency: Upper GI: Single infusion all via nasoduodenal tube (originally placed endoscopically). A subgroup of patients receiving donor FMT had a second infusion; lower GI: nil.  
Bowel purgative: PEG solution.  
PPI: Not described.  
Antimotility: Not described.  
Prokinetics: None.  
DONOR FMT ARM: **Improved peripheral insulin sensitivity at week 6** (from 25.8 to 28.8 μmol/kg/min, , p < 0.05. This change was no longer significant at week 18 (including those that had a second infusion).  
AUTOLOGOUS FMT ARM: **FMT had no effect at week 6** (from 22.5 to 20.8 μmol/kg/min, NS)  
Quality of Life Assessment: Not described.  
Secondary outcomes: No significant changes in fecal butyrate levels (butyrate from 13 to 20 mmol/g faeces, p = 0.096). Fecal acetate levels, however, were significantly increased from 62 to 85 mmol/g feces (p < 0.05) after allogenic FMT, whereas fecal propionate was borderline significantly altered (from 23 to 28 mmol/g faeces, p = 0.062).  
No adverse events |
Cochrane Collaboration risk of bias assessment: low risk of bias.
Appendix D.  Excluded clinical studies

D.1.  *Clostridium difficile* infection:

D.1.1.  Studies excluded at Sift 2 by working group:

<table>
<thead>
<tr>
<th>Paper</th>
<th>Grounds for exclusion</th>
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<tbody>
<tr>
<td>Mah XI, Paramsothy R, Lo-Cao E, et al. Faecal</td>
<td>Case series of FMT for CDI, but</td>
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<tr>
<td>Reference</td>
<td>Summary</td>
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<tr>
<td>Tvede M, Tinggaard M, Helms M. Rectal</td>
<td>Case series of ‘FMT’ for CDI, but abstract only.</td>
</tr>
</tbody>
</table>
Abstracts not fulfilling selection criteria:


Haran M, Tsang T, Kupfer Y, Tessler S. Intravenous immunoglobulins in severe Clostridium difficile colitis. Chest 2011; [Supplement]:270A


Roediger R, Grinspan A. Safety and efficacy of fecal microbiota transplantation for Clostridium difficile in a cohort of patients with a severe infection and/or IBD. Am J Gastroenterol 2016;111 [Suppl 1]:S446.


Wilcox GM. Early experience with a Fecal Bacteriotherapy (FB) program for recurrent and C-difficile infection (CDI). Gastroenterology 2011;140 [Suppl]:S361.

Zhou E, Kumar V, Mansoor MS, Feuerstadt P. Pseudomembranes are infrequently seen in patients undergoing fecal microbiota transplant (FMT) for recurrent C. difficile infection (CDI). Am J Gastroenterol 2016;111 [Suppl]:S68.


D.1.3. Case series not fulfilling selection criteria


Atkins KA, Kao D. Potential cost savings associated with timely fecal microbiota transplantation (FMT) for recurrent Clostridium difficile infection (RCDI). Gastroenterology 2014;146 [Suppl 1]:S252.


D.1.4. Case reports


Bartosz C, Marino D, DeCross A. A highly illustrative case report detailing the profound subjective and objective response of severe pseudomembranous colitis (from Clostridium difficile) to fecal transplant. Am J Gastroenterol 2016;111 [Suppl 1]:S620.


Didesch MM, Averill A, Oh-Park M. Peripheral neuropathy after fecal microbiota transplantation for
Clostridium difficile infection: a case report. PM R 2016;8:813–6.


Kakkar E, Othman M. Fecal transplant in recurrent Clostridium difficile enteritis. J Gen Intern Med 2017;32


Lingala S. Fecal microbiota transplantation in critically ill patient with severe Clostridium difficile colitis. Gastroenterology 2014;144 [Suppl 146]:S251.


Neelakanta A, Moudgal V, Upadhyay N, Valenstein P, Gunaratnam NT. Title: Successful treatment of refractory Clostridium difficile infection (CDI) with intestinal microbiota transplant (IMT) in two patients with inflammatory bowel disease (IBD) and its effects on IBD. Gastroenterology 2012;142 [Suppl]:S395.


Stein D, Rizvi S, Modiri AN, Fang T, Naik AS. Two case reports of toxic megacolon from Clostridium difficile infection successfully treated with fecal microbiota therapy. Gastroenterology 2015;148 [Suppl 1]:S645.


D.1.5. Non-English language:


French Seksik P. Clostridium difficile-associated colitis. Hepato-Gastro Oncol Dig 2016;23:775–84.


German Hibbeler B. Clostridium difficile: Fecal bacteriotherapy as an option. Dtsch Arztebl Int 2016;113:A185.


German Schmitz F. Fecal transplantation is highly effective in the treatment of recurrent Clostridium difficile infection. Gastroenterologe 2013;8:54–5.


German Stallmach A. Clostridium difficile infection : What is currently available for treatment?. Internist 2016;57:1182–90.

German Stallmach A. Clostridium difficile infection: What is currently available for treatment?. Internist 2016;57:1182–90.

German Storr M, Starostzik C. Stool transplantation: also an option for irritable bowel syndrome?. MMW Fortschr Med 2014;156:16.

German Storr M. Donor stool now available in capsules. MMW Fortschr Med 2015;157 Suppl 1:32.


D.1.6. Basic sciences:


Kumar V, Zhou E, Mansoor MS, Feuerstadt P. Treatment of initial recurrence of C. Difficile infection (CDI) with vancomycin may not prevent eventual need for fecal microbial transplantation (FMT). Am J Gastroenterol 2016;111 [Suppl ];S93.


Schenck LP, Hirota SA, Armstrong GD, MacDonald JA, Beck PL. Elucidating intestinal microbiota components that play a protective or deleterious role during clostridium difficile infections. Gastroenterology 2013;144 [Suppl 1]:S185.


1.7. Narrative reviews


Anonymous. Probiotics are beneficial in Clostridium difficile infection: Healthy microbiota by probiotics or fecal transplantation prevent diarrhea. Pharm Weekbl Wet Platf 2014;149:10.


Anonymous. Treat Clostridium difficile infection based on its severity and number of previous episodes. Drugs Ther Perspect 2012;28:10–3.


Antonopoulos DA, Chang EB. Transplanting a microbial organ: The good, the bad, and the unknown. MBio 2016;7:e00572-16.


Health Quality, Ontario Fecal Microbiota Therapy for Clostridium difficile Infection: A Health Technology Assessment.


Jones JD, Murphy DW. Rescue fecal microbiota transplantation in refractory severe and complicated clostridium difficile infection using frozen stool specimens. Gastroenterology 2015;148 [Suppl 1]:S641.


Korman TM. Diagnosis and Management of Clostridium difficile Infection. Semin Respir Crit Care Med 2015;36:31–43.


Marra F, Ng K. Controversies around epidemiology, diagnosis and treatment of Clostridium difficile infection. Drugs 2015;75:1095–118.


Rabe SM. Treatment of recurrent Clostridium difficile infection with fecal transplantation. Gastroenterol Nurs 2014;37:156–63,64.


Rogers GB, Bruce KD. Challenges and opportunities for faecal microbiota transplantation therapy. Epidemiol Infect 2013;141:2235–42.


Russell GH. Too early to determine whether fecal microbiota transplant has therapeutic promise for ulcerative colitis? J Pediatr Gastroenterol Nutr 2015;60:3.


Singh B, Qin N, Reid G. Microbiome regulation of autoimmune, gut and liver associated diseases. Inflamm Allergy - Drug Targets 2015;14:84–93.


Tariq R, Khanna S. Clostridium difficile infection: Updates in management. Indian J Gastroenterol 2016;36:3-10.


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D.1.8. Commentary/ editorials/ opinion:


Heuer AH. Fecal transplantation with side effect: Bearer of hope for Clostridium difficile patients is still insufficiently researched. Dtsch Apotheker Zeitung 2016;156:46.


Mayor S. Donor faecal transplantation is highly curative in recurrent C difficile infection, trial finds. BMJ 2016;354:i4638.


McKinney M. Despite “eww” factor... fecal transplants gain ground against C. diff. Mod Healthc 2013;43:12–3.

McKinney M. FDA slaps regs on fecal transplants. Increased steps for C. diff treatment draw mixed reactions from providers. Mod Healthc 2013;43:10.


D.1.9. Letters


Mawer DP, Wilcox MH. Clarifying the management of Clostridium difficile infection. BMJ 2015;351:h6130.


Youngster I, Hohmann EL. Fecal microbiota transplantation for Clostridium difficile infection--reply. JAMA 2015;313:726.

D.1.10. Not relevant, miscellaneous


Blosser R. Probiotic infusion during colonoscopy is an effective therapeutic alternative for refractory or recurrent C. Difficile colitis. Am J Gastroenterol 2013;108 [Suppl 1]:S181.


Bruminhent J, Cawcutt KA, Thongprayoon C, Petterson TM, Kremers WK, Razonable RR. Epidemiology, risk factors, and outcome of Clostridium difficile infection in heart and heart-lung transplant recipients. Clinical Transplantation 2017;31:e12968.


Claassen E. Healthy microbiota by probiotics or fecal transplantation prevent diarrhea: Probiotics are beneficial in case of Clostridium difficile infection. Pharm Weekbl 2014;149:16–7.


