NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of faecal microbiota transplant for recurrent *Clostridium difficile* infection

Infections caused by bacteria called *Clostridium difficile* (*C. difficile*) in the gut can cause severe diarrhoea and illness. It usually occurs after antibiotic therapy, which can upset the balance of bacteria in the gut. Faecal microbiota transplant involves putting faeces from a healthy donor into the gut of the affected person, to restore the normal balance of bacteria.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2013.

Procedure name

- Faecal microbiota transplant for recurrent *Clostridium difficile* infection.

Specialist societies

- British Society of Gastroenterology
- Royal College of Pathologists (Microbiology).

Description

Indications and current treatment

Clostridium difficile (*C. difficile*) is a commensal bacterium that lives harmlessly in the gut of approximately 5% of healthy people. The use of broad-spectrum antibiotics and immunosuppressive agents can alter the balance of bacterial species in the gut, resulting in an overgrowth of *C. difficile.* Symptoms of mild *C. difficile* infections (CDIs) include purulent watery diarrhoea, abdominal cramps, nausea and dehydration. In more severe cases the infection can cause bloody diarrhoea and fever. In a few people CDIs can lead to pseudomembranous colitis, sepsis, toxic megacolon, colonic rupture, and death. The risk of death increases in patients with multiple comorbidities.

First-line treatment involves rehydration and antibiotic therapy. Clinical responses are generally favourable but some patients have recurrent or refractory CDIs. For these people, further courses of antibiotics are used. An example of management algorithms can be found in Public Health England's Updated guidance on the management and treatment of Clostridium difficile infection (June, 2013).

What the procedure involves

Faecal microbiota transplants (FMTs) aim to restore a healthy balance of bacteria in the gut of people who have recurrent *C*DIs by introducing enteric bacteria from the faeces of healthy donors. Although this procedure is called a transplant, it does not involve the transplantation of body tissues.

Before FMT, donors (who can be family members or unrelated) are screened for enteric bacterial pathogens, viruses and parasites. Donor faeces are taken and diluted with water, saline or another liquid such as milk or yogurt, and subsequently strained to remove large particles. The resulting suspension is introduced into the recipient's gut via a nasogastric tube, nasoduodenal tube, rectal enema or via the biopsy channel of a colonoscope. Recipients may receive a bowel lavage before transplantation, in order to reduce the *C. difficile* load in the intestines.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to faecal microbiota transplant for *Clostridium difficile* infections. Searches were conducted of the following databases, covering the period from their commencement to 30 April 2013: MEDLINE, PREMEDLINE, EMBASE,

Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with recurrent *Clostridium difficile* infection.
Intervention/test	Faecal microbiota transplant.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on 526 patients from 1 systematic review[1], 1 randomised controlled trial[2], 1 non-randomised comparative study[3] and 2 retrospective case series[4,5].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on faecal microbiota transplant for recurrent *Clostridium difficile* infection

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Van Nood (2013)[1]

Randomised controlled trial

Netherlands

Recruitment period: 2008 to 2010

Study population: Patients with recurrent CDI

n=43 (17 FMT vs 13 vancomycin and bowel lavage vs 13 vancomycin-only)

Mean age: FMT: 73, vancomycin and lavage: 69, vancomycin-only: 66
Sex: 42.9% female

Patient selection criteria: age >18 years, life expectancy >3 months, relapse of CDI after at least one course of vancomycin or metronidazole therapy.

Exclusion criteria: Immunocompromised due to</td>
<td>Number of patients analysed: 42 (16 vancomycin, lavage and FMT, 13 vancomycin and lavage, 13 vancomycin-only)

Cure rate: Absence of diarrhoea with 3 negative tests for C. difficile toxin.
<table>
<tr><th>Group</th><th>Cure rate
% (n/N)</th></tr>
<tr><td>Initial FMT treatment</td><td>81.3 (13/16)</td></tr>
<tr><td>Second FMT treatment</td><td>66.6 (2/3)</td></tr>
<tr><td>Overall FMT treatment</td><td>93.8 (15/16)</td></tr>
<tr><td>Vancomycin with lavage</td><td>23.1 (3/13)</td></tr>
<tr><td>Vancomycin-only</td><td>30.8 (4/13)</td></tr>
</table>
Significant differences observed when comparing initial FMT cure rates (p<0.01) and overall FMT cure rates (p<0.001) with comparison groups. Exact p-values were not stated.

