Patients with recurrent *Clostridium difficile* infections (CDI) in hospitals and the community constitute an increasing treatment problem. While most patients with a first infection respond to either metronidazole or oral vancomycin, therapy in recurrent *C. difficile* infections tends to fail repeatedly. Lack of alternative treatment options can be a tremendous burden, both to patients and their treating physicians. Most guidelines recommend prolonged oral vancomycin pulse and/or tapering schedules, but evidence-based treatment strategies are lacking. The role of immunoglobulins, whey prepared from vaccinated cows, probiotics or other antibiotics is unclear. Since 1958 several case series and case reports describe a treatment strategy where faecal infusions are successfully given for the treatment of recurrent CDI. Restoring intestinal flora has been historically thought of as the mechanism responsible for cure in these patients. In the literature, more than 150 patients have received faeces from a healthy donor, either infused through an enema, or through a nasoduodenal or nasogastric tube. We summarise the literature regarding treatment with donor faeces for recurrent CDI, and introduce the FECAL trial, currently open for inclusion.

**Introduction**

Described as a commensal bacterium in 1935, it took until the late seventies, before *Clostridium difficile* was recognised as the most important causative agent of antibiotic-associated diarrhoea and colitis [1-3]. *C. difficile* infection (CDI) nowadays is a common nosocomial disease with substantial morbidity and mortality. The increasing incidence, partly due to the recent epidemics caused by the hypervirulent toxinotype III, ribotype 027 strain, and recent reports of community-associated infection in patients without predisposing conditions, illustrate the changing epidemiology of CDI [4-7]. Asymptomatic intestinal carriage of *C. difficile* in the normal population is estimated at 3-15%, but is much higher in hospitalised patients [8]. A prerequisite for the development of clinical *C. difficile* infection (CDI) is a disturbed homeoeostasis of the normal intestinal flora, most often caused by previous antibiotic use or gastrointestinal surgery. Toxins produced by *C. difficile* disrupt the colonic epithelium, leading to an inflammatory response and clinical symptoms varying from mild diarrhoea to severe life-threatening pseudomembranous colitis [9].

Although most patients with a first episode of clinical infection respond either to withdrawal of prescribed antibiotics or to additional treatment with metronidazole or oral vancomycin, about 15–30% experience recurrent episodes [10]. Recurrent CDI can be defined as recurrence of symptoms within 8-10 weeks after cessation of specific antibiotic therapy, with exclusion of other enteropathogens and a positive diagnostic test for CDI. A subset of patients with recurrent CDI get into a spiral with several subsequent recurrences. In these cases, *C. difficile* becomes the largest hurdle for recovery, it contributes to increased mortality and morbidity and leads to prolonged isolation measures and additional costs [11,12]. Relapses or reinfections occur due to prolonged disturbance of intestinal flora, persistence of spores, incapacity to mount specific antibodies against *C. difficile* toxin, or an immunocompromised state.

**Box 1**

**First recurrence**

- Mild to moderate infection: metronidazole at a dose of 500 mg orally three times daily for 10 to 14 days
- Severe infection or unresponsiveness to or intolerance of metronidazole: Vancomycin at a dose of 125 mg orally four times daily for 10 to 14 days

**Second recurrence**

Prolonged vancomycin orally in tapered and pulsed doses, for example: 125 mg four times daily for 14 days; 125 mg twice daily for seven days; 125 mg once daily for seven days; 125 mg once every two days for eight days (four doses); 125 mg once every three days for 15 days (five doses)

**Third recurrence**

Vancomycin at a dose of 125 mg orally four times daily for 14 days, combined with any of the other options for recurrent infection (not evidence based):
- Intravenous immunoglobulin at a dose of 400 mg per kg body weight once every three weeks, for a total of two or three doses depending on effect.
- Vancomycin, followed by rifampicin at a dose of 400 mg twice daily for 14 days
- Healthy donor faeces installation*

*We feel that there is at this point not enough evidence to recommend the optimal time to introduce the procedure.

