Fecal transplantation as a treatment for recurrent Clostridium difficile infection: a follow-up on patients treated at the Infections clinic at Örebro University Hospital

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Abstract

**Background:** Clostridium Difficile is a common nosocomial pathogen and infection often occurs as a consequence of antibiotics administration. Standard treatment of oral metronidazole or oral vancomycin has a relapse rate of about 20%. After an initial relapse, the risk of relapsing again is about 45% and many patients develop a chronic relapse pattern. Fecal transplantation has been performed as an alternative treatment, aiming to restore the disrupted microbiota which plays a major role in the pathophysiology of the infection.

**Aim:** This was a follow-up on patients treated at the Infections clinic, where we evaluated the quality of their treatment with fecal transplantation.

**Materials and Method:** The patients had been treated at the infections clinic during the past four years. The patients received an enema with 30-200 ml of fresh stool mixed with 500 ml Saline solution. In this follow-up the patients were contacted via telephone and were asked to answer what their current state was and which effect the enema had had on their bowel habits. They were also asked if they had experienced any relapse of diarrhea after the enema, and if they had taken any course of antibiotics after the FT.

**Result:** Out of 21 patients treated, 14 took part in the follow-up. Out of these 14, 9 had a successful treatment and were cured at the follow-up. There were only two patients who had experienced a diagnosed relapse of infection after the FT. The remaining patients were categorized as unspecified.

**Discussion:** Our results, as well as other studies, show that FT as treatment for recurrent CDI is both simple and effective, with cure rates ranging from 60% to over 90%.
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Background

Bacteriology
Clostridium difficile (C. difficile) is an anaerobe, gram positive, rod-shaped bacterium, which can exist both in vegetative form as well as a spore. As a spore the bacterium can survive harsh environments and also treatment with antibiotics. [1,2] The main virulence factors of C. difficile are its toxins which it produces when in its vegetative state. These toxins are toxin A (TcdA) and toxin B (TcdB), which have a cytotoxic activity by altering the actin skeleton of epithelial cells, causing barrier disruption and apoptosis. Moreover the toxins cause an inflammation, which leads to additional tissue damage. [1-3] The tissue damage and inflammation is what causes the diarrhea associated with C. difficile. The bacterium is transmitted via the fecal-oral route and is one of the most common nosocomial pathogens. [4] Clostridium Difficile infection (CDI) is believed to occur due to antibiotic administration, which causes a disruption of the normal microbiota. However, it can also occur in healthy individuals without preceding antibiotics. [5] The most common antibiotics that cause CDI are florourquinolones, cephalosporins and clindamycin. [6]

Colonization resistance
The microbiota in the colon is a complex composition of more than 400 different species of anaerobe bacteria [7] which perform a number of different biological tasks, such as degradation and digestion of food, vitamin production, stimulation of the immune system and protection against exogenous pathogens. [8] For example, the microbiota limits the potential pathogens by production of antimicrobial factors, by competing for binding sites in the epithelium and also by having more efficient nutrient utilization. [6] This protection limits the concentration of potential pathogens in the colon, thereby protecting it from infection by exogenous bacteria. This is known as colonization resistance. [7] Antibiotic agents disrupt the normal microbiota in the colon, which may result in colonization and outgrowth of the potential pathogens including C. difficile. [6,7] Since the spore can survive antibiotics it can therefore after the disruption of antibiotics germinate back into its vegetative state. If the remaining microbiota cannot suppress C. difficile it proliferates and starts to produce toxins which then causes diarrhea. [9] The clinical presentation of CDI ranges from an asymptomatic carrier state to mild diarrhea, and further on to severe fulminant pseudomembranous colitis and toxic megacolon, which is associated with significant morbidity and mortality. [6] Typical symptoms of acute CDI are
watery diarrhea (≥3 unformed stool/24 h), anorexia, nausea and leukocytosis. Other symptoms of a severe episode of CDI also include acute renal failure and hypotension.

**Epidemiology**

The last decade the number of patients diagnosed with CDI has increased with 60% in Sweden. To investigate and keep track of the incidence of CDI in Sweden, a national databank was founded in 2009, to which laboratories can report their findings. In 2010 there were 5999 reported cases of CDI. Since then there has been an increase in the number of laboratories reporting to the data bank and now all 26 laboratories in Sweden that perform analysis for *C. difficile* report their finding to this databank. Because of this, there has been an increase in the number of reported cases; in 2012 the number of reported CDI was 10 820, meaning an incidence of 85/100 000. However, there was no increase in number of new diagnosed patients from 2011 and 2012, which was considered a positive trend. In the year 2012 more than half of the diagnosed were women (54%) with a median age of 74 years in women and 73 years in men. Moreover, in 2013 the number of diagnosed cases of CDI in Sweden was 9989 and out of these 7611 were new diagnosed cases.