Recurrence during 5-week follow-up period.
<table>
<tr><th>Group</th><th>Percentage recurrence
% (n/N)</th><th>Median time of recurrence days (range)</th></tr>
<tr><td>FMT</td><td>6.3 (1/16)</td><td>35 (N/a)*</td></tr>
<tr><td>Vancomycin with lavage</td><td>53.8 (7/13)</td><td>25 (18 to 70)</td></tr>
<tr><td>Vancomycin-only</td><td>61.5 (8/13)</td><td>23 (13 to 43)</td></tr>
</table>
*Only 1 patient relapsed during 5-week follow-up period.</td>
<td>Incidence of adverse events reported in the 16 patients who received FMT.
<table>
<tr><th>Adverse Events</th><th>On the day of FMT
% (n/16)</th><th>During follow-up
% (n/16)</th></tr>
<tr><td>Non-CDI diarrhoea</td><td>93.8 (15)</td><td>0 (0)</td></tr>
<tr><td>Abdominal cramps</td><td>31.3 (5)</td><td>0 (0)</td></tr>
<tr><td>Belching</td><td>18.8 (3)</td><td>0 (0)</td></tr>
<tr><td>Abdominal pain</td><td>12.5 (2)</td><td>0 (0)</td></tr>
<tr><td>Abdominal cramps</td><td>31.3 (5)</td><td>0 (0)</td></tr>
<tr><td>Constipation</td><td>0 (0)</td><td>18.8 (3)</td></tr>
<tr><td>Infection</td><td>0 (0)</td><td>12.5 (2)[a]</td></tr>
<tr><td>Symptomatic choledocholithiasis</td><td>0 (0)</td><td>6.3 (1)</td></tr>
<tr><td>Other</td><td>6.3 (1)[b]</td><td>0</td></tr>
</table>
[a] One patient had urinary tract infection while another presented with a fever during haemodialysis.
[b] Patient with autonomic dysfunction had dizziness combined with diarrhoea.

NB: 1 patient in the vancomycin group died from heart failure and chronic obstructive pulmonary disease: included in analysis as treatment failure.</td>
<td>Follow-up issues:
• One patient in the FMT group was excluded from analysis because of deviation from the study protocol: required high-dose prednisolone.
• Patient who died in the vancomycin group from heart failure was included in analysis.

Study design issues:
• Open-label RCT: Study physicians performed randomisation. Adjudication committee were unaware of group assignments, reviewed results.

Study population issues:
• Study underpowered: Initial power calculations indicated 38 patients were needed per group to confer 80% power.

Other issues:
• Study closed early after</td>
</tr>
</table>

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
chemotherapy **or** HIV with CD4 count less than 240 **or** prolonged use of more than 60 mg of prednisolone a day; pregnancy; use of antibiotics other than for treatment of *C. difficile*; admission to an intensive care unit; need for vasopressor medication. Technique: 1. FMT group: Abbreviated vancomycin regimen for 4 or 5 days, followed by bowel lavage, then FMT via nasoduodenal tube. A second FMT was administered if needed. 2. Vancomycin and lavage group: vancomycin, for 14 days. Bowel lavage performed on day 4 or 5. 3. Vancomycin-only group: vancomycin for 14 days. **Follow-up: 10 weeks following initiation of treatment. Patients who received a second FMT were followed-up for another 10 weeks.** Conflict of interest/source of funding: not reported			interim analysis due to Haybittle-Peto rule ($p<0.001$ was accepted as the primary endpoint).

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Sofi AA (2013)[2] **Systematic review and meta-analysis** Review of studies from multiple countries Search date: April 2012 Search period: 1946 to April 2012 Study population: Patients with refractory CDI. **n=289** (25 studies: 15 case series and 10 case reports) Age: mean 68.5 years; Sex: 62.7% female Study/patient selection criteria: Patients who received FMT and had symptomatic diarrhoea with laboratory confirmed CDI **and/or** presence of pseudomembranes. Exclusion criteria: Studies that; assessed patients less than 18 years; used FMT for treating conditions other than CDI; used a non-faecal source of colonic bacteria for transplant; used FMT for antibiotic-associated diarrhoea without laboratory	Number of patients analysed: **289** **Overall pooled FMT success rate**: 91.2% (Success defined as resolution of all CDI symptoms at follow-up) **Factors associated with successful treatment** Univariate comparisons revealed that treatment failed in 22.4% (13/58) of patients with symptom duration of ≤60 days, and in 4.7% (9/191) of patients with symptom duration >60 days (p<0.0001). Multivariate logistic regression confirmed the significant association of shorter duration of symptoms before FMT with treatment failure (OR=11.1, 95% CI: 2.4 to 28.9, p=0.0009) comparing duration of symptoms ≤60 days with >60 days. Furthermore, multivariate analysis found no significant associations between treatment failure and age, gender, FMT delivery route, pre-treatment strategy or donor source. **CDI relapse** (Complete resolution of CDI followed by recurrence of symptoms with laboratory confirmation of CDI) • Relapse was reported in 5/25 of the included studies. • 7 (2.4%) patients had a relapse between 29 days and 4 years following FMT.	**Adverse events** • Suspected peritonitis (n=1)* • Symptoms of irritable bowel syndrome (n=1)* • 3 patients exhibited symptoms of enteritis, within 2 days of receiving FMT * The timings of adverse event(s) were not reported.	**Follow-up issues:** • Individual patient data was extracted from each study by 2 independent reviewers. • Follow-up data were not reported in 18 patients. **Study design issues:** • Although authors indicate that pre-treatment was defined as any medication used for CDI within 3 days before FMT, it also states that studies that withheld vancomycin 24–72 hours before FMT patients were considered to be in the no pre-treatment group. • Information of excluded studies was not presented. • There was heterogeneity of FMT sample size/volume. • All but one of the included case series were retrospective. **Study population issues:** • Heterogeneity of study population regarding whether treatment was for initial CDI or