Adapted from Kelly CP, LeMont JT. *Clostridium difficile*—more difficult than ever. N Engl J Med. 2008;359(18):1932-40 [9]; Copyright© 2008 Massachusetts Medical Society. All rights reserved.
state [13,14]. Few studies have addressed treatment strategies for recurrent CDI. In general practice, oral vancomycin is prescribed, with limited efficacy. Restoring intestinal flora has been historically thought of as a logical mechanism to repair the host-defense against CDI. Infusion of faeces from healthy donors in patients with severe antibiotic-associated colitis was first described in 1958 [15]. We summarise the treatment options for recurrent CDI and give an overview of literature reports about the use of donor faeces as unconventional therapy in patients with recurrent CDI.

### Treatment options for recurrent C. difficile infection

#### Antibiotic treatment

Vancomycin or metronidazole

Results of randomised clinical trials uniquely designed for treatment of recurrent CDI are lacking. Prospectively collected data can be derived from subgroup analysis of placebo-controlled studies comparing the combination of probiotics (or placebo) with oral vancomycin for treatment of CDI. Antibiotic treatment of a first recurrence in observational studies shows a success rate of 67%, both for metronidazole and vancomycin [16]. For additional recurrences, success rates as low as 35% are reported [10]. A subset of patients experience numerous recurrent episodes, and repeated antibiotic courses can be required for treatment of CDI, which may even persist for years [17]. Oral vancomycin is preferred for recurrent CDI because of the neurotoxic side effects of longstanding metronidazole therapy [18]. For a second recurrence, vancomycin taper and/or pulse schedules are commonly advised (Box 1) [19]. The aim of these interrupted regimens is to eradicate germinating C. difficile spores. In a stratified analysis including 136 patients with recurrent CDI derived from different study groups, tapered or pulsed therapy seemed with a recurrence rate of 14.3% more successful than a short course with vancomycin (recurrence rate 31%) [19].

#### Other antibiotic therapies

According to case reports and case series, rifamycin appeared effective for initial episodes of CDI. Rifamycin was also reported to be successful in 18 of 21 patients with recurrent CDI, in three different dosing regimens [20]. Of concern are reports about rifamycin-resistance of C. difficile after treatment failure [21,22] and the spreading of rifampicin–resistant C. difficile clones in hospitals with frequent use of rifamycins [23].