**Normal treatment of CDI**

Diagnosis of CDI is based on clinical symptoms as well as microbiology such as detection of toxins and/or bacteria in stool, or via a colonoscopy showing pseudomembranous colitis. When the CDI is caused by a known antibiotic, the first treatment step is immediate termination of that antibiotic agent and, if possible, initiation of antibiotics against the CDI.

Different antibiotics are recommended depending on the severity of the disease. For an initial, non-severe disease the recommendation is oral metronidazole or oral vancomycin. For a severe CDI the recommendation is oral vancomycin or oral fidaxomicin. This is also the recommended treatment for a first recurrence or when a patient is at risk for recurrence. When a patient suffers from multiple recurrences the treatment recommendation is oral fidaxomicin or oral vancomycin, or oral vancomycin in a tapered or pulsatile regime.

**Recurrence of CDI**

The problem with treatment of CDI is its high recurrence rate. Recurrence is defined as when CDI reoccurs within 8 weeks after onset of the previous episode, and symptoms of the previous episode were completely resolved after the initial treatment. A recurrent CDI can either be a relapse of earlier infection or a reinfection with a new strain.
of bacteria.[6,14] The pathophysiology of recurrent CDI is still poorly understood, but it is believed that the disruption of normal microbiota due to vancomycin and metronidazole treatment facilitates the reinfection of C. Difficile, which in its spore state survives the antibiotics used to treat the initial infection. [5,15] Recurrence rate range is on average about 20% for patients treated for an initial infection, and there is no significant difference in recurrence rate between treatment with metronidazole or vancomycin. [5,16,17] Patients who experience an initial recurrence have later on a higher risk for another recurrence of CDI, with the risk being as high as 40% for another relapse. The risk for yet another relapse after this could be as much as 60%. [5] These patients often develop a chronic recurrent CDI which can persist for a long period of time. [19] In addition, there are several factors associated with increased risk of recurrent CDI, such as age >65 years, concomitant use of other antibiotics or if the patient has had a recurrence before. [14,20] Another risk factor for recurrent CDI is long hospital stays, because of the bacteria’s nosocomial spread. [4]

**Fecal Transplantation**

Fecal transplantation (FT) has been performed as a treatment for diarrhea since the 1950’s and has over the past 30 years become a more common treatment option for diarrhea.[6] There is no available standard protocol for how to perform the FT. Administrations routs vary from enemas, colonoscopy or infusion via nasojejunal tube, and all of these show successful results however, nasojejunal seem to be the least effective out of these. [21,22] The exact mechanism of FT is still unknown, however it is believed that the instillation of donated stool will provide the patient with enteric bacteria from the donor, thus restoring the microbiota in the patient that was disrupted by previous antibiotic treatment. [23,24] Studies have shown that there is a reduction in the diversity of bacterial species in patients with recurrent CDI, compared control groups as well as compared to patients with an initial CDI. Specifically, the patients with CDI had a reduction in Bacterioides and an increase in Proteobacteria. [24] Furthermore, other studies have shown that patients treated with FT have a different bacterial composition prior to the FT compared to the composition after the FT. The microbiota after the FT has shown to be the same as the donor’s microbiota. [25] Since there has been an increase in incidence of CDI and rate of recurrence is frequent, it is not surprising that there has been a search for an alternative treatment for recurrent CDI. Fecal transplantation is an alternative that shows great potential.
Two articles concerning FT in Sweden have been published during the past two years. Jorup-Rönström et al. treated 32 patients with fecal enemas (or by infusion via colonoscope) with stool donated from one single healthy donor. The stool had been donated in 1994 and re-cultivated every second week and stored at -70°C ever since. [26] This study showed a cure rate of 69%. Another recent Swedish study by Emanuelsson et al. investigated the effect of FT either as donated stool given as enemas, or as a mixture of Saline solution and individually cultured enteric bacteria given as enemas. [27] For the patients treated with donated stool the cure rate was 70% and for patients treated with cultivated enteric bacteria the cure rate was 88%. Other case reports and case studies show similar results with cure rates ranging from 73% to 94% [28-30]

A resent systematic review made by Gough et al., described the result of 317 patients treated over 27 case series and reports, and showed a cure rate of 92% for patients treated with fecal transplantation. 89% experienced recovery after one infusion. 4% of successfully treated patients experienced a relapse of diarrhea after the FT. [21]

Also, recently the first randomized study comparing fecal transplantation to a 14-day vancomycin treatment with or without bowl lavage was conducted by van Nood et al. in Amsterdam. [25] This study was performed on patients who already had suffered from earlier relapses, and showed a cure rate of 81% after an initial FT and a 94% cure rate following a second infusion for the patients not cured after the first infusion. By comparison the vancomycin only group showed a cure rate of 31% and in the vancomycin and bowl lavage group the cure rate was 23%. Hence, this study showed that FT is superior to both traditional vancomycin treatment, as well as superiority towards a treatment with vancomycin combined with bowl lavage.