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
confirmation of CDI or colonoscopic confirmation of pseudomembranes; failed to report the outcome of FMT. Technique: Donor faeces samples were screened in 19/25 of the included studies. Patients were pre-treated with vancomycin (3/25 studies); *Saccharomyces boulardii*, nystatin; methicillin (1/25 studies); polyethylene glycerol (3/25 studies); PPIs, adenocorticotropic hormone (2/25 studies); or received no treatment. Amount of donor faeces used ranged from 10 g to 50 g **or** 30 ml to 500 ml. FMT delivery occurred via various modalities. **Follow-up: mean 12.6 months (range: 10 days to 65 months)** Conflict of interest/source of funding: none reported			recurrent CDI. • Most studies included patients with recurrent or refractory CDI. **Other issues:** • Subgroup comparisons involve small groups with unequal sample sizes. This may affect statistical significance. • Unclear how many studies actively monitored the occurrence of adverse events.

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Hamilton (2012)[3] **Non-randomised comparative study of 3 approaches to FMT** USA Recruitment period: Not specified Study population: Patients with recurrent CDI **n=43** (10 fresh from related donor vs 12 fresh from unrelated donor vs 21 frozen from unrelated donor) Age: mean 59, Sex: 72% female Patient selection criteria: Symptomatic, toxin positive CDI and at least 2 recurrences despite antibiotic therapy. Exclusion criteria: age <18 years, life expectancy <1 year. Technique: Vancomycin regimen and polyethylene glycol purge preceded FMT. Concentrated samples were stored in glycerol solution and frozen for up to 8 weeks. When needed they were diluted and administered colonoscopically. **Follow-up: 12 months** Conflict of interest: None	Number of patients analysed: **43** **(10 fresh from related donor vs 12 fresh from unrelated donor vs 21 frozen from unrelated donor)** **Primary success rate (Resolution of diarrhoea and negative stool samples 2 months after FMT)** • Fresh from related donor: 70% (7/10) • Fresh from unrelated donor: 92% (11/12) • Frozen from unrelated donor: 90% (19/21) • Combined success rate: 86% (37/43) No significant difference between related vs unrelated donor comparison or fresh vs frozen sample comparison. **Secondary success rates.** 4 out of the 6 participants with recurrent CDI after initial FMT agreed to secondary infusion from an unrelated donor: All were cleared of CDI infection. Thus, overall <u>combined</u> success rate: 95% (41/43).	• No serious adverse events observed. • 'Approximately 1/3 of patients' experienced irregular bowel movements and flatulence within the first 2 weeks of receiving FMT.	**Follow-up issues:** **Study design issues:** • Majority of unrelated samples were acquired from 1 donor and used in 90.9% (30/33) of patients **Study population issues:** • Possible selection bias: proportion of patients with underlying Irritable Bowel Disease unevenly distributed across comparison groups. • Uneven distribution of patients receiving PPIs across comparison groups; patients receiving fresh FMT from related donor had the highest proportion (60%) **Other:** • No power calculations reported • Small sample sizes may affect statistical significance.

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Rubin (2012)[4] **Retrospective case series** USA Recruitment period: 2003–2010 Study population: Patients with refractory CDI. **n=74 patients** (75 courses) Age: median 63 years, Sex: 65.3% female Patient selection criteria: Laboratory confirmed initial CDI; >2 laboratory confirmed recurrences following standard antibiotic therapy; had evaluable clinical and laboratory follow-up during 60 days or longer after FMT. Exclusion: FMT used for indication other than CDI; surgically shortened GI tract; deviation from FMT protocol; documentation of eligibility or follow-up incomplete; patient was included in previous study. Technique: Vancomycin pre-treatment for 3 days; PPI given; FMT via NG, gastroscopic or percutaneous endoscopic gastronomy tube.	Number of patients analysed: **74 patients (75 courses)** **Primary success rate:** 78.7% (59/75 courses) [Defined as resolution of diarrhoea without recurrence within 60 days of FMT] NB: 2 of the asymptomatic patients were found to be toxin positive (*C. difficile* carriers). Classified as clinically cured. **Secondary/overall success rate:** 90.7% (68/75 courses) [Defined as resolution of diarrhoea without CDI recurrence following additional FMTs] **Chi-square subgroup comparisons:** No statistically significant results were observed when the following comparisons were made: • Male vs female • Age: <65 years vs ≥65 years • Diabetes mellitus vs No diabetes mellitus • Malignant disease vs No malignant disease • Steroid use in prior 3 months vs No steroid use in prior 3 months	**Adverse events** No patient experienced an adverse event or died before or after the FMT 60-day follow-up period.	**Follow-up issues:** • 14 courses were excluded from analysis because of exclusion criteria outlined in study details. **Study population issues:** • Study quantifies the number of successful courses rather than cured patients. • All donors were related to the recipient • Case series included 2 paediatric patients.

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Follow-up: 60 days Conflict of interest: None reported			

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Brandt (2012)[5]

Retrospective case series (Self-reported questionnaire)

USA

Recruitment period: Not specified

Study population: Patients with refractory CDI

n=77

Age: mean 65 years, Sex: 73% female

Patient selection criteria: Recurrent CDI and unresponsive to standard antibiotic therapy, undergone FMT ≥3 months to data collection.
Exclusion: Patients who were not contactable; unable to complete the questionnaire themselves; or have a reliable third party complete it on their behalf.