Crabtree S, Gupta J. Knowledge and attitudes towards faecal bacteriotherapy on ITU. Intensive Care Med 2014;40 [Suppl]:S106.


Donnelly SC. Elements: In this month’s issue. QJM 2015;108:351.

Dore J, Multon MC, Behier JM, participants of Giens Xxii RTN. The human gut microbiome as source of


Kashani A, Shih DQ. Fecal microbiota transplantation is highly effective for treatment of Clostridium difficile infection in patients with inflammatory bowel disease; a meta-analysis. Gastroenterology. 2017;152 [Suppl 1]:S988.


with improvement of ulcerative colitis after antibiotic combination therapy using fecal metagenomic analysis. United European Gastroenterology Journal 2017;5 [Suppl 1]:A264-A5.


Khanna S, Hecht GA, Dubberke ER, Orenstein R, Lee C, Gerding DN. Alterations in microbial diversity are associated with treatment success with RBX2660, a microbiota-based drug for the prevention of recurrent Clostridium difficile infection: Results from punch CD 2, a randomized doubleblind placebo-controlled trial. Gastroenterology 2017;152 [Suppl 1]:S46-S7.


Muenyi V, Kerman DH. Changes in the body mass index (BMI) of patients treated with fecal microbiota transplant (FMT) for recurrent C. difficile infection. Gastroenterology 2017;152 [Suppl 1]:S820-S1.


Niccum BA, Stein DJ, Behm BW, Hays RA. Zinc deficiency predicts fecal microbiota transplant failure in recurrent Clostridium difficile infection. Gastroenterology 2017;152 [Suppl 1]:S347.


Park HK, Millan B, Hotte N, Kao DH, Madsen K. Altered phage diversity and increased growth rate of escherichia coli are associated with fecal transplantation failure in patients with Clostridium difficile

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Ray A, Jones CR, Shannon B, Carter S. Donors are universal in the fight against Clostridium difficile: Results from two trials investigating the safety and efficacy of RBX2660, a microbiota-based drug. Gastroenterology 2017;152 [Suppl 1]:S950.


Seril DN, Shen B. Clostridium difficile infection in the postcolectomy patient. Inflamm Bowel Dis United States; 2014;20:2450–69.


Smith JD, Roach B, Silva M, Louie T, Xu H, Kao DH. Donor body mass index (BMI) does not impact recipient BMI following fecal microbiota transplantation for recurrent Clostridium difficile infection. Gastroenterology 2017;152 [Suppl 1]:S1007.


Staley C, Kelly CR, Brandt LJ, Khoruts A, Sadowsky MJ. Complete microbiota engraftment is not essential for recovery from recurrent Clostridium difficile infection following fecal microbiota transplantation. MBio 2016;7:e01965-16.

Staley C, Khoruts A, Sadowsky MJ. Contemporary Applications of Fecal Microbiota Transplantation to Treat...

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Tariq R, Khanna S. Clostridium difficile infection: Updates in management. Indian J Gastroenterol 2017;36:3-10.


Taylor KN, McHale MT, Saenz CC, Plax SC. Diagnosis and treatment of Clostridium difficile (C. diff) colitis: Review of the literature and a perspective in gynecologic oncology. Gynecol Oncol 2017;144:428-37


Wilson M, Ritz N, Singh S, Lin HC. Successful fecal microbiota transplant depends on the gut microbial community of the recipient to be already perturbed. Gastroenterology 2017;152 [Suppl 1]:S1039.


D.2. Non-CDI indications:

D.2.1. Abstracts not fulfilling selection criteria:


D.2.2. Case series not fulfilling selection criteria:


D.2.3. Narrative reviews:


D.2.4. Miscellaneous, not relevant:


Davis SC, Yadav JS, Barrow SD, Robertson BK. Gut microbiome diversity influenced more by the Westernized dietary regime than the body mass index as assessed using effect size statistic. Microbiology Open 2017;6:e00476.


Goyal A, Chu A, Calabro K, Firek B, Bush B, Morowitz M. Safety and efficacy of fecal microbiota transplant...


Gregory CR, Gourley IM, Cain GR, Patz JD, Imondi KA, Martin JA. Mizoribine serum levels associated with enterotoxicity in the dog. Transplantation 1991;51:877-81.


Hadengue A, Spahr L. From bench to bedside: Is the road trickier in alcoholic liver disease? Alcoholism: Clinical and Experimental Research 2010;34:53A.


Kallarackal GU, Ansari EA, Amos N, Martin JC, Lane C, Camilleri JP. A comparative study to assess the clinical use of Fluorescein Meniscus Time (FMT) with Tear Break up Time (TBUT) and Schirmer's tests (ST) in the diagnosis of dry eyes. Eye 2002;16:594-600.


Kao SS, Wu DC, Tsay FWT, Tsai KW, Hsu PI. A randomized controlled study comparing 14-day reverse hybrid and bismuth quadruple therapies for helicobacter pylori infection and impacts on clarithromycin resistance of gut microbiota. Gastroenterology 2017;152 [Suppl]:S183.


Ogholikhan S, Franciscovich A, Mogul D. Poop MD. A mobile application to screen for biliary atresia, accurately identifies Acholic Stools in the Field. Hepatology 2016;64 [Suppl 1]:152A.


Orr DW, Myint H, Murphy R. Probiotic supplementation after Very Low Calorie Diet does not aid improvement of the metabolic syndrome or maintenance of weight loss post Liver Transplant. A randomised double-blind placebo controlled trial. Hepatology 2016;64 [Suppl]:113A-4A.


Roth B, Birkhauser FD, Zehnder P, Burkhard FC, Thalmann GN, Studer UE. Readaptation of the peritoneum following extended pelvic lymphadenectomy and cystectomy has a significant beneficial impact on early postoperative recovery and complications: Results of a prospective randomized trial. Eur Urol 2011;59:204-10.


Rzepecki P, Barzal J, Oborska S. Blood and marrow transplantation and nutritional support. Supportive Care in Cancer 2010;18 [Suppl 2]:S57-S65.

Sabharwal S, Abraham JM, Grand R, Mascarenhas M. "Ins and outs" of constipation and DIOS. Pediatric Pulmonology 2016;51:147.


Shukla A. Those spots on his penis: It is bannayan riley ruvalcaba syndrome!! Pediatric Dermatology 2017;34:S141-S2.


Stockfleth E. Sonidegib tolerability across 30-months: Results from the phase 2 randomized BOLT trial. Journal of Investigative Dermatology 2017;137 [Suppl 2]:S285.

Stockfleth E. Sonidegib duration of response across 30 months: Results from the randomized phase 2 BOLT trial. Journal of Investigative Dermatology 2017;137 [Suppl 2]:S284.


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Appendix E. Peer review

Healthcare Infection Society

Consultation – The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

Closing date: 5pm on 18 January 2018

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Royal College of General Practitioners</th>
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<tbody>
<tr>
<td>Title (e.g. Dr, Mr, Ms, Prof)</td>
<td>Drs</td>
</tr>
<tr>
<td>Name</td>
<td>Clinical Adviser: Kevin Barrett</td>
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<tr>
<td></td>
<td>Medical Director: Matthew Hoghton</td>
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<td>Job title or role</td>
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<tr>
<td>Email address</td>
<td><a href="mailto:clinicaladvisers@rcgp.org.uk">clinicaladvisers@rcgp.org.uk</a></td>
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Please note: comments will only be accepted electronically on this proforma.