To summarize, fecal transplant has in several reports shown great potential for treatment of recurrent CDI, with a high rate of resolution of diarrhea.

At Örebro University Hospital patients with recurrent may be treated with fecal transplantation if the standard treatment has not been successful. The aim of this follow-up was to evaluate the quality of treatment with fecal transplantation performed at the Infections clinic at Örebro University Hospital during the past five years.
Materials and Methods

Patient selection

The patients which took part in the follow-up were treated at the Infections clinic at Örebro University Hospital sometime between 2010 and 2014. At Örebro University Hospital patients from Örebro county as well as Uppsala County are treated with FT, since this procedure is not performed in Uppsala. Out of the patients contacted in this follow-up, 7 were patients from Uppsala County.

The data concerning which patients were treated with FT was obtained from the hospitals KVÅ-register, were patients treated with FT were registered. The original plan for this follow-up was to look at the patients treated during the past five years. However, there were no patients treated in 2009 and furthermore, before 2009 the journals were not digitized and this limited the selection of patients. Therefore the patients that were followed up were treated year 2010, 2012, 2013 and early 2014. There were no patients treated in 2011.

Six patients died in between their treatment and this follow up and their cause of death was followed-up to rule out CDI as cause of death.

As a result there were 15 patients, 3 men and 12 women with a mean age of 65 years (SD ±25), of which 14 took part in the follow-up.

Data abstraction and analysis

Data concerning time and number of enemas, as well as information about other chronic diseases, such as inflammatory bowel disease (IBD) and polymyalgia rheumatica (PMR) were obtained from the patients journals.

The patients included in the follow-up were contacted via telephone after receiving a letter informing them about the follow-up. When contacted, they were asked to answer what their current state was and the effect they had experienced from the enema. They were also asked if they had experienced any period of diarrhea since the FT, and lastly if they had taken any curse of antibiotics after the FT. If the patient had experienced diarrhea after the treatment they were asked if this was due to another CDI. If the patient had taken another course of antibiotics after the enema they were asked if this had any effect on their stool, and if so, if they experienced a relapse of CDI.

Out of the 15 patients, 14 were contacted via telephone. The remaining patient had a hearing disability, making it impossible to obtain the information via telephone and thus this patient was contacted by letter and was asked to answer the same questions in writing and later on send in the answers. However, this patient chose not to take part in the follow-up.
The result would either be failure to treatment, meaning no resolution of diarrhea or recurrence of CDI within 8 weeks after the enema or a successful treatment, meaning that the patient was cured of diarrhea without recurrence within 8 weeks following the enema.

After contacting the patients a third group was formed, with patients who had an unspecified treatment outcome. The patient who were categorized as unspecified were for example, patients who had suffered from diarrhea after the transplantation, but after an extra course of vancomycin were free from diarrhea, as well as patients who had successful treatment but at the time of the follow-up still had loose stools.

From the journals of the 6 patients who had died in the time between the treatment and the follow-up, data concerning cause of death was obtained. This was done to investigate if the patients died of CDI or of other causes.

**Fecal Transplantation protocol**

Before the patients received the FT they were asked to end their treatment with vancomycin or metronidazole at least 24 hours prior to the FT.

As premedication, the patients were given Loperamide and, if requested, Diazepam one hour before the FT.

Preferably the donors of stool were asked to be a family member of the patient, since that is the standard recommendation. [6]

The donor’s blood was tested for HIV, Hepatitis B and Hepatitis C. Thereafter the donor’s stool was screened for different pathogens including C. difficile.

Then the enema was prepared by mixing between 30-50 ml of fresh (i.e, used within 24 hours) donated stool with 500 ml Saline solution, in an ordinary kitchen mixer until the mixture was evenly thin. The protocol for the amount of stool used for the transplant was changed in December 2013, since using more stool caused the enema tube to be clogged.

Prior to this change, the amount of stool used ranged between 100 ml and 200 ml.

Thereafter the solution was filtered through gauze to remove any large particles which could have clogged the enema tube later on.

The enema was given via either a standard enema bag and tube or tube or via a Foley catheter.