Technique: Antibiotic therapy ceased 2 to 3 days before FMT, All FMTs were administered colonoscopically.

Follow-up: mean 17 months (range 3 to 68 months)</td>
<td>Number of patients analysed: 77

Primary success rate: 91% (70/77)
[Defined as resolution of diarrhoea without recurrence within 90 days of FMT]

Secondary success rate:
7 participants required additional vancomycin therapy with or without another FMT. 6/7 participants were cured. Thus, overall success rate was 98% (76/77).

46.1% (35/76) of asymptomatic participants were confirmed to be toxin-negative at an unspecified period following FMT.

Symptom improvement/resolution:
<table>
<tr><th>Symptom</th><th>No improvement % (n/N)</th><th>Improved % (n/N)</th><th>Resolved % (n/N)</th></tr>
<tr><td>Diarrhoea</td><td>1 (1/77)</td><td>17 (13/77)</td><td>82 (63/77)</td></tr>
<tr><td>Abdominal pain</td><td>7* (4/56)</td><td>23 (13/56)</td><td>70 (39/56)</td></tr>
<tr><td>Fatigue</td><td>7 (5/74)</td><td>42 (31/74)</td><td>51 (38/74)</td></tr>
</table>
* Amended percentage: Author used denominator of 77 instead of 56 in the calculation.

Mean days to symptom improvement/resolution:
<table>
<tr><th>Symptom</th><th>Mean time to improvement (range)</th></tr>
<tr><td>Diarrhoea</td><td>5 days (1–60 days)</td></tr>
<tr><td>Abdominal pain</td><td>10 days (1–120 days)</td></tr>
<tr><td>Fatigue</td><td>4 weeks (1–28 weeks)</td></tr>
</table>
Weight gain/loss:
53% (41/77) of participants gained weight, 3% (2/77) of participants lost weight and 44% (34/77) of participants experienced no change in weight.</td>
<td>Self-reported new conditions after FMT:
4 patients reported the following conditions:
• Peripheral neuropathy
• Sjogren's disease
• Idiopathic thrombocytopenic purpura
• Rheumatoid arthritis

NB:
• No time of occurrence was reported for the aforementioned conditions.
• Authors note that there was no evidence that reported conditions were associated with the procedure.</td>
<td>Study design issues:

• Questionnaire had not been previously validated. However, a copy has been attached in the appendix.
• Self-reported retrospective questionnaire prone to responder and recall biases.
• Secondary success rate is misleading because it includes patients with resolved C. difficile-associated diarrhoea after additional course of vancomycin with or without FMT.

Study population issues:

• 7/77 patients had died before the time of data collection and their questionnaires were completed by family members or partners.
• 56/77 donors resided in the same household as the patients. 1 donor was unrelated to the patient.

Other issues:
• Self-reported conditions after FMT had no</td>
</tr>
</table>

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Conflict of interest/source of funding: None reported	**CDI recurrence:** • 9% (7/77) of participants experienced CDI-associated diarrhoea within 90 days of FMT (authors defined this as treatment failure) – 4 of these patients were cured with additional vancomycin therapy with or without probiotics. – 2 patients were cured with subsequent FMT. • 10% (8/77) of participants experienced CDI-associated diarrhoea over 90 days after FMT (authors did not define this as treatment failure)		confirmed association with the procedure by a physician.

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Patel (2013)[6]

Retrospective case series

USA

Recruitment period: January 2011 to January 2013

Study population: Patients with refractory CDI

n=31

Age: mean 61.3 years, Sex: 55% female

Patient selection criteria: Patients with 2 or more documented episodes of CDI and ongoing diarrhoea, in the absence of antimicrobial therapy, were included.
Exclusion criteria: <u>Donors</u> with chronic gastrointestinal disorders, active peptic ulcer disease, gastro-oesophageal reflux disease requiring daily proton pump inhibitor therapy, irritable or inflammatory bowel disease, history of colonic polyps or malignancy, who received antibiotics during the preceding 3 months or were hospitalised during the preceding 3 months were excluded.</td>
<td>Number of patients analysed: 30

Symptom improvement/resolution:
<table>
<tr><th>Symptom</th><th>No improvement % (n/N)</th><th>Improved % (n/N)</th><th>Resolved % (n/N)</th></tr>
<tr><td>Diarrhoea</td><td>3.3 (1/30)</td><td>23.3 (7/30)</td><td>73.3 (22/30)</td></tr>
<tr><td>Abdominal pain</td><td>26.1 (6/23)</td><td>21.7 (5/23)</td><td>52.2 (12/23)</td></tr>
<tr><td>Fatigue</td><td>44.8 (13/29)</td><td>27.6 (8/29)</td><td>27.6 (8/29)</td></tr>
</table>
• The median time to improvement or resolution of diarrhoea was 3 days.
• The median time to improvement or resolution of abdominal pain was 3 days.