Please provide comments on the draft guideline on the form below, putting each new comment in a new row. When feeding back, please note the section you are commenting on (for example, section 1 Introduction and line number). If your comment relates to the guideline as a whole then please put ‘general’. Add extra rows if required.
<table>
<thead>
<tr>
<th>Section</th>
<th>Comments</th>
<th>Working group response</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>This is an important consultation of an important treatment for recurrent or refractory CDI. The recommendations are sensible and will help produce a universal service to patients across the UK.</td>
<td>Thank you for your comment.</td>
</tr>
<tr>
<td>B</td>
<td>Hudson et al doi: 10.1128/CMR.00049-16Clin. Microbiol. Rev. January 2017 vol. 30 no. 1 191-2311 January 2017 review suggests that faecal microbiota transplant in the United States is used not only in refractory or recurrent Clostridium Difficile (CDI) but also in initial CDI and Ulcerative colitis</td>
<td>We cannot find mention of FMT use as treatment for initial CDI in this review. Updated searches have identified a small RCT evaluating the use of FMT as treatment for first CDI (Camacho-Ortiz et al, 2017), and this is now evaluated by the working group within the guideline (Section 8.1.1.3). All published RCTs evaluating the use of the FMT as treatment for ulcerative colitis have been reviewed by the working group within the guideline (Section 8.6.2).</td>
</tr>
<tr>
<td>C</td>
<td>There is a lack of GP representation on the working group (5.6) and this is reflected in the consultation with a lack of a suggested referral pathway for community based patients.</td>
<td>We agree that the implications of this guideline for primary care were not well-described, and we have strengthened this within the guideline. In particular, we have more strongly highlighted the responsibility of microbiology staff in clinical laboratories to liaise proactively with primary care teams regarding the possibility of FMT when recurrent positive stool samples are received from the community on a particular patient (Section 8.7.1).</td>
</tr>
<tr>
<td>D</td>
<td>There has also been a reported case of the development of obesity following FMT from an overweight donor but this has not been substantiated in other studies. The BMI restriction on donors (8.3.2) may restrict donors.</td>
<td>The recruitment of suitable donors is relatively restrictive by necessity since FMT is an unlicensed and poorly-studied medicinal product. There is a growing literature base demonstrating an association between a high or low BMI and perturbation of the structure and/or function of the gut microbiota and subclinical chronic inflammation. The implications of this for the safety and efficacy of FMT are not well-defined. The suggested BMI range does not make it prohibitively difficult to find suitable donors. As such, the working group believes that their existing recommendation is reasonable.</td>
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<td>Working group response</td>
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<tr>
<td>E</td>
<td>It would be useful to have a standard UK pre and post questionnaire for patients to standardise recording (8.1.2.3)</td>
<td>We agree that the introduction of standardised questionnaires would have clear potential advantages for clinical care and/or research. We now discuss this further in Section 10, ‘further research’.</td>
</tr>
<tr>
<td>F</td>
<td>It may useful to consider measuring the microbiol strains of donors to monitor the impact of combinations of specific microbial strains to understand the undefined nature of faecal preparations</td>
<td>We agree of the importance of this, and this is now discussed in more detail in Section 10, ‘further research’.</td>
</tr>
<tr>
<td>G</td>
<td>The lack of universal definitions of cures (8.1.2.4) is likely to hamper future studies</td>
<td>We agree with this comment. Section 10, ‘further research’ has been amended accordingly. Furthermore, we expect that the attention generated by this guideline will highlight this inadequacy.</td>
</tr>
<tr>
<td>H</td>
<td>With the introduction of the clinical term SNOMECT across primary care in 2018 and secondary care in 2020 it is important to record faecal microbiota transplant so that long term sequelae can be measured and patients can be potentially contacted in the future.</td>
<td>We agree that there should be specific procedure codes for FMT (according to route of administration), so that this can be accurately recorded in the patient’s medical record. This would also lay the foundation for a future HRG code and tariff for the procedure which is not currently funded by CCGs. Members of the working group are in discussion with NHS England about this.</td>
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<table>
<thead>
<tr>
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<th>NHS Highland</th>
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<tbody>
<tr>
<td>Title (e.g. Dr, Mr, Ms, Prof)</td>
<td>Dr</td>
</tr>
<tr>
<td>Name</td>
<td>Alex Cochrane</td>
</tr>
<tr>
<td>Job title or role</td>
<td>Consultant Microbiology and Infectious Diseases</td>
</tr>
<tr>
<td>Address and post code</td>
<td>Raigmore Hospital, Perth Road, Inverness IV2 3UJ</td>
</tr>
<tr>
<td>Telephone number</td>
<td>01463 704000</td>
</tr>
<tr>
<td>Email address</td>
<td><a href="mailto:Alexandra.cochrane@nhs.net">Alexandra.cochrane@nhs.net</a></td>
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<tbody>
<tr>
<td>8.1.1.1</td>
<td>I don’t think you should limit FMT for first recurrence to those with specific risk factors. If clinicians wish to use FMT rather than fidaxomicin for the first recurrence on cost effectiveness grounds then that is reasonable. Suggest that you recommend FMT may be offered for the first or second or subsequent recurrences.</td>
<td>As FMT is currently an unlicensed medicinal product with poorly-studied long term sequelae, the working group considered that it should generally be reserved for patients who have had more than three episodes of infection. There are no studies directly comparing its effectiveness with some of the newer agents such as fidaxomicin or bezlotoxumab, hence this recommendation is made on the basis of safety. However, the working group felt that it may be reasonable in certain patient groups (with ongoing risk factors for</td>
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<td>Working group response</td>
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<tr>
<td>8.1.1.3 (ii)</td>
<td>I disagree that patients should have previously been treated with extended/pulsed vancomycin or fidaxomicin before being offered FMT. You don’t present any evidence to show that these antibiotic treatment is superior to FMT. Where FMT is the preferred treatment for the first recurrence it is quite likely that the patient will not have had a prolonged or tapered course, and this should not be a barrier to giving FMT which as you say is highly efficacious.</td>
<td>As above, there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT (Hota et al, 2017). The safety profile of these medications is well-established from large randomised controlled trials, whilst randomised studies involving FMT have tended to be smaller, and have more variable patient follow-up. As such, on the balance of safety, the working group agreed that antimicrobial/antitoxin therapy associated with reduced CDI recurrence should be considered prior to FMT. Reflecting the uncertainties in this area within the reviewed literature, the relevant recommendation is ‘conditional’ rather than ‘strong’.</td>
</tr>
<tr>
<td>8.1.1.3 (iii)</td>
<td>You don’t cite any evidence that fidaxomicin or bezlotoxumab have better cure rates than FMT. My practice has been not to use fidaxomicin in life threatening C. difficile due to lack of evidence of efficacy in this setting, though I may be out of date with this.</td>
<td>Pre-planned subgroup analysis of patients with severe CDI in a randomised trial demonstrated a significantly lower recurrence rate when treated with fidaxomicin (13.0%, n=12/92) than when treated with vancomycin (26.6%, n=29/209) (Louie et al, 2011); this finding was replicated in another randomised controlled trial, with 8.3% (n=4/48) and 32.6% (n=14/43) experiencing a recurrence respectively (Cornely et al, 2012). In a further randomised trial, bezlotoxumab (together with standard of care antibiotics) was shown to reduce recurrence of severe CDI compared to standard of care antibiotics alone (10.9% (n=6/55) vs 20% (n=13/65) respectively) (Wilcox et al, 2017). The working group noted that there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT (Hota et al, 2017). The working group agreed that in the absence of this</td>
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### Section 8.5.1.1 (iii)

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<tr>
<td>Is there adequate published material or experience to ensure the safety of loperamide? It is usually avoided in <em>C. difficile</em> disease due to increased risk of complications.</td>
<td>We agree that loperamide should not be used expressly for the treatment of CDI diarrhoea. However, a number of studies (references within the guideline) have used a single dose of loperamide after lower GI FMT to retention, and no potential safety issues associated with this use have been identified.</td>
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### Table

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<tr>
<td>Title (e.g. Dr, Mr, Ms, Prof)</td>
<td>Dr</td>
</tr>
<tr>
<td>Name</td>
<td>Ewan Olson</td>
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<tr>
<td>Section</td>
<td>Comments</td>
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<tr>
<td>8.3.4.</td>
<td>Laboratory Screening of donors</td>
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<td>“Whilst vancomycin-resistant Enterococci (VRE) carriage is relatively common in the community, they are of low pathogenicity, and screening for them was not felt to be justified.”</td>
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<td></td>
<td>VRE can cause life threatening infections that are difficult to treat. Any patient who is VRE positive requires isolation in a sideroom with ensuite facilities.</td>
</tr>
<tr>
<td></td>
<td>I would suggest that donors should be screened for VRE before accepting stool for donation. If there is a shortage of donor patients should be offered VRE positive donations only with informed consent.</td>
</tr>
</tbody>
</table>

**Working group response**

Whilst vancomycin-resistant Enterococci (VRE) carriage is relatively common in the community (probably related to food consumption) (Endtz et al, 1997), community strains of VRE are genetically distinct from (and generally of much lower pathogenicity than) those found nosocomially (Willems et al, 2005); as such, the working group felt that routine screening was not justified. However, the working group acknowledged that the potential infection risk from VRE (and MRSA) would vary regionally dependent upon local prevalence and pathogenicity, and as such recommended that a risk assessment was performed to assess whether screening for these organisms should be considered.
## Comments

<table>
<thead>
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<td></td>
<td>consent.</td>
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**Healthcare Infection Society**