### Faecal therapy for recurrent C. difficile infections: overview of the literature

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients [male/female]</th>
<th>Mean age</th>
<th>No. of relapses</th>
<th>Entry diagnosis</th>
<th>Cured (%)</th>
<th>Follow-up</th>
<th>Donor related to recipient?</th>
<th>Prepared with whole bowel lavage</th>
<th>No. of faecal infusions</th>
<th>Amount of faeces</th>
<th>Route of installation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1958</td>
<td>4 (3/1)</td>
<td>56</td>
<td>*</td>
<td>PMC</td>
<td>4 (100)</td>
<td>10 days</td>
<td>Md</td>
<td>No</td>
<td>1-3</td>
<td>Md</td>
<td>0-4</td>
<td>[15]</td>
</tr>
<tr>
<td>1981</td>
<td>16 (7/9)</td>
<td>56</td>
<td>*</td>
<td>PMC</td>
<td>13 (81)</td>
<td>5 days-3 years</td>
<td>If possible</td>
<td>No</td>
<td>1-24</td>
<td>Md</td>
<td>1-15</td>
<td>[34]</td>
</tr>
<tr>
<td>1984</td>
<td>1 (0/1)</td>
<td>65</td>
<td>6</td>
<td>CDI</td>
<td>1 (100)</td>
<td>9 months</td>
<td>Spouse</td>
<td>No</td>
<td>2x2</td>
<td>Md</td>
<td>0-1</td>
<td>[35]</td>
</tr>
<tr>
<td>1989</td>
<td>2 (1/1)</td>
<td>60</td>
<td>3</td>
<td>CDI</td>
<td>1 (50)</td>
<td>6 months</td>
<td>Spouse/daughter</td>
<td>No</td>
<td>1</td>
<td>50 g</td>
<td>0-2</td>
<td>[36]</td>
</tr>
<tr>
<td>1991</td>
<td>1 (0/1)</td>
<td>64</td>
<td>7</td>
<td>CDI</td>
<td>1 (100)</td>
<td>3 days</td>
<td>Spouse</td>
<td>No</td>
<td>1</td>
<td>10 g</td>
<td>1-0</td>
<td>[37]</td>
</tr>
<tr>
<td>1994</td>
<td>7**</td>
<td>56</td>
<td>1-4</td>
<td>CDI</td>
<td>7 (100)</td>
<td>2 years</td>
<td>Spouse/relative</td>
<td>No</td>
<td>3</td>
<td>200 ml</td>
<td>0-7</td>
<td>[38]</td>
</tr>
<tr>
<td>1998</td>
<td>18**</td>
<td>Md</td>
<td>Md</td>
<td>CDI</td>
<td>15 (83)</td>
<td>Md</td>
<td>No</td>
<td>Md</td>
<td>1</td>
<td>Md</td>
<td>1-17</td>
<td>[39]</td>
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<tr>
<td>1999</td>
<td>32 (14/18)</td>
<td>27-89</td>
<td>Md</td>
<td>AAD</td>
<td>32 (100)</td>
<td>4-6 weeks</td>
<td>No</td>
<td>Md</td>
<td>1-2</td>
<td>5-10 g</td>
<td>0-32</td>
<td>[40]</td>
</tr>
<tr>
<td>2000</td>
<td>1 (0/1)</td>
<td>60</td>
<td>&gt;5</td>
<td>CDI</td>
<td>1 (100)</td>
<td>1-6 months</td>
<td>Spouse</td>
<td>Yes</td>
<td>1</td>
<td>500 ml</td>
<td>0-1</td>
<td>[41]</td>
</tr>
<tr>
<td>2002</td>
<td>6 (1/5)</td>
<td>53</td>
<td>2-6</td>
<td>CDI/PMC</td>
<td>6 (100)</td>
<td>9-50 months</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>30 ml</td>
<td>0-6</td>
<td>[42]</td>
</tr>
<tr>
<td>2003</td>
<td>18 (5/13)</td>
<td>73</td>
<td>2-7</td>
<td>CDI</td>
<td>15 (83)</td>
<td>90 days</td>
<td>15 yes/3 no</td>
<td>No</td>
<td>1</td>
<td>30 g</td>
<td>18-0</td>
<td>[43]</td>
</tr>
<tr>
<td>2003</td>
<td>24 (11/13)</td>
<td>19-59</td>
<td>Md</td>
<td>CDI</td>
<td>20 (83)</td>
<td>Nd</td>
<td>Related and non-related donors</td>
<td>Yes</td>
<td>1-10</td>
<td>200-300 g</td>
<td>8-16</td>
<td>[44]</td>
</tr>
<tr>
<td>2006</td>
<td>5 (0/5)</td>
<td>82</td>
<td>&gt;2</td>
<td>CDI</td>
<td>5 (100)</td>
<td>2.5-21 months</td>
<td>No</td>
<td>No</td>
<td>1</td>
<td>30 ml</td>
<td>0-5</td>
<td>[45]</td>
</tr>
<tr>
<td>2007</td>
<td>16 (5/11)</td>
<td>11-87</td>
<td>Md</td>
<td>CDI</td>
<td>15 (94)</td>
<td>4-6 weeks</td>
<td>Related and non-related donors</td>
<td>Yes</td>
<td>1-24</td>
<td>200-300 g</td>
<td>0-16</td>
<td>[46]</td>
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<tr>
<td>2008</td>
<td>7 (4/3)</td>
<td>67</td>
<td>3</td>
<td>CDI</td>
<td>7 (100)</td>
<td>30 days-1 year</td>
<td>6 yes/1 no</td>
<td>Yes</td>
<td>1</td>
<td>50-100 g</td>
<td>3-4</td>
<td>[47]</td>
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<tr>
<td>2008</td>
<td>1 (1/0)</td>
<td>69</td>
<td>1</td>
<td>CDI</td>
<td>1 (100)</td>
<td>2 days</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>45 g</td>
<td>0-1</td>
<td>[48]</td>
</tr>
<tr>
<td>159</td>
<td>14/159 (91)</td>
<td>144/159</td>
<td>(91)</td>
<td>Related and non-related donors</td>
<td>Yes</td>
<td>1</td>
<td>500 ml</td>
<td>0-1</td>
<td>[44]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AAD: antibiotic-associated diarrhoea; CDI: C. difficile-associated disease; GI: gastrointestinal tract; Md: missing data; Nd: not determined; PMC: pseudomembranous colitis