As the enema was given, the patients were asked to lie on their left side and then remain in bed for at least one hour. After a while at bed rest the patients were asked to shift to lying on their backside and lastly lie on their right side, making sure the enema stayed within the bowl for as long as possible. Moreover, to prevent leakage an anal plug could be provided if needed.
**Ethics**

Since this was a follow-up ordered by the Infections clinic to improve the quality of their treatments, and the student who contacted the patients and took part of their journals worked as a representative of the clinic, no ethics approval was needed. Approval for the follow-up was granted by the clinic manager.
Results

Patient Data

From 2010 to early 2014 there were 21 patients treated with a fecal enema at the Infections clinic. Out of these 15 were alive at the time of the follow-up. Patient 3 was contacted via letter but did not respond, and was therefore excluded from the follow-up.

Out of the patients treated there were two patients with IBD (ulcerous colitis) where one of them in addition had primary sclerosing cholangitis and was liver-transplanted. Furthermore there were two patients with PMR, one of which in addition had hypothyroidism. Other comorbidities among the patients were hypertension (4 patients) and other heart conditions as well as diabetes. However out of 15 patients treated there were five patients without chronic illnesses. For a complete view of patient data, see table 1.

Table 1. Demographics

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Uppsala County</th>
<th>Gender</th>
<th>Age</th>
<th>Treatment</th>
<th>Chronic Illnesses</th>
<th>Number of enemas</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>female</td>
<td>51</td>
<td>2010-03-02</td>
<td>PMR</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>female</td>
<td>83</td>
<td>2010-11-25</td>
<td>PMR</td>
<td></td>
<td>2 (2010-11-25 &amp; 2010-12-16)</td>
</tr>
<tr>
<td>3</td>
<td>female</td>
<td>71</td>
<td>2010-11-30</td>
<td>Trigeminal neuralgia. Cardiovascular lesions in cerebellum &amp; brainstem. Hearing disability</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>female</td>
<td>65</td>
<td>2012-02-07</td>
<td>Hypertension, heart failure, atrial fibrillation, mitral valve insufficiency</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>female</td>
<td>21</td>
<td>2012-07-17</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>female</td>
<td>85</td>
<td>2012-11-27</td>
<td>Ulcerous colitis, primary sclerosing cholangitis. Liver transplanted</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>male</td>
<td>94</td>
<td>2012-12-10</td>
<td>Hypertension, chronic anemia</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>female</td>
<td>85</td>
<td>2012-12-18</td>
<td>Tetraplegia, atrioventricular block III</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>female</td>
<td>86</td>
<td>2013-12-11</td>
<td></td>
<td></td>
<td>1 (also in 2012)</td>
</tr>
<tr>
<td>11</td>
<td>female</td>
<td>67</td>
<td>2013-07-03</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>female</td>
<td>45</td>
<td>2013-04-09</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>male</td>
<td>32</td>
<td>2013-11-11</td>
<td>Ulcerous colitis</td>
<td></td>
<td>1 (also in 2009)</td>
</tr>
<tr>
<td>15</td>
<td>female</td>
<td>86</td>
<td>2014-03-18</td>
<td>PMR, hypothyroidism</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Number of enemas

Some patients received more than one FT as part of the same course of treatment. Three patients, number 2, 9 and 14, received two enemas with intervals varying from 5 days to 26
days. All three patients still had diarrhea after the initial enema. Also, there were two patients who had previously received FT; number 10, who was treated 2012 and then again in 2013, and number 13, who was treated in 2009 without effect, and was then treated later on in 2013.

Outcome
The immediate treatment outcome was categorized into three different groups; treatment success, meaning resolution of symptoms and no recurrence within 8 weeks and treatment failure, meaning no resolution of symptoms or relapse of CDI within 8 weeks after the treatment. However, due to unspecific answers from patients, there were also a third group; an unspecified group. Patients who were categorized as unspecified were the ones who still had loose stool to some extent, patients who had vancomycin treatment after the enema without diagnosed CDI, patients who suffered from a CDI but with uncertainty if this occurred within 8 weeks after the initial episode and patients who received two enemas and in between these received a course of vancomycin.

The treatment outcome for the follow-up was either cured from CDI, relapse of CDI or unspecified.

Immediate effect
Initially when the patients were contacted they were asked about the effect of the treatment when they received the enema. Out of the 14 patients contacted, 10 had a successful treatment immediately after the enema. The immediate success rate was therefore 71%.

There were three patients who were categorized as unspecified (21%), meaning the effect of the enema was not clear. Patient 6 experienced an improvement in her bowel habits, but still had some loose stools after the enema. Patient 13 experienced a resolution of symptoms after the enema; however he had a relapse of CDI soon after the FT after treatment for his IBD. Due to uncertainty if this occurred within 8 weeks after the initial episode, this caused the patient to be categorized as unspecified. Patient 14 received two enemas and between these a course of vancomycin. After this course and a second enema, the patient’s symptoms were resolved. However, if this was because of the vancomycin or the enema could not be distinguished.

Out of the 14 patients treated