**Consultation – The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.**

<table>
<thead>
<tr>
<th>Organisation</th>
<th>On behalf of European Study Group for <em>C. difficile</em> (ESGCD), and the National Donor Feces Bank at Leiden University Medical Center (dr. E. Terveer, drs. E. Boeije-Koppenol, prof. Hein Verspaget, dr. Y van Beurden, drs. R Ooijevaar, dr. Josbert Keller) and Department of Infectious Diseases, University of Koln (dr. Maria Vehreschild).</th>
</tr>
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<tbody>
<tr>
<td>Title (e.g. Dr, Mr, Ms, Prof)</td>
<td>Prof. Dr.</td>
</tr>
<tr>
<td>Name</td>
<td>Ed Kuijper</td>
</tr>
<tr>
<td>Job title or role</td>
<td>Head of Experimental Bacteriology</td>
</tr>
<tr>
<td>Address and post code</td>
<td>LUMC, Albinusdreef2, 2333 ZA, Leiden</td>
</tr>
<tr>
<td>Telephone number</td>
<td>31-71-5263574</td>
</tr>
<tr>
<td>Email address</td>
<td><a href="mailto:e.j.kuijper@lumc.nl">e.j.kuijper@lumc.nl</a></td>
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<tr>
<td>general</td>
<td>The literature was searched until April 2017, but please use the recently published document of E.M Terveer et al. entitled &quot;How to: Establish and run a stool bank&quot; and published in Clin Microbiol Infect. 2017 Dec;23(12):924-930. This document has considerable overlap with the proposed guideline, but also shows some important unresolved issues.</td>
<td>This reference has been added. Literature searches have been updated, to January 2018.</td>
</tr>
<tr>
<td>Lay summary, line 3</td>
<td>Capsules may also be prepared by use of non-freeze dried microbiota. Also, the possibility of using frozen products in general may be mentioned in this sentence.</td>
<td>We agree that these changes are important, and these amendments have been accordingly.</td>
</tr>
<tr>
<td>8.1.1.1</td>
<td>The authors are correct that CDI due to Type 07 responds less to FMT compared with CDI due to other PCR ribotypes. We register all infections by PCR ribotype to obtain more insights in successes and failures associated with strain characteristics and think that this is relevant for future recommendations, such as repeated FMT treatments for specific PCR ribotypes.</td>
<td>We presume that this refers to ribotype 027, and agree that this is important, and further reference has been made to this in Section 10, further research.</td>
</tr>
<tr>
<td>recommendation</td>
<td>&quot;FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including severe CDI (strong).” Please elucidate how this risk assessment can be performed.</td>
<td>The working party noted that these risk factors are well-described in previous studies, and do not require further elucidation within the manuscript.</td>
</tr>
<tr>
<td>8.1.1.2</td>
<td>Refractory CDI is also considered as an indication for FMT. Can the authors please provide a recommendation on the number of FMTs</td>
<td>In Section 8.2.1, the working group reviewed the literature on contraindications to receiving FMT, and noted that certain</td>
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<td>that should be used? Are patients on Intensive Care Units with refractory CDI also eligible? in 8.2.1 IC admission can be considered as a contraindication, but there are sufficient publications supporting to apply it for patients with severe CDI at ICU.</td>
<td>studies have made ‘admission to Intensive Care’ such a contraindication. However, the working group have not themselves at any point stated that this is a contraindication to receiving FMT. As stated in Section 8.1.1.2, there are a relatively small number of cases reported in the reviewed literature of refractory CDI. As such, the working group are unable to give recommendations that patients with refractory CDI receiving FMT should be managed in any particular way differently to those with recurrent CDI.</td>
</tr>
<tr>
<td>8.1.1.3</td>
<td>Antibiotic treatment of rCDI. Though the literature search was until April 2017, please mention the recent trials of tapered doses of vancomycin and fidaxomicin (PMID 29273269, PMID: 28591789; PMID 29255732).</td>
<td>We agree that these trials are all relevant, and have updated the guideline accordingly.</td>
</tr>
<tr>
<td></td>
<td>Recommendation II is less clear. How have the authors interpreted the literature that a tapered dosage of vancomycin before FMT increases the success rate of FMT? Are these studies also available for fidaxomicin?</td>
<td>There are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT (Hota et al, 2017). The safety profile of these medications is well-established from large randomised controlled trials, whilst randomised studies involving FMT have tended to be smaller, and have more variable patient follow-up. Furthermore, FMT remains (in the UK) an unlicensed medicine. As such, on the balance of safety, the working group agreed that antimicrobial/ antitoxin therapy associated with reduced CDI recurrence should be considered prior to FMT. Reflecting the uncertainties in this area within the reviewed literature, the relevant recommendation is ‘conditional’ rather than ‘strong’.</td>
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<tr>
<td></td>
<td>Recommendation iii is difficult to understand; do the authors recommend to treat severe and complicated CDI not with vancomycin, but with fidaxomicin or vanco+bezlo? If a recurrence</td>
<td>The wording of this recommendation has been amended, along with expansion of the explanatory text of Section 8.1.1.4.</td>
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<tr>
<td>24</td>
<td>occurs, then followed by a FMT?</td>
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<td>25</td>
<td>A recommendation for FMT treatment in severe (refractory), complicated CDI is missing (e.g. multiple sequential FMTs); should this also be accompanied with anti-CDI antibiotics? See review v. Beurden, Ther Advances in Gast, 2017 and Fischer, Ali Pharm Ther 2015</td>
<td>As stated in Section 8.1.2.2, there are a relatively small number of cases reported in the reviewed literature of refractory CDI. As such, the working group are unable to give recommendations that patients with refractory CDI receiving FMT should be managed in any particular way differently to those with recurrent CDI.</td>
</tr>
<tr>
<td>8.1.2.1</td>
<td>We suggest to differentiate between &quot;non-responding&quot; and &quot;late failure&quot;. The latter can be defined as a relapse of CDI after an initial response to FMT. For instance, use of antibiotics in the first month after FMT may provoke a new episode of CDI. This new episode doesn’t need a FMT and can be treated with conventional anti-CDI treatment, preferably microbiota sparing such as fidaxomicin.</td>
<td>We agree that this distinction is useful, and have amended the guideline accordingly.</td>
</tr>
<tr>
<td>8.1.2.2</td>
<td>Should a psychological questionnaire routinely be taken from recipients (before and after FMT) and from donors (regularly)? A ten-week follow-up is too short to recognize long term side-effects of FMT.</td>
<td>The working group did not consider that this was a priority.</td>
</tr>
<tr>
<td>8.1.2.3</td>
<td>We consider swallowing disorders a contraindication for upper GI delivery; death of a patient due to aspiration pneumonia with upper GI delivery has been described (PMID: 29026601); this patient had a swallowing disorder following oropharyngeal radiation after surgical removal of a maxillary carcinoma.</td>
<td>We note that this patient received a very large volume (500ml) of nasoduodenal FMT. This guideline recommends a much lower maximum volume with the specific aim of minimising this problem. Nevertheless, we agree that this is an important consideration, and have amended Section 8.1.2.3 and Section 8.5.2.2 accordingly.</td>
</tr>
<tr>
<td>8.2.1</td>
<td>What is the advice of the committee for coeliac patients with recurrent CDI?</td>
<td>The working group did not have any specific advice regarding patients with coeliac disease.</td>
</tr>
<tr>
<td>8.2.2</td>
<td>FMT in immunocompromised patients: we think that the presence of neutropenia (&lt;0.5 x 10^9/L) can be considered as a contraindication for FMT, especially if hematological patients are treated with selective gut decontamination to prevent translocation and infections with aerobe Gram-negatives. Second, should donors and immunocompromised recipients be matched for the EBV and CMV</td>
<td>The working group have recommended that FMT is offered ‘with caution’ to immunosuppressed patients, reflecting the careful individualised assessment required for each patient. We agree with the comment regarding matching donors and immunosuppressed recipients for EBV and CMV status, and</td>
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<tr>
<td>8.2.3</td>
<td>The effect of FMT on the IBD status for IBD patients with rCDI is under discussion. Is it possible that FMT will result in cure of CDI but an exacerbation of IBD. Should we differentiate UC from CD? Ref 71 suggests that IBD can worsen. The recommendation &quot;strong&quot; is debatable. Is the IBD group not a better candidate for vancomycin tapering, fidaxomicin (tapering) or bezlotoxumab before FMT is given?</td>
<td>We agree that there is evidence that FMT to treat CDI in patients with IBD may be associated with a flare of IBD activity (Qazi et al, 2017); we have updated the recommendation accordingly.</td>
</tr>
<tr>
<td>8.3.2</td>
<td>Age and BMI of the donor. We agree with the BMI of the donor but have some difficulties with the age, We consider an age above 50 as a contraindication, based on the risks to develop colon carcinoma and metabolic (diabetes) diseases. Additionally, older people seem to have a less stable gut microbiota.</td>
<td>We note from a recent paper that Bacteroides: Firmicutes ratio and microbial diversity were similar in donors &gt; 60 years compared to younger donors, and donations from older donors had similar efficacy and no higher rate of adverse outcomes (Anand et al, 2017). As such, the working group agreed to uphold their prior recommendation.</td>
</tr>
<tr>
<td>8.3.3</td>
<td>Donor screening history. Donors should also undergo a long term follow-up to recognize microbiota related diseases, including colon malignancies, autoimmune diseases, metabolic diseases and psychiatric illnesses.</td>
<td>We agree with the principle of this statement, and allude to this in Section 8.7.7.</td>
</tr>
<tr>
<td>8.3.4</td>
<td>Screening of the donor. Table 4. The Dutch guideline advises screening donors for multi-drug resistant bacteria (MDR), including VRE, MRSA, CPE and ESBL-producing Gram-negatives, and quinolone/aminoglycoside resistant Enterobacteriaceae. Most of the patients with rCDI have much comorbidity and are frequently hospitalized or encounter nosocomially acquired infections, such as UTI. Infections with MDR are more difficult to treat, mostly with intravenously administered antibiotics. If these patients become colonized with MDR they should be nursed with specific infection</td>
<td>The working group reviewed their recommendation regarding screening for multi-drug resistant bacteria, and Section 8.3.4 has been updated accordingly. We agree with the principle of a ‘window period’/quarantine prior to repeat donor screening in centres using frozen FMT; Section 8.3.5 has been updated accordingly, and a new flow chart to illustrate the process (Figure 1) added.</td>
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<tr>
<td>control precautions. We also apply a &quot;window period&quot;; donors stools samples are stored in quarantine for 2 months and only become available after a negative second screening.</td>
<td>The working group agreed that recommendations should be made to test for Shiga toxin-producing <em>Escherichia coli</em>, hepatitis E IgM, <em>Entamoeba histolytica</em> serology and <em>Strongyloides stercoralis</em> IgG (Table 3). However, the working group consensus was that screening with the other tests suggested is not justified.</td>
<td></td>
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<tr>
<td>We additionally screen for: <em>Yersinia enterocolitica</em>, <em>Yersinia pseudotuberculosis</em>, <em>Plesiomonas shigelloides</em>, shiga toxin producing <em>E. coli</em> (not only 0157 <em>E.coli</em>), Astrovirus, Sapovirus, Adenovirus, Enterovirus, Parechovirus, Hepatitis E, <em>Entamoeba histolytica</em>, <em>Microsporidium</em> species, <em>Blastocystis hominis</em>, <em>Dientamoeba fragilis</em>, and Strongyloides (if a travel history to Middle and South America, Africa, or Asia is present). We advise to include carriership of <em>E. histolytica</em> and Strongyloides to the mandatory screening, because of the serious infections that occur in immunocompromised patients. We have detected unexpectedly a donor carrying <em>E. histolytica</em> (Terveer, CMI, 2017).</td>
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</table>