Weight gain/loss:
47.3% (9/19) of participants with weight loss gained weight, following FMT.
NB: percentage was corrected as author stated 46%</td>
<td>Adverse events
• A microperforation was observed in one patient during a biopsy of an area of presumed ischemic small-bowel injury during the FMT procedure.</td>
<td>Follow-up issues:
• One patient was lost to follow-up

Study design issues:

• Patients were asked to suggest possible healthy stool donors: these were not limited to family members.
• Patients were assessed using a telephone-based retrospective questionnaire which may be prone to responder and recall biases.

Study population issues:

• 55% (17/31) of patients had a gastrointestinal comorbidity; including diverticulosis (n=5), irritable bowel syndrome (n=5), ulcerative colitis (n=3), Crohn’s disease (n=2), gastroparesis (n=1) and coloanal fistula (n=1)
• 26% (8/31) of patients were immunosuppressed.

Other issues:
• Initial FMT was performed without a</td>
</tr>
</table>

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Technique: Patients received a polyethylene glycol-based bowel preparation 1 day prior to receiving FMT. FMT recipients discontinued their antibiotic therapy 4 hours prior to receiving treatment. Donors provided stool that was passed within 6 hours of the procedure. FMT was administered into the terminal ileum or cecum using a colonoscope. **Follow-up: 12 months** Conflict of interest/source of funding: None reported			standardised protocol or evaluation process. Subsequent FMTs were performed following the development of a standardised protocol and evaluation process.

Abbreviations used: CDI, *Clostridium difficile* Infection; FMT, faecal microbiota transplant; GI, gastrointestinal; NG, nasogastric; PPIs, proton pump inhibitors.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
James (2012) [7] **Abstract of a Case report** Country: Unclear Age: 78 Sex: male Patient selection criteria: N/A Follow-up: Unclear	A 78 year old man with history of panhypopituitarism (requiring low-dose prednisone) and inactive ulcerative colitis, for 20 years was referred for FMT for relapsing CDI. After a course of cephalexin he had developed severe CDI which required treatment with intravenous metronidazole and oral vancomycin. He was subsequently hospitalized twice for CDI relapses and a tapering course of vancomycin failed to cure CDI. FMT was delivered via colonoscopy. At the time of FMT, colonoscopy showed diverticulosis and a few pseudopolyps, with otherwise normal mucosa. A suspension of donor stool in saline was administered to the terminal ileum and colon. Nine days post FMT, the patient developed abdominal cramping and loose stool with blood and mucus. Symptoms differed from those experienced during CDI relapses and gradually worsened. Sigmoidoscopy on day 19, post FMT, showed moderate erythema and friability from the rectum to the splenic flexure with adherent blood and mucus. The appearance was consistent with ulcerative colitis flare and biopsies showed active colitis (irritable bowel disease type). Prednisone was increased to 20 mg per day and oral and topical mesalamine were added. At 2-week follow-up the patient reported no diarrhoea or abdominal pain. The patient has not experienced further CDI relapse and is currently taking 5 mg of prednisone for hypopituitarism and oral mesalamine to maintain ulcerative colitis remission.		

Efficacy

Resolution of symptoms with or without laboratory confirmation of negative stool samples

A randomised controlled trial of 43 patients treated by faecal transplant versus vancomycin with a bowel lavage versus vancomycin only, reported a primary cure rate of 81% (13/16), 23% (3/13) and 31% (4/13) respectively at 10-week follow-up. The faecal transplant group had statistically significantly higher cure rates compared against the vancomycin with bowel lavage and vancomycin-only groups ($p<0.001$). Patients for whom an initial faecal transplant failed (n=3) had another transplant; 66% (2/3) of these patients were cured resulting in an overall cure rate of 94% (15/16)[1].

A systematic review of 25 studies, which included 289 patients with refractory CDI treated by faecal transplant, reported complete resolution of symptoms in 91% of patients at a mean follow-up of 12.6 months[2].

A non-randomised comparative study of 43 patients treated by FMT using fresh stool from a related donor, FMT using fresh stool from an unrelated donor or FMT using frozen stool from an unrelated donor, reported resolution of symptoms with negative stool samples in 70% (7/10), 92% (11/12) and 90% (19/21) of patients respectively at 12-month follow-up. There were no statistically significant differences between the success rates of related and unrelated faeces or between the success rates of fresh and frozen faeces[3].

A retrospective case series of 75 FMT courses reported resolution of diarrhoea in 79% (59/75 courses) of the initial courses. The secondary/overall success rate was 91% (68/75 courses)[4].

A retrospective case series of 77 patients reported resolution of diarrhoea without recurrence within 90 days of FMT in 91% (70/77) of patients. The study reported that no improvements, some improvements and complete resolution of diarrhoea were reported in 1% (1/77), 17% (13/77) and 82% (63/77) of patients respectively, at a mean follow-up of 17 months. In terms of abdominal pain, 7% (4/56), 23% (13/56) and 70% (39/56) of patients had no improvement, some improvement and complete resolution of abdominal pain respectively. No improvement in fatigue was reported in 7% (5/74) of patients, some improvement was reported in 42% (31/74) of patients and resolution of fatigue was reported in 51% (38/74) of patients. The mean time taken for the improvement or resolution of diarrhoea, abdominal pain and fatigue were 5 days, 10 days and 4 weeks, respectively[5].