*unclear, since C. difficile at that time was not identified as the causative organism, so adequate antibiotics where not given.

** Sex unknown.

1 = Two patients treated with a faecal enema of which one failed. The failing patient and four others were treated with a new enema, consisting of a bacterial culture.
Teicoplanin (although not widely available and expensive) is another antibiotic with high reported efficacy against CDI, and limited data suggest that it may be effective in recurrent CDI [24,25]. A new and specific antibiotic against C. difficile is OPT-80 (PAR-101), which belongs to a new class of antibiotics, the macrocycles [26]. Data from a phase 3 study are awaited, and its role in recurrent disease is yet to be determined.

Non-antibiotic treatment modalities for recurrent CDI

Toxin targeted therapy
Binding of the pathogenic toxins (A and B) of C. difficile may contribute to clinical improvement and subsequent regression of CDI. However, toxin-targeted therapy (e.g. cholestyramine) has not been investigated for recurrent disease. Tolevaler, a non-antibiotic toxin-binding polymer appeared less successful for treatment of an initial episode of CDI than metronidazole or oral vancomycin [27]. Future studies should address the efficacy of combination regimens of tolevamer and antibiotics for treatment of (recurrent) CDI.

A whey product (mucomilk) isolated from cows inoculated with C. difficile and inactivated C. difficile toxin, containing high amounts of secretory IgA seems to prevent recurrence of CDI if given as adjuvant therapy in patients treated with metronidazole or vancomycin [28]. However, a randomised placebo-controlled study is lacking and the value for recurrent CDI is unknown. Vaccines containing formaldehyde-inactivated toxins A and B have been developed and some promising initial experience has been gained in a few patients with recurrent CDI [29].

Intravenous immunoglobulins
Intravenous administration of immunoglobulins (IVIG) can be considered a last resort for recurrent disease, in particular for patients with a suspected impaired immune response to C. difficile. Although case series suggest a beneficial effect of IVIG at a dose of 300-400 mg/kg body weight once every three weeks, a case control study did not show a reduction in recurrences [30,31].

Probiotics treatment for recurrent CDI
Several randomised trials have compared probiotics (containing Lactobacillus species or Saccharomyces) to placebo as an additional treatment to antibiotics in patients with CDI. Although the results are not uniformly negative, a recent Cochrane systematic review concludes that there is insufficient evidence to recommend the addition of probiotics to antibiotics in recurrent disease [32]. Furthermore, the occurrence of Saccharomyces fungaemia in patients treated with Saccharomyces strains merits attention [33].

Donor faeces infusion
In 1958, the surgeon Eiseman successfully treated four patients with severe antibiotic-induced colitis with an enema that consisted of donor faeces [15]. Following this initial publication, more than 150 patients with recurrent CDI have been described, the vast majority of whom was cured by the infusion of faeces. Recovery of normal intestinal flora was (and is) postulated to be the mechanism for cure.