8.4.1 Recommendation i. Please elucidate how donors should deliver their stools. We favour the use of specific device systems to prevent contamination with environmental microorganisms. Recommendation ii. Processing within 6 hours is proven effective, consider changing 'conditional' to 'strong' recommendation Recommendation iii. A meta-analysis concludes that less than 50 gram of feces is related to a 4-fold increase in recurrence rates. The recommendation status should be changed to 'strong'. |
| i. We think that the text as it stands gives sufficient information about best practice in this area. ii. We agree with this suggestion, and have amended Section 8.4.1 accordingly. iii. We agree with this suggestion, and have amended Section 8.4.1 accordingly. |

8.4.2 An important advantage of frozen FMT is the possibility to use a "window period" of, for example, two months. When donors are screened after this window period, the results determine if the stored FMTs can be used. |
| We have cross-referenced Section 8.4.2 to Section 8.3.5, where the concept of a window period/ quarantine is discussed in more detail. |

8.4.3 We think that there is not enough evidence to state that feces | A trend towards decrease in the viability of certain gut
Section | Comments | Working group response
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suspensions can only be used up to six months from preparation. There is no sufficient data that show a decreased efficacy with feces suspensions stored over 6 months. Additionally, multiple stool banks set the expiration date at 1 year after storage. | bacterial groups was noted when faecal aliquots were frozen in 10% glycerol for six months (Costello et al, *Alimentary Pharm & Ther*, 2015), and as such, the working group agreed that six months was the acceptable limit for freezing of an FMT in glycerol. This rationale is now within the text. | 

Good practice point: Thawing overnight in a 4C refrigerator is also a good and much used alternative. | None of the working group had sufficient experience with this means of thawing FMT, and as such were unable to make this good practice point. | 

8.5.1.1. | It is not clear, why the administration of a bowel lavage in upper GI administration, of PPI, of loperamide and of metoclopramide are recommended. There is no evidence to support their use, and all of them are drugs with known side effects. The only reason why they are used is that the first RCT used them. However, the RCT did not assess their importance, and there are many case series showing that FMT has a high success rate even without their use. | All of these interventions have a clear biological or practical rationale for their use. Significant side effects in association with a single dose of these medications are generally rare, and their use has not been associated with adverse outcomes in FMT studies. Our recommendations for their use are only conditional. As such, the working group uphold their recommendations. | 

8.5.2.1. | Not all capsules necessarily contain lyophilized microbiota, frozen preparations have also been shown to be effective. | We agree with this comment, and have updated the guideline accordingly. | 

8.5.2.2 | Are there studies indicating that 50 ml for upper gastrointestinal have comparable efficacy as 250 ml? If not, this should be more pronounced mentioned, also in the research session. We use at least 50 gram suspended in 200 ml and a slow infusion of 10cc/min. | As described in the text, the working group considered that mass of stool was a more important consideration than volume of diluent. They also noted that as low as 25ml of FMT has been demonstrated to be effective as upper GI FMT (Aas et al, *Clin Infect Dis*, 2003). However, the working group revised their decision, and now recommend 100ml as the threshold volume for upper GI FMT administration. | 

8.5.2.4. | The recommendation not to use capsules seems rather strong. It is unlikely that concerning transmission of infection, the risk would differ in any way from other ways of administration. Also, no safety concerns based on endoscopic complications can possibly arise. We would therefore not pronounce a recommendation against use. | We agree with this statement. Of note, whilst the Kao et al, 2017 study (RCT of capsulised vs colonoscopic FMT) was not published at the time of initial searches, it has been identified by updated searches and has now been reviewed by the working group. As such, the guideline has been updated accordingly. | 

8.6 | Consider to add that specific donor microbiota may have better | Reference to Donor B in this paper has been added to Section |
outcomes (e.g. donor B in Moayyedi, gastroenterology, 2015)
FMT for other conditions than rCDI. Why have the authors not
included the role of FMT to eradicate MDR from the intestinal tract?

8.6.2.
In keeping with NICE methodology, for the consideration of
FMT as treatment for non-CDI conditions, only RCTs could be
considered. The working group are aware of case studies and
case series using FMT to attempt gut decolonisation of
multidrug resistant microorganisms. Members of the working
party have themselves contributed to the literature in this
field. But no RCTs currently exist.

8.6.3.
Consider adding: characterisation of specific CU patient population
that would potentially benefit from FMT. “However,
recommendations for clinical use for this indication cannot be made
until there is clearer evidence of the most appropriate CU patient
characteristics, methodology for its preparation, route of delivery,
and intensity of administration of FMT”

We agree with this comment, and have updated the guideline
accordingly.

8.7.2 and 8.7.4
FMT is considered as a medicinal product under supervision of
MHRA and licensing should follow the GMP guidelines. The activities
should be performed in a dedicated containment level 2 laboratory
with personal protective equipment and a quality assessment
system. Does this indicate that FMTs should be prepared under
GMP conditions at the Pharmacy Department and not within the
Medical Microbiology? Or is this statement too strong?

No. MHRA guidance does not specify where the manufacture
should take place. This could be pharmacy, the microbiology
laboratory, or another place.

8.7.6
Please consider to add that aliquots of donor FMT materials (and
original feces samples) used for patients treatment should be
stored, enabling to use these samples when adverse effects after
FMT developed. This should also been included in 6.3 (auditing).

We agree, and we have updated Sections 6.3 and 8.7.6
accordingly.

Table 4
PCRs are more sensitive than conventional microscopy and antigen
tests for parasites. Second, can the authors please specify the
parasites? There is some debate on the significance of Blastocystes
spp. and Dientamoeba spp. Why is only E. coli 157 excluded and not

Table 4 has been updated to specify Shiga toxin-producing
Escherichia coli screening by PCR. The working group did not
consider that specific screening for Blastocystis spp or
Dientamoeba spp was justified.
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<td>24</td>
<td>other STEC pathogens?</td>
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<tr>
<td><strong>Propose to add: Eligibility of patients for FMT</strong></td>
<td>At the NDFB, all requests by the treating physician are evaluated by at least two clinical members of our feces bank board to determine the eligibility of the patient. It is required that patients have a laboratory documented episode of recurrent CDI following at least one course of adequate CDI antibiotic therapy. Recurrent CDI is defined as the re-appearance of diarrhoea (≥ 3 unformed stools per 24 hours for two consecutive days; or ≥ 8 unformed stools per 48 hours) within eight weeks after cessation of antibiotic therapy in combination with a positive diagnostic test for <em>C. difficile</em>. We strongly recommend a two-stage testing algorithm, as recently advised by the <em>C. difficile</em> working group/ESCMID (ESGCD). Using this algorithm, we reject approximately 20% of all requests for FMT. We would like to add our experience that of 79 candidate patients for FMT, only 75% were considered as suitable candidates for FMT treatment; most rejected requests were patients with underlying IBD who concomitantly carried <em>C. difficile</em>.</td>
<td>Thank you for this comment. Definitions of recurrent CDI are outside of the remit of this working group. Testing is discussed in Section 8.1.1., where we refer to current ESCMID guidance.</td>
</tr>
<tr>
<td><strong>Need for antimicrobial stewardship after FMT (also for 8.5.1.3)</strong></td>
<td>After FMT, we advise that an infectious disease specialist or medical microbiologists should be involved for antibiotic treatment (or prophylaxis) of the patient during the first month after FMT, since 50% of our registered failures were patients who received antibiotics within one month after FMT. Interestingly, all patients responded to conventional anti-CDI treatment and did not need a second FMT. It can be considered to use microbiota sparing fidaxomicin after FMT.</td>
<td>We agree with this comment, and have updated Section 8.5.1.3 accordingly.</td>
</tr>
</tbody>
</table>

**Closing date:** Please forward this electronically by 5pm on January 2018 at the very latest to consultations@his.org.uk

**Healthcare Infection Society**
Consultation – The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

Closing date: 5pm on January 2018

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<tr>
<th>Organisation</th>
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<tbody>
<tr>
<td>Title (e.g. Dr, Mr, Ms, Prof)</td>
<td>Dr</td>
</tr>
<tr>
<td>Name</td>
<td>Majdi Osman</td>
</tr>
<tr>
<td>Job title or role</td>
<td>Clinical Program Director, OpenBiome; Visiting Assistant Professor, Harvard Medical School</td>
</tr>
<tr>
<td>Address and post code</td>
<td>200 Inner Belt Road, Somerville, MA 02143</td>
</tr>
<tr>
<td>Telephone number</td>
<td>+1 (617) 575-2201</td>
</tr>
<tr>
<td>Email address</td>
<td><a href="mailto:majdi@openbiome.org">majdi@openbiome.org</a></td>
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Please note: comments will only be accepted electronically on this proforma.