Treatment failure

The systematic review of 25 studies, which included 289 patients, revealed a significant difference in treatment failure rates in people with symptom duration of less than 60 days (22%) compared with people with symptom duration of more than 60 days (5%; $p<0.0001$)[2].

Relapse

The randomised controlled trial of 43 patients treated by FMT, vancomycin with bowel lavage or vancomycin only reported CDI relapses within 5 weeks of therapy commencement in 6% (1/16), 54% (7/13) and 62% (8/13) of patients respectively. The median number of days until relapse was 25 days (range 18 to 70 days) in the vancomycin with lavage group and 23 days (range 13 to 43 days) in the vancomycin only group: p-values were not reported. Only 1 patient in the FMT group experienced a relapse, 35 days after therapy[1].

The systematic review of 25 studies reported that 2% (7/289) of patients had a relapse between 29 days and 4 years after FMT[2].

The retrospective case series of 77 patients reported CDI relapse in 9% (7/77) of patients within 90 days of FMT. Subsequent vancomycin therapy, with or without probiotics, was successful in 4/7 of these patients, while subsequent FMT was successful in 2/7 patients. CDI relapse 90 days after FMT was reported in 10% (8/77) of patients[5].

Safety

Infections

A urinary tract infection was reported in 1 patient from the FMT group (n=16), and another patient presented with a fever during the 10-week follow-up period in the randomised controlled trial of 43 patients[1].

Suspected peritonitis was reported in 1 patient, and 3 patients exhibited symptoms of enteritis within 2 days of receiving FMT, in the systematic review of 25 studies[2].

Gastrointestinal symptoms

Belching, abdominal cramps and abdominal pain, on the day of FMT, were reported in 19% (3/16), 31% (5/16) and 13% (2/16) of patients respectively in the randomised controlled trial of 43 patients treated by faecal transplant, vancomycin with a bowel lavage or vancomycin only[1]. In the same study, diarrhoea that was not considered to be due to CDI was reported in 94% (15/16)

of patients on the day of FMT. Constipation (during the 10-week follow-up period) was reported in 19% (3/16) patients[1].

Symptoms of irritable bowel syndrome were reported in 1 patient in the systematic review of 25 studies[2].

Irregular bowel movements and flatulence were reported in approximately 33% (14/43) of all patients during the first 2 weeks following FMT in the non-randomised comparative study of 43 patients[3].

Other

On the day of FMT, dizziness was observed in 1 patient with autonomic dysfunction in the FMT group (n=16) of the randomised controlled trial of 43 patients. The same study reported symptomatic choledocholithiasis in 1 patient, from the FMT group, during a 10-week follow-up period[1].

1 case of peripheral neuropathy, 1 case of Sjogren's disease, 1 case of idiopathic thrombocytopenic purpura and 1 case of rheumatoid arthritis were reported in the retrospective case series of 77 patients. However, these were patient-reported outcomes with no timing of occurrence and no confirmation of a clinical association with the FMT procedure[5].

An ulcerative colitis flare-up was reported in one patient after FMT in a case report. The patient had a previous history of panhypopituitarism and had had inactive ulcerative colitis for over 20 years. It was unclear whether the flare-up was caused by the FMT procedure. The ulcerative colitis flare-up was treated with prednisone and oral mesalamine[7].

Validity and generalisability of the studies

- Only 1 randomised controlled trial was identified that assessed the efficacy of FMT. The small sample size may affect statistical power in this study[1].
- One systematic review, published in 2013, included all the relevant case series to date[2].
- One study assessed the efficacy of standardised frozen donor samples for FMT[3].
- One study, which was not included in the aforementioned systematic review, analysed FMT efficacy according to age, gender, steroid use and malignant disease[4].
- One study utilised patient-reported outcomes to assess specific symptoms of CDI; however, this study may be prone to recall bias[5].

- There are no available studies that specifically assess the efficacy of FMT for treating initial CDIs.
- There is a lack of randomised controlled trials.
- No studies specifically focused on FMT efficacy in paediatric patients.
- There is no standardised procedure for administering FMT: heterogeneity in quantity of stool administered, pre-treatment regimen, pre-treatment period, and FMT delivery method.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

There is currently no NICE guidance related to this procedure.

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Dr Stephen Barrett (Royal College of Pathologists); Dr Alisdair MacConnachie (British Infection Association); Dr Gopal Rao (British Society of Gastroenterology).

- One specialist adviser stated that he regularly performs the procedure. The other 2 specialist advisers reported that they have never performed this procedure.
- One specialist adviser described the procedure as established practice. Another specialist adviser described this procedure as the first in a new class of procedure. The third adviser indicated that the procedure is novel with uncertain safety and efficacy profiles.
- Comparator treatments include antibiotic regimens of vancomycin or fidaxomicin.
- All specialist advisers highlighted that less than 10% of specialists are engaged in this area of work.