Success rate of faecal therapy
Taken together, 91% of all reported patients with recurrent CDI treated with donor faeces (n=159, see Table 1) were cured after one or more infusions. Clinical improvement can be noticed within a few days following donor faeces infusion. Follow-up rates vary from one week to two years. Many patients had a reported follow-up of less than one month, which implies that definite success rates are often lacking.

Necessity of donor screening
Early reports on faecal installation only mention that donors who had used antibiotics in the preceding months were excluded [15]. Although transmission of infectious diseases has not been reported after faecal infusions, most publications from the past decade report extensive screening of donors [40,43]. Our protocol for screening of (healthy) donors is summarised in Table 2. Most donors are sought in relative proximity of the patient (partners, relatives, household members). However, there is no rationale to exclude healthy volunteers. Many reports fail to mention the exact origin of the donors and an investigation of patient preferences is lacking. We do not apply any restrictions concerning the food intake of donors prior to donation. Although there can be potential important differences in the quality of the microbiota present in donor faeces from different individuals, historically their intestinal flora has not been analysed prior to use for faecal infusion. Information is lacking with regard to the specific groups and amount of bacteria necessary for optimal restoration of intestinal flora, thereby preventing C. difficile to become clinically significant.

Route of instillation
Of the reported patients, 80% were given a faecal installation through enema or colonoscope, and 20% received the faeces through a nasogastric or nasoduodenal/jejunal tube [43]. From our own experience, infusing faeces through colonoscopy is more difficult and strenuous, whereas (slow) infusion through a nasoduodenal tube seems safe and time-efficient [47]. To our knowledge, no other authors have discussed their experiences with different routes of administration. A disadvantage of a nasoduodenal/jejunal tube is that donor faeces may be difficult to install if patients have signs of diminished passage of fluids through their intestines. On the other hand, infusing faeces using this route has the advantage that the infused flora reaches the whole bowel. In the reported cases, no specific side effects were reported related to installation of faeces in the upper or lower tract. With the limited numbers available it is not possible to predict which route of installation is more successful in curing patients from CDI.

Virtually all publications report diluting or homogenising the faeces in saline or water, prior to infusion either in the upper gastrointestinal tract through a tube, or in the colon through enema or colonoscopy. Gustafsson et al. report homogenising faeces in pasteurised cow’s milk [40]. Almost all faecal preparations are processed in a normal aerobic environment. Only Schwan et al. specifically describe preparing enemas in an anaerobic cabinet [35]. In several reports it is stated that faeces are processed and infused as quickly as possible following production by the donor, in order to preserve faecal flora. Due to lack of detailed data it is not possible to establish a relationship between a prolonged time that has passed between production and infusion, and failure of therapy.

Pre-treatment
Most early reports fail to mention antibiotic usage directly preceding the treatment. Aas et al. gave a protocolised antibiotic

Literature review and experiences with fecal infusions
Publications that contained original data (case reports, case series, uncontrolled studies) were selected in PubMed and Embase. From references and through Google, additional publications were collected. A total of 16 publications (two abstracts, 14 full publications) were found (Table 1).
regimen of 500 mg vancomycin orally four times a day during four days preceding faecal installation [43]. In addition to antibiotics, four publications describing 48 patients report pre-treatment with a laxative directly prior to donor faeces infusion [41,44,46,47]. Most publications do not report any other preparation, apart from Aas et al. who gave patients an oral proton pump inhibitor before intragastric installation of donor faeces [43].

We treat patients with 500 mg orally four times a day during four days and oral whole bowel lavage with a macrogol solution in an attempt to remove the pre-existent (pathological) flora and C. difficile spores prior to donor faeces installation. It is not known, however, whether this contributes to the efficacy of donor faeces infusion for recurrent CDI.