Please provide comments on the draft guideline on the form below, putting each new comment in a new row. When feeding back, please note the section you are commenting on (for example, section 1 Introduction and line number). If your comment relates to the guideline as a whole then please put ‘general’. Add extra rows if required.

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<tr>
<td>8.1.1.1. Recurrent <em>Clostridium difficile</em> infection</td>
<td>“FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or those who have had one recurrence and have risk factors for further episodes, including</td>
<td>We agree with this statement, and have updated the guideline accordingly.</td>
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<tr>
<td><strong>8.1.1.2. Refractory Clostridium difficile infection:</strong></td>
<td>&quot;FMT should be considered in cases of refractory CDI (conditional).&quot;</td>
<td>Thank you for this comment.</td>
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<td><strong>8.1.1.3. Antimicrobial therapy prior to considering FMT for patients with CDI:</strong></td>
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<tr>
<td>i.</td>
<td>FMT for recurrent CDI should only be considered after failure of antimicrobial anti-C. difficile therapy which has been administered for a minimum of 10 days (conditional).</td>
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<tr>
<td>ii.</td>
<td>Recipients of FMT as treatment for recurrent CDI should have previously been treated with extended/pulsed vancomycin and/or fidaxomicin (conditional).</td>
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<td>iii.</td>
<td>For those with severe or complicated CDI, which appears to be associated with reduced cure rates, consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin and bezlotoxumab), before offering FMT (conditional).</td>
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We suggest rewording point iii, that recommends fidaxomicin or bezlotoxumab should be offered to patients with severe or complicated CDI before FMT. There is little evidence on the role of bezlotoxumab and fidaxomicin in severe or severe-complicated CDI. Although the evidence base is similarly lacking for FMT in severe or severe-complicated CDI.

Pre-planned subgroup analysis of patients with severe CDI in a randomised trial demonstrated a significantly lower recurrence rate when treated with fidaxomicin (13.0%, n=12/92) than when treated with vancomycin (26.6%, n=29/209) (Louie *et al*, 2011); this finding was replicated in another randomised controlled trial, with 8.3% (n=4/48) and 32.6% (n=14/43) experiencing a recurrence respectively (Cornely *et al*, 2012). In a further randomised trial, bezlotoxumab (together with standard of care antibiotics) was shown to reduce recurrence of severe CDI compared to standard of care antibiotics alone (10.9% (n=6/55) vs 20% (n=13/65) respectively) (Wilcox *et al*, 2017).

The working group noted that there are no studies comparing FMT to fidaxomicin or bezlotoxumab, and only one study comparing a vancomycin taper to FMT (Hota *et al*, 2017). The working group agreed that in the absence of this evidence, on the balance of safety and potential risks,
severe-complicated disease, there is a growing body of evidence from trials, multiple case series and reports indicating the potential for FMT in this population.

**Bezlotuxumab:** The performance of bezlotuxumab has not been evaluated in a severe or severe-complicated population. Results from MODIFY I and II suggest a modest 10% improvement in rates of sustained cure with bezlotuxumab. Importantly, only 15.6% were severe CDI. Based on the modest gains in efficacy and the few severe/severe-complicated patients in the MODIFY trials, we feel that further evidence is required before proposing bezlotuxumab be offered ahead of FMT in this patient population.

In comparison, across similar patient populations FMT has demonstrated in several randomized controlled trials reduced risk of recurrence. Based on the available evidence we therefore feel that the statement that bezlotuximab is “associated with reduced risk of recurrence” compared to FMT is not supported by the evidence.

**Fidaxomicin:** Similarly, there is a dearth of evidence on the role of fidaxomicin in the severe CDI population. We agree that it has demonstrated superior efficacy compared to vancomycin in the general CDI population. In an RCT comparing extended-pulsed fidaxomicin versus vancomycin for CDI, Guery et al (2017) observed increased recurrence in severe CDI compared to non-severe CDI with an odds ratio 0.57 (95% CI 0.36–0.91) p=0.019. We therefore recommend that fidaxomixin should be offered to patients with severe CDI. However, there is no evidence to suggest that the performance of fidaxomicin would be better than FMT. We acknowledge that access to fidaxomicin is likely to be more timely consideration should be given to using antimicrobial/antitoxin therapy associated with reduced CDI recurrence prior to considering the use of FMT.
The role of FMT in severe CDI: In their recent review, Van Beurden et al (2017) reviewed the literature on FMT in severe CDI and found 23 reports (12 case reports; 11 case series) about FMT as treatment for severe or complicated CDI. The patients described (n=200) all had severe or complicated CDI, did not respond to conventional CDI antibiotic treatment and received FMT as last resort treatment. In all studies, patients were treated with (sequential) FMT, whether or not followed by additional antibiotic treatment for CDI. FMT, with or without additional antibiotic CDI treatment, appears to be a promising curative treatment option in patients with severe and complicated CDI who do not respond sufficiently to conventional antibiotic treatment. FMT has been proposed by Fischer et al (2015) as an option utilizing an endoscopic response-guided approach, which may be particularly useful in non-surgical candidates. In an open-label cohort study (n = 17), FMT was delivered by colonoscopy. If pseudomembranes were identified, patients reinitiated oral vancomycin 24 hour after FMT and continued for 5 days. A repeat FMT by colonoscopy was given on day 7. If pseudomembranes persisted, vancomycin was restarted the following day for a 5 days course and a third FMT was offered on day 13. If pseudomembranes were absent during any colonoscopy, no further therapy was initiated. The results were promising with a combined clinical cure rate of 88%.

In conclusion, we agree that there is a lack of evidence available to make a strong recommendation on the role of FMT in severe CDI. However, there is insufficient evidence to suggest that fidaxomicin or bezlotoximab would be superior to FMT in this population. On the contrary, the growing pool of experience in using FMT in severe
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<td>and severe-complicated CDI patients demonstrates that it appears to be generally safe and effective (quality of evidence: 3).</td>
<td>We would therefore suggest re-wording point iii to:</td>
<td></td>
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<td><strong>iii. For those with severe or complicated CDI, which appears to be associated with reduced cure rates, consideration should be given to offering patients treatment with medications which are associated with reduced risk of recurrence (e.g. fidaxomicin or bezlotoxumab), or offering FMT (conditional).</strong></td>
<td>Fischer M, Sipe BW, Rogers NA, et al. Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated Clostridium difficile infection: description of a protocol with high success rate. Aliment Pharmacol Ther. 2015;42(4):470-476. doi:10.1111/apt.13290.</td>
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<tr>
<td>8.1.2.2. General approach to follow-up post-FMT:</td>
<td>All FMT recipients should routinely receive follow-up. Given the relative novelty of FMT and the potential for unexpected sequelae, clinicians should follow-up FMT recipients for long enough to fully establish efficacy/adverse events, and at least ten weeks in total (strong).</td>
<td>Thank you for this comment. In light of other comments from the working group and stakeholders, this follow-up period has been adjusted to ‘at least eight weeks in total’.</td>
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<td>We agree.</td>
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<td><strong>8.1.2.3. Management of the FMT recipient:</strong></td>
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<tr>
<td>i. Immediate management after endoscopic administration of FMT should be as per endoscopy unit protocol (strong).</td>
<td>Thank you for this comment.</td>
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<td>ii. Patients should be warned about short term adverse events, in particular the possibility of self-limiting GI symptoms. They should be advised that serious adverse events are rare (strong).</td>
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<td>iii. After enteral tube administration, patients may have the tube removed and oral water given from 30 minutes post-administration (strong).</td>
<td>We agree.</td>
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<td>We agree.</td>
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<td><strong>8.1.2.4. Definition of cure post-FMT for CDI:</strong></td>
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<td>A decision regarding cure/remission from CDI should be recorded during follow-up. However, this has no uniformly-agreed definition, and should be decided on a case-by-case basis (strong).</td>
<td>Thank you for this comment.</td>
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<tr>
<td>We agree.</td>
<td></td>
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<tr>
<td><strong>8.1.2.5. Definition of treatment failure post-FMT for CDI:</strong></td>
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<td>Treatment failure/recurrence should be defined on a case-by-case basis. Routine testing for C. difficile toxin after FMT is not recommended, but is appropriate to consider in the case of persistent CDI symptoms/suspected relapse (strong). When testing is to be performed, we would recommend clinicians follow the 2016 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for CDI testing, which state that no single commercial test can be used as a stand-alone test for diagnosing CDI, and recommend a 2-step approach (highly sensitive with reflex to highly specific test). These guidelines recommend performing an initial test with a high negative predicative value; therefore, if negative, no further testing needs to be done.</td>
<td>We agree on the use of ESCMID guidelines in CDI testing, and refer to these clearly in Section 8.1.1.1. However, Section 8.1.2.5 specifically refers to diagnosing failure post-FMT for CDI rather than initial diagnosis of CDI, and no good uniform definition exists for this. We think that the guidance given, to define treatment failure on a case-by-case basis, is the most fair summary of the current literature on this topic.</td>
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Specifically, they suggest glutamate dehydrogenase (GDH) EIA or NAAT/PCR testing. Our recommendation is GDH EIA as it is less expensive and has a slightly superior NPV at higher CDI prevalence compared with NAAT/PCR (98 vs 96 at hypothetical CDI prevalence of 50%), and an NPV of 100% at lower CDI prevalence. The second test should be a test with a high positive predictive value, such as EIA for toxin A/B. Obtaining CDI testing at each suspected CDI recurrence and working with institutional laboratories to use an appropriate testing algorithm is a key component to ensuring appropriate patient selection for FMT.