- Adverse events reported in the literature were bloating, abdominal cramps, loose stool, irritable bowel syndrome, enteritis and peritonitis.
- Theoretical adverse events include the transmission of known biological agents and infections, as well as the administration of microbiologically uncharacterised material.
- Key efficacy outcomes highlighted by the specialist advisers were the cure of infection and the cessation of relapses of CDI.
- One specialist adviser noted that the main uncertainty surrounding the procedure is its long-term efficacy. Two advisors highlighted that there are also uncertainties about what delivery route is most efficacious. Finally, there are uncertainties about who are optimal donors (related versus unrelated donors).
- Both specialist advisers considered the procedure to potentially have a minor impact on the NHS due to the current decreasing rates of CDI in the UK. Furthermore, the use of fidaxomicin may further reduce the number of patients requiring FMT because this drug is considered to be superior to vancomycin in the treatment of recurrences.

Patient commentators' opinions

NICE's Public Involvement Programme sent 8 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received no completed questionnaires.

Issues for consideration by IPAC

Ongoing trials:

- NCT01398969: A prospective randomized multi-centre trial of fresh vs. frozen-and-thawed human biotherapy (fecal transplant) for recurrent *Clostridium difficile* infection; type: randomised controlled trial; estimated enrolment: 136; location: Multi-centre (Canada); estimated study completion date: March 2014.

- NCT01372943: A study using ‘synthetic stool’ or pure cultures of probiotic intestinal bacteria from healthy donor stool that can be used as an enema to replace the use of stool transplant, for treatment of recurrent and refractory CDI; type: non-randomised comparative study; estimated enrolment: 30; location: Canada; estimated study completion date: January 2013.
- NCT01704937: Faecal microbiota transplant (FMT) for relapsing *C. difficile* infection in adults and children using a frozen inoculum; type: Open-label randomised controlled trial; estimated enrolment: 20; location: USA; estimated study completion date: December 2014.
- NCT01703494: Fecal microbiota transplantation for relapsing *Clostridium difficile* infection; type: randomised controlled trial; estimated enrolment: 53; location: USA; estimated study completion date: July 2014.

This overview is specific to the treatment of CDI. However, there is evidence that FMT has been used to treat ulcerative colitis, irritable bowel syndrome, non-*C. difficile*-associated diarrhoea and constipation.

References

1. Sofi, A. A., Silverman, A. L. et al. (2013) Relationship of symptom duration and fecal bacteriotherapy in *Clostridium difficile* infection-pooled data analysis and a systematic review. Scandinavian Journal of Gastroenterology 48 (3): 266-273
2. van Nood E., Vrieze, A. et al. (2013) Duodenal infusion of donor feces for recurrent *Clostridium difficile*. New England Journal of Medicine 368 (5): 407-415
3. Hamilton, M. J., Weingarden, A. R. et al. (2012) Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. American Journal of Gastroenterology 107 (5): 761-767
4. Rubin, T. A., Gessert, C. E. et al. (2013) Fecal microbiome transplantation for recurrent *Clostridium difficile* infection: report on a case series. Anaerobe 19: 22-26
5. Brandt, L. J., Aroniadis, O. C. et al. (2012) Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. American Journal of Gastroenterology 107 (7): 1079-1087

Appendix A: Additional papers on faecal microbiota transplants for *Clostridium difficile* infection

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies: Only studies with more than 10 patients are included in the table below.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Yoon, S. S. and Brandt, L. J. (2010) Treatment of refractory/recurrent *C. difficile*-associated disease by donated stool transplanted via colonoscopy: a case series of 12 patients. Journal of Clinical Gastroenterology 44 (8): 562-566	n=12 Follow-up: 3 weeks - 8 years	All patients exhibited "immediate and durable" response to FMT: 100% cure rate. No adverse events were observed.	Included in systematic review[1].
Mattila, E., Uusitalo-Seppala, R.et al. (2012) Fecal transplantation, through colonoscopy, is effective therapy for recurrent *Clostridium difficile* infection. Gastroenterology 142 (3): 490-496	n=70 Follow-up: 12 weeks	89% (32/36) of patients with 027 *C. difficile* infection exhibited a favourable response. 100% (34/34) of patients with non-027 *C. difficile* infection exhibited a favourable response. No adverse events were observed	Included in systematic review[1].
Garborg, K., Waagsbo, B.et al. (2010). Results of faecal donor instillation therapy for recurrent *Clostridium difficile*-associated diarrhoea. Scandinavian Journal of Infectious Diseases 42 (11-12): 857-861	n=40 Follow-up: 80 days	The initial FMT treatment was successful in 73% (29/33) of patients. 6/11 of the patients who failed to respond the initial FMT responded to the second treatment: Overall cure rate was 83% (33/40) No adverse events were observed	Included in systematic review[1].
Kelly, C. R., de, Leon L.et al. (2012) Fecal microbiota transplantation for relapsing *Clostridium difficile* infection in 26 patients: methodology and results. Journal of Clinical Gastroenterology 46 (2): 145-149	N=26 Follow-up: mean 10.7 months	92% (24/26) patients remained free of diarrhoea and CDI. 1 patient experienced diarrhoea and resumed antibiotic therapy despite testing negative for *C. difficile*. 1 patient relapsed 11 months after FMT following cephalexin therapy.	Included in systematic review[1].