**Table 2**

<table>
<thead>
<tr>
<th>Screening of donors*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor</strong></td>
</tr>
<tr>
<td><strong>Parasitology</strong></td>
</tr>
<tr>
<td><strong>Microbiology</strong></td>
</tr>
<tr>
<td><strong>Virology</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Prior to screening of faeces and blood, potential donors have to fill in an extensive questionnaire. Donors with abnormal bowel motions, abdominal complaints, symptoms indicative of irritable bowel syndrome, an extensive travel history or predisposing factors for potentially transmittable diseases are excluded. If they are considered eligible after completing the questionnaire, they are screened using the protocol above.

**Figure**

Design of the FECAL trial

The FECAL trial

Oral vancomycin
500 mg qid, 14 days

Oral vancomycin
500 mg qid, 14 days

Bowel lavage 1x

Oral vancomycin
500 mg qid, 4 days

Bowel lavage 1x

Donor faeces 1x

Endpoints:
Diarrhoea (≥3 x/day) and C. difficile toxin on days 35 and 70.
Quality of life, days spent in isolation, days admitted to the hospital, attributable costs.
Psychological analysis of effect of faecal transplant.
Follow up 10 weeks, cross-over if failure in antibiotic group.

**Box 2**

Amsterdam protocol used for the preparation of donor faeces

1. Faeces are collected and weighed (ca. 60–120 g, depending on production);
2. 300–400 cm³ saline (6.9% NaCl) is added and mixed until a smooth suspension is created;
3. Faeces are poured through a double gauze and put in a glass bottle;
4. Within six hours after production by the donor, the faeces are installed through a nasojejunal tube.
third (experimental) arm consists of treatment with a suspension of faeces. Patients are pre-treated with vancomycin given orally for four days and a whole bowel lavage on the fourth day. In the period before randomisation and faecal infusion, treatment is often necessary to prevent spread and deterioration of the clinical condition. Furthermore, it is logistically difficult to give a faecal infusion directly after verifying the diagnosis. We believe it may be beneficial to prepare the bowel with a short course of vancomycin for the above mentioned reasons. In the protocol, a standardised preparation period of four days prior to the faecal infusion was chosen. On the fifth day, donor faeces (Box 2 and Table 2) are infused through a nasoduodenal tube. The nasoduodenal tube is placed radiologically or endoscopically. If there is any doubt regarding the position, an abdominal X-ray will be performed. Faeces are installed within six hours after production by the donor. After this treatment, all antibiotics are stopped. Patients will be followed for 10 weeks after randomisation by a weekly telephone assessment of diarrhoea and by C. difficile culture and toxin stool tests (ELISA) done four times, on days 14, 21, 35 and 70.

Outpatients from the Netherlands as well as from outside the Netherlands are eligible for the trial if they are willing to travel to Amsterdam for inclusion and donor faeces installation. Patients who fail in one of the antibiotic arms (i.e. the vancomycin arm or the arm which combines vancomycin with a whole bowel lavage) are offered a treatment with a faecal infusion following their proven failure.

**Conclusion**

Recurrent C. difficile infections are a growing burden and a therapeutic challenge for patients and physicians. Current therapy consists of repeated courses of antibiotics with limited success rates and new therapeutic options are urgently needed. Faecal installations from healthy donors for the treatment of recurrent CDI seem a promising approach, restoring a normal bowel flora and preventing further outgrowth of C. difficile and its spores. To date, more than 150 patients treated with donor faeces have been reported in the literature. A 91% success rate is reported in case series and case reports. Due to a lack of clinical trials, faecal installations often are offered only to patients with more than two relapses, since it is still considered a last, uncommon, and rather distasteful rescue therapy. Currently, adult patients with proven recurrent CDI can be included in the first randomised controlled study comparing donor faeces installation with antibiotic therapy (FECAL trial).

Competing Interest and funding

The FECAL trial is funded by a grant from ZonMW, the Netherlands Organisation for Health Research and Development.

**References**