As currently worded, the recommendations risk encouraging over testing in a context where patients may develop post-infectious IBS. This concept is highlighted by evidence suggesting that up to 25% of patients referred to an FMT center for “C difficile infection” were found to have an alternative diagnosis, with younger patients being more likely to have a non-CDI diagnosis (Jackson 2016).


8.2.1. General approach to co-morbidities and FMT:

*FMT should be offered with caution in patients with decompensated chronic liver disease and should be avoided in those with anaphylactic food allergy (strong).*

The authors may want to consider the approach recommended by Allegretti et al (2017). In patients with a severe food allergy, a potential option for FMT could be from a patient identified donor living with the patient (e.g. spouse) who avoids the same allergens.

Allegretti JR, Kassam Z, Osman M, Budree S, Fischer M, Kelly CR. The working group thought it important to emphasise the ‘good practice point’ that in patients with true anaphylaxis, the risks of FMT administration were likely to outweigh the benefits. As such, this suggestion has not been incorporated.
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<td><strong>8.2.2.</strong> Immunosuppression and FMT:</td>
<td><em>FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects (strong).</em></td>
<td>Thank you for this comment.</td>
</tr>
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</table>
| **8.2.3.** Other comorbidities and FMT: | **Recommendation:**  
1. *FMT should be offered to those with recurrent CDI and inflammatory bowel disease (strong).*  
2. *FMT should be considered for appropriate patients with recurrent CDI regardless of other comorbidities (conditional).* | Thank you for this comment. |
| **8.3.1.** General approach to donor selection: | *Related or unrelated donors should both be considered acceptable. However, where possible, FMT is best sourced from a centralised stool bank, from a healthy unrelated donor (conditional).* | Thank you for this comment. |
| **8.3.2.** Age and BMI restrictions for potential donors: | *People should only be considered as potential FMT donors if they are ≥18 and ≤60 years old, and have a BMI of <30 kg/m² (conditional).* | Thank you for this comment. |
| **8.3.3.** General approach to the donor screening assessment: | *A donor-screening history/ questionnaire is mandatory (Table 2) (strong).*  
1. *Receipt of antimicrobials within the past three months.* | |
2. Known prior exposure to HIV and/or viral hepatitis, and known previous or latent tuberculosis.
3. Risk factors for blood-borne viruses - including high risk sexual behaviours, use of illicit drugs, any tattoo/ body piercing/ needlestick injury/ blood transfusion/ acupuncture, all within previous six months.
4. Receipt of a live attenuated virus within the past six months.
5. Underlying gastrointestinal conditions (e.g. history of IBD, IBS, chronic diarrhoea, chronic constipation, coeliac disease, bowel resection or bariatric surgery).
6. Family history of any significant gastrointestinal conditions (e.g. family history of IBD, or colorectal cancer).
7. History of atopy (e.g. asthma, eosinophilic disorders).
8. Any systemic autoimmune conditions.
9. Any metabolic conditions, including diabetes and obesity.
10. Any neurological or psychiatric conditions, or known risk of prion disease.
11. History of chronic pain syndromes, including chronic fatigue syndrome and fibromyalgia.
12. History of any malignancy.
13. Taking particular regular medications, or such medications within the past three months, i.e. antimicrobials, proton pump inhibitors, immunosuppression, chemotherapy
14. History of receiving growth hormone, insulin from cows, or clotting factor concentrates.
15. History of receiving an experimental medicine or vaccine within the past six months.
8.3.4. Laboratory screening of potential donors: Blood and stool screening of donors is mandatory (Tables 2 and 3) (strong).

Table 3: Recommended blood screening for stool donors:

Pathogen screening:
- Hepatitis A IgM
- Hepatitis B (HBsAg and HBcAb)
- Hepatitis C antibody
- Hepatitis E IgM
- HIV-1 and -2 antibodies
- HTLV-1 and -2 antibodies
- Treponema pallidum antibodies (TPHA, VDRL)
- Epstein-Barr virus IgM
- Cytomegalovirus IgM
- Strongyloides stercoralis IgG
- Entamoeba histolytica serology

General/metabolic screening:
- Full blood count with differential.
- Creatinine and electrolytes
- Liver enzymes (including albumin, bilirubin, aminotransferases, gamma-glutamyltransferase and alkaline phosphatase).
- C-reactive protein

Table 4: Recommended stool screening for stool donors:
- Clostridium difficile PCR
- Campylobacter, Salmonella, and Shigella by standard stool culture and/or PCR
- Escherichia coli 0157 H7 by culture and/or PCR

Working group response

We agree with the comment regarding matching donors and immunosuppressed recipients for EBV and CMV status, and have updated Section 8.2.2 and Section 8.3.4 accordingly.

The working group did not think that screening for adenovirus was justified.

Whilst vancomycin-resistant Enterococci (VRE) carriage is relatively common in the community (probably related to food consumption) (Endtz et al, 1997), the form of VRE in the community is genetically distinct from that found nosocomially, with much lower pathogenicity in community forms (Willems et al, 2005). As such, the working group strongly opined that routine screening was not justified. However, it was acknowledged that the potential infection risk from VRE (and MRSA) would vary regionally depending on local prevalence and pathogenicity, and as such a local risk assessment has been recommended to decide whether screening for these organisms should be considered.
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| | • *Multi-drug resistant bacteria, specifically carbapenemase-producing Enterobacteriaceae.*  
| | • *Stool ova, cysts and parasite analysis, including for Microsporidia.*  
| | • *Faecal antigen for Cryptosporidium and Giardia.*  
| | • *Acid fast stain for Cyclospora and Isospora.*  
| | • *Helicobacter pylori faecal antigen.*  
| | • *Norovirus and Rotavirus PCR.*  

We recommend:

**CMV and EBV:** Given the high rates of carriage for both EBV and CMV in a healthy, adult population, excluding EBV or CMV positive donors would make it prohibitively difficult to identify suitable donors to provide access to care (Bate et al). Moreover, excluding EBV or CMV positive candidates is not expected to provide a significant benefit to the majority of the patients that would be served by a centralized stool bank, who are not severely immunocompromised.

Given the need to ensure a reliable supply of material for the vast majority of rCDI patients while protecting severely immunocompromised patients, until now OpenBiome has chosen not to test for EBV and CMV. Instead, we treat material as presumptively CMV and EBV positive and discourage use in severely immunocompromised patients who are seronegative for CMV or EBV.

We are sensitive to the fact that this leaves clinicians with an additional challenge for managing these already difficult cases (severely immunocompromised rCDI patients). Should FMT be
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<td>indicated then we would suggest that in the immunocompromised patient at risk of CMV or EBV infection either: 1) CMV and EBV testing of the recipient to confirm positive serology, in which case FMT may be considered after extensive discussion of the risks, benefits, and alternatives in the informed consent process; or 2) the use of a directed donor with matching serology. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988-2004. Clin Infect Dis. 2010;50:1439–1447.</td>
<td></td>
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<td>32-37</td>
<td>Adenovirus: We recommend including adenovirus on stool in addition to norovirus and rotavirus.</td>
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<td>38-45</td>
<td>Vancomycin resistant enterococcus (VRE): VRE should be specifically mentioned in “Multi-drug resistant bacteria”. VRE is a leading cause for donor exclusion despite prospective donors having no known risk factors for colonization.</td>
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<tr>
<td>47-48</td>
<td>8.3.5. Final donor checks prior to donation: Further final screening should take place prior to collection of a stool sample for processing into FMT (strong). We agree.</td>
<td>Thank you for this comment. In light of this and other comments, the recommendation on repeat screening has been strengthened.</td>
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<td>50-57</td>
<td>8.4.1. General principles of FMT preparation: Recommendation: i. Donor stool collection should follow a standard protocol (strong). ii. Donor stool should be processed within 6 hours of defecation (conditional). iii. Both aerobically and anaerobically prepared FMT treatments should be considered suitable when preparing FMT for the treatment of recurrent CDI (strong).</td>
<td>Thank you for this comment.</td>
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<td>iv.</td>
<td>Sterile 0.9% saline should be considered as an appropriate diluent for FMT production, and cryoprotectant such as glycerol should be added for frozen FMT (strong).</td>
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<td>v.</td>
<td>Consider ≥50g of stool for use in FMT preparation (conditional).</td>
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**Good practice points:**  

i. Stool should be mixed 1:5 with diluent to make the initial faecal emulsion (conditional).  

ii. Homogenisation and filtration of FMT should be undertaken in a closed disposable system (conditional).  

We agree.

| 8.4.2. Fresh vs frozen FMT: | The use of banked frozen FMT material should be considered preferable to fresh preparations for CDI (strong). | Thank you for this comment.  

We agree.

| 8.4.3. Use of frozen FMT: | Recommendation: FMT material stored frozen at -80°C should be regarded as having a maximum shelf life of six months from preparation (strong).  

**Good practice point:** Consider thawing frozen FMT should at ambient temperature and using within six hours of thawing (conditional). | Thank you for this comment.  

We agree.

| 8.5.1. Use of specific medications in the period around FMT administration: 8.5.1.1. General | **Recommendation:** Bowel lavage should be administered prior to FMT via the lower GI route, and bowel lavage should be considered prior to FMT via the upper GI route; polyethylene glycol preparation is preferred (conditional). | Thank you for this comment.  

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<td><strong>principles of FMT administration:</strong></td>
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  *ii.* For upper GI FMT administration, a proton pump inhibitor should be considered, e.g. the evening before and morning of delivery (conditional).  
  *iii.* Loperamide (or other anti-motility drugs) should be considered following lower GI FMT delivery (conditional).  
  **Good practice point:**  
  *i.* Prokinetics (such as metoclopramide) should be considered prior to FMT via the upper GI route (conditional).  
  *ii.* Best practice for prevention of further transmission of CDI should be applied throughout when administering FMT to patients with CDI (nursing with enteric precautions, sporicidal treatment of endoscope, etc). | We agree. |
| **8.5.1.2. Additional antibiotics pre-FMT:** | Consider further antimicrobial treatment for CDI for at least 72 hours prior to FMT (conditional).  
We agree. | Thank you for this comment. |
| **8.5.1.3. Washout period between antibiotic use and FMT:** | To minimise any deleterious effect of antimicrobials on the FMT material, there should be a minimum washout period of 24 hours between the last dose of antibiotic and treatment with FMT (strong).  
We agree. | Thank you for this comment. |
| **8.5.2.2. Upper gastrointestinal tract administration of FMT:** | **Recommendation:**  
  *i.* Upper GI administration of FMT as treatment for recurrent or refractory CDI should be used where clinically appropriate (strong).  
  *ii.* Where upper GI administration is considered most | Thank you for this comment. In light of further discussion by the working group, the maximum volume of FMT recommended by upper GI administration is now 100ml. |
appropriate, FMT administration should be via nasogastric, nasoduodenal, or nasojejunal tube, or alternatively via upper GI endoscopy. Administration via a permanent feeding tube is also appropriate (strong).

**Good practice point:**
It is recommended that no more than 50ml of FMT is administered to the upper GI tract (conditional).

We agree.

8.5.2.3. Lower gastrointestinal tract administration of FMT:

**Recommendation:**

i. Colonscopic administration of FMT as treatment for recurrent or refractory CDI should be used where appropriate (strong).

ii. Where colonscopic administration is employed, consider preferential delivery to the caecum or terminal ileum, as this appears to give the highest efficacy rate (conditional).

iii. FMT via enema should be used as a lower GI option when colonscopic delivery is not possible (strong).

We recommend rewording point iii. Although there is limited data, flexible sigmoidoscopy may be the preferred route of delivery where colonscopic delivery is not possible. Several experts have advised less invasive modalities such sigmoidoscopy in high risk patients (Brandt 2013; Kelly 2014). This may provide a more effective method for delivering material as proximally as possible and improving retention. We therefore recommend re-wording point iii to:

**FMT via enema should be used as a lower GI option when colonscopic or flexible sigmoidoscopy delivery is not possible.**

We agree with this suggestion, and have updated the guideline accordingly.
8.5.2.4. Capsulised FMT:

**Capsulised FMT holds promise as a treatment option for recurrent CDI, but further evidence regarding its safety and efficacy is awaited, and it should not be considered for use at present (conditional).**

There is a growing body of evidence on encapsulated FMT and the delivery modality presents a potential option in circumstances where it may be inappropriate, contraindicated, or contrary to patient preferences to deliver material via traditional routes of administration for CDI.

In terms of patient perceptions, Zipursky and colleagues report that more aesthetically appealing FMT formulations, such as capsules, would both eliminate potential barriers to treatment and reduce the necessity for healthcare resources and procedure time for clinicians. Capsules appear well tolerated. For example, the mean time of 30 capsule administration is approximately 20 minutes (range 10-30 minute) (Allegretti, unpublished data).

Although the optimal dose is still under investigation (as with other FMT delivery modalities), there have been several studies that have
shown equivalent efficacy rates. Youngster and colleagues reported their experience with a capsule formulation that averaged 1.6 grams of stool per capsule in which they dosed 15 capsules on 2 consecutive days. They reported a 70% cure rate after an initial dose in a cohort of 140 patients. Those that failed to achieve cure were re-treated, bringing the cumulative cure rate up to 90%.

Similarly, Hirsch and colleagues demonstrated a clinical cure rate of 68% in the 19 participants, using capsules containing purified, concentrated, and cryopreserved fecal bacteria and this increased to 89% with retreatment.

Allegretti and colleagues conducted the first dose-finding study for FMT capsules (0.75 grams of stool per capsule with upper GI release) assessing 30 capsules once (low dose) versus 30 capsules on 2 consecutive days (high dose). Efficacy rates between the groups were similar on initial dose (70%) and there were no adverse events reported.

Lastly the largest randomized control trial to date of FMT used encapsulated FMT with good safety and efficacy outcomes equivalent to colonoscopy FMT. In Kao et al’s non-inferiority randomized clinical trial (cited in the guidelines) that included 116 adults with rCDI, the proportion without recurrence over 12 weeks was 96.2% after a single treatment in a group treated with oral capsules and in a group treated via colonoscopy. Given this 1+ level of evidence, in addition to multiple smaller studies of encapsulated FMT, we feel that there is a good body of evidence to support the short-term safety of encapsulated FMT. We agree that further evidence is needed on optimal dosing and formulation, however this applies to all delivery modalities.
We agree that capsule availability is very limited in the UK at present however this shouldn’t preclude guidelines recommending this as a potential FMT delivery option.

We therefore recommend rewording the 8.5.2.4 to:

*Capsulised FMT holds promise as a treatment option for recurrent CDI and should be offered to patients as a potential treatment modality. Capsule preparations should follow a standard protocol. Further evidence regarding its optimal dosing and formulation is needed (conditional).*


Zipursky JS, Sidorsky TI, Freedman CA, Sidorsky MN, Kirkland KB.
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<td>8.6. What is the clinical effectiveness of faecal microbiota transplant in treating conditions other than Clostridium difficile infection?</td>
<td><strong>FMT is not currently recommended as treatment for inflammatory bowel disease. There is insufficient evidence to recommend FMT for any other gastrointestinal or non-gastrointestinal disease (strong).</strong> We agree.</td>
<td>Thank you for this comment.</td>
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<td>8.7. Basic requirements for implementing a FMT service</td>
<td><strong>The development of FMT centres should be encouraged (strong).</strong> We agree.</td>
<td>Thank you for this comment.</td>
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<td>8.7.5. FMT manufacturing:</td>
<td><strong>Ensure traceability of supply (strong).</strong> We agree.</td>
<td>Thank you for this comment.</td>
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<td>FMT in patients with IBD</td>
<td>We recommend emphasizing the importance of counselling patients with IBD on the risk of flare or worsening IBD activity post-FMT.</td>
<td>We agree with this comment, and have updated Section 8.2.3. accordingly.</td>
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<td>FMT in paediatric populations</td>
<td>A recommendation on paediatric FMT should be include. The evidence base is limited but safety and efficacy appears comparable to adult FMT. Patients and caregivers should be counselled on the unknown long-term risks of FMT. <strong>Recommendation:</strong> i. <strong>FMT should be offered to paediatric patients with recurrent CDI.</strong> ii. <strong>Paediatric patients and caregivers should be counselled on the unknown short and long-term risks of FMT.</strong></td>
<td>FMT in the paediatric setting is outside of the remit of this working group. We have updated Section 5.4 to clarify this.</td>
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**Closing date:** Please forward this electronically by 5pm on January 2018 at the very latest to consultations@his.org.uk
Donor personal interview and health questionnaire

Interview and health questionnaire results assessed by clinical team

Inclusion criteria met

Laboratory screening – blood and stool assays

~ 14 days to receive all results

Review laboratory screening

Any tests unsatisfactory

Potential donor excluded

All tests satisfactory

Provisionally accept as donor

• Start stool collection and FMT preparation
• FMT in quarantine/not for use until repeat screening

Period of donation to be locally-defined

Repeat donor screening at end of donation period:
• Health questionnaire
• Laboratory screening

Inclusion criteria not met, and/or any tests unsatisfactory

Potential donor excluded

Inclusion criteria still met, and all tests still satisfactory

Release FMT from quarantine for clinical use