		No adverse events noted.	
Jorup-Ronstrom, C., Hakanson, A.et al. (2012) Fecal transplant against relapsing *Clostridium difficile*-associated diarrhoea in 32 patients. Scandinavian Journal of Gastroenterology 47 (5): 548-552	n=32 Follow-up: 68 months	69% (22/32) patients were durably cured. 15 of the 22 patients that were cured responded to treatment within the first 7 days of transplantation. 3 patients were healed after a second enema whilst 4 were healed by colonoscopy. No adverse events were noted.	Included in systematic review[1].
Rohlke, F., Surawicz, C. M.et al. (2010) Fecal flora reconstitution for recurrent *Clostridium difficile* infection: results and methodology. Journal of Clinical Gastroenterology. 44 (8): 567-570	n=19 Follow-up:	95% (18/19) patients were cured after initial FMT. The remaining patient responded to second FMT. 3 patients relapsed after remaining symptom-free for 6 months to 4 years. No adverse events were noted.	Included in systematic review[1].

Kassam, Z., Lee, C. H.et al. (2013) Fecal Microbiota Transplantation for *Clostridium difficile* Infection: Systematic Review and Meta-Analysis. American Journal of Gastroenterology 108 (4): 500-508	n=273 Follow-up: 3 weeks – 8 years	89.8% 2(45/276) of patients experienced clinical resolution. No statistically significant results were observed in sub-group comparisons. Peritonitis and enteritis were reported. An upper gastrointestinal bleed was also reported in the systematic review but was not associated with FMT in the original paper.	All studies included in this systematic review were also included in the systematic review in table 2[1].
Aroniadis, O. C., Brandt, L. J., Greenberg, A., Borody, T. J., Kelly, C., Mellow, M., Surawicz, C., Cagle, L. A., and Neshatian, L (2013) Long term follow-up study of Faecal Microbiota Transplantation (FMT) for severe or complicated clostridium difficile infection. Gastroenterology. Conference. 144 (5 SUPPL.1): S185	n = 13 FU = 1-42 months	After FMT, diarrhoea resolved in 9 pts (75%) within 1-7 days (mean: 4.5 days) and improved in the remaining 3 pts (25%). Of the 8 pts (62%) with abdominal pain, resolution was seen after FMT in 6 pts (75%) within 1-7 days (mean 3.3 days) and improvement was seen in 2 pts (25%). The primary cure rate was 84%. 2 pts were continued on short courses of vancomycin (4 days) and fidaxomicin (10 days) post- FMT.	Article is an abstract from a conference proceeding. Furthermore, it is unclear whether faecal transplants were used to treat initial C. difficile infections or recurrent infections
Burke, K. E., Lamont, J. T. (2013) Fecal transplantation for recurrent clostridium difficile infection in older adults: A review. Journal of the American Geriatrics Society. 61 (8): 1394-1398	n=115 FU = 5 years	CDI cure was achieved in 103 (89.6%) individuals over a follow-up period of 2 months to 5 years (mean 5.9 months). There was no significant difference in cure rate between older and younger participants in included studies.	This study is a narrative review that provides some pooled descriptive statistics; however no true meta-analysis was performed.

Appendix B: Related NICE guidance for faecal microbiota transplant for recurrent *Clostridium difficile* infection

There is currently no NICE guidance related to this procedure.

Appendix C: Literature search for faecal microbiota transplant for *Clostridium difficile* infection

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	30/04/2013	Issue 4 of 12, April 2013
Database of Abstracts of Reviews of Effects – DARE (CRD website)	30/04/2013	Issue 2 of 4, April 2013
HTA database (CRD website)	30/04/2013	Issue 1 of 4, January 2013
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	30/04/2013	Issue 4 of 12, April 2013
MEDLINE (Ovid)	30/04/2013	1946 to April Week 3 2013
MEDLINE In-Process (Ovid)	30/04/2013	April 29, 2013
EMBASE (Ovid)	30/04/2013	1974 to 2013 Week 17
CINAHL (NLH Search 2.0/EBSCOhost)	30/04/2013	1981 to present
BLIC (Dialog DataStar)	30/04/2013	1993 to current

Trial sources searched on

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- Evidence Updates (NHS Evidence)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases

1	Clostridium difficile/
2	exp Clostridium Infections/
3	(Clostridium* adj3 difficile*).tw.
4	(c adj1 diff*).tw.
5	CDI.tw.
6	Enterocolitis, Pseudomembranous/
7	(Pseudomembran* adj3 (enterocolitis* or colitis*)).tw.
8	Diarrhea/
9	diarrh?ea.tw.
10	or/1-9
11	((Fecal* or faecal*) adj3 (transplant* or infus* or transfus* or reconstruct* or instil* or enema*)).tw.
12	bacteriotherap*.tw.
13	IMT.tw.
14	FMT.tw.
15	((Poo* or stool* or faeces* or feces*) adj3 transplant*).tw.
16	(Intestin* adj3 microbiot* adj3 transplant*).tw.
17	(Donor* adj3 (feces* or faeces* or stool*)).tw.
18	(Microbiota adj3 restor*).tw.
19	(Rectal adj3 infus* adj3 (faeces* or feces*)).tw.
20	or/11-19
21	10 and 20
22	animals/ not humans/
23	21 not 22