Struggling with recurrent Clostridium difficile infections: is donor faeces the solution?

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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 homoeostasis 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

Box 1

Treatment schedule for recurrent *C. difficile* infection

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 rifamycin 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, LaMont 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].

Table 1

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

Year	Patients (male/ female)	Mean age	No. of relapses	Entry diagnosis	Cured (%)	Follow-up	Donor related to recipient?	Prepared with whole bowel lavage	No of faecal infusions	Amount of faeces	Route of installation		Reference
											Upper GI	Lower GI	
1958	4 (3/1)	56	*	PMC	4 (100)	10 days	Md	No	1-3	Md	0	4 (e)	[15]
1981	16 (7/9)	56	*	PMC	13 (81)	5 days-3 years	If possible	No	1-24	Md	1	15	[34]
1984	1 (0/1)	65	6	CDI	1 (100)	9 months	Spouse	No	2x2	Md	0	1	[35]
1989	2 (1/1) i	60	3	CDI	1 (50)	6 months	Spouse/ daughter	No	1	50 g	0	2	[36]
1991	1 (0/1)	64	7	CDI	1 (100)	3 days	Spouse	No	1	10 g	1	0	[37]
1994	7**	56	1-4	CDI	7 (100)	2 years	Spouse/ relative	No	3	200 ml	0	7	[38]
1998	18**	Md	Md	CDI	15 (83)	Md	No	Md	1	Md	1	17	[39]
1999	32 (14/18)	27-89	Md	AAD	32 (100)	4-6 weeks	No	Md	1-2	5-10 g	0	32	[40]
2000	1 (0/1)	60	>5	CDI	1 (100)	1-6 months	Spouse	Yes	1	500 ml	0	1	[41]
2002	6 (1/5)	53	2-6	CDI/PMC	6 (100)	9-50 months	Yes	no	1	30 ml	0	6	[42]
2003	18 (5/13)	73	2-7	CDI	15 (83)	90 days	15 yes/3 no	No	1	30 g	18	0	[43]
2003	24 (11/13)	19-59	Md	CDI	20 (83)	Nd	Related and non-related donors	Yes	1-10	200-300 g	8	16	[44]
2006	5 (0/5)	82	>2	CDI	5 (100)	2,5-21 months	No	No	1	30 ml	0	5	[45]
2007	16 (5/11)	11-87	Md	CDI	15 (94)	4-6 weeks	Related and non-related donors	Yes	1-24	200-300 g	0	16	[46]
2008	7 (4/3)	67	3	CDI	7 (100)	30 days-1 year	6 yes/1 no	Yes	1-3	50-100 g	3	4	[47]
2008	1 (1/0)	69	1	CDI	1 (100)	2 days	Yes	No	1	45 g	0	1	[48]
	159				144/159 (91)						32	127	Total

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.
i = 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. Tolevamer, 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.

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).

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

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 pretreat 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

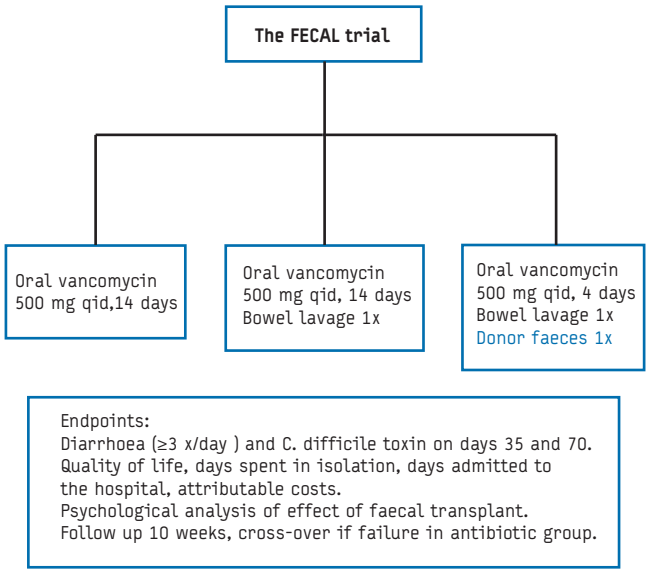
Screening of donors*

Donor	Faeces	Blood
Parasitology	Stool ova and parasites test ("Triple faeces test"[49] *Cryptosporidium* *Microsporidium*	*Strongyloides* *Entamoeba*
Microbiology	Faecal culture for common enteropathogens and *Clostridium difficile*	*Treponema pallidum*
Virology		Cytomegalovirus, Epstein-Barr virus, hepatitis A/B/C viruses Human immunodeficiency virus, human T-lymphotropic virus

*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



qid: four times a day.

Side effects or potential adverse effects

Side effects are absent or not mentioned in all but one study which mentions (transient) side effects such as a sore throat following placement of the nasoduodenal tube, rectal discomfort following colonoscopy, flatulence, nausea and bloating [46]. We did not notice side effects in our patients treated with donor faeces infusions [47]. A possible complication could be bacterial overgrowth in the small intestine after intragastric or duodenal installation of faeces. In patients who have signs of diminished intestinal passage, infusion of faeces via the upper gastrointestinal tract should be avoided.

Faecal therapy to Eliminate *Clostridium difficile*-Associated Longstanding diarrhoea: the FECAL trial

To investigate the efficacy of faecal installations for recurrent CDI, a randomised trial comparing donor faeces infusion to conventional antibiotic treatment with oral vancomycin has been initiated in 2008 in the Netherlands. The trial follows a pilot study in which seven consecutive patients with recurrent CDI were successfully treated with one or more infusions of donor faeces [47]. Patients (over 18 years of age) are eligible if they have a proven relapse of CDI and are able to give informed consent. They are excluded if they are severely immunocompromised, have a life expectancy of less than three months, are admitted to the intensive care unit, need vasopressive therapy or if they are using antibiotics other than for the treatment of *C. difficile* for a prolonged period of time. The primary endpoint is response to treatment at 10 weeks after initiation of therapy. Secondary endpoints are response at five weeks, time nursed in isolation, and quality-adjusted life-years.

Response is defined as: absence of diarrhoea (diarrhoea is defined as ≥3 loose or watery stools per day for at least two consecutive days or ≥8 loose or watery stools in 48 hours), or persisting diarrhoea (due to other causes) with repeating (three times) negative stool tests for toxins of *C. difficile*. Treatment failure is defined as persisting diarrhoea with a positive *C. difficile* toxin stool test.

Eligible patients who have signed informed consent are randomised to one of three different treatment arms (Figure).

The conventional treatment arm (the control arm) consists of 500 mg vancomycin, given orally four times a day, for 14 days. The second treatment arm consists of 500 mg vancomycin, given orally four times a day for 14 days, combined with a whole bowel lavage by drinking four litres of a macrogol solution, taken on day four or five after initiation of the antibiotics. This arm serves as a second control arm to assess the role of whole bowel lavage in the treatment of recurrent CDI [50], since patients randomised to donor faeces infusion are also pre-treated with a bowel lavage. The

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 (0.9% 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 (FECAI trial).

Competing interest and funding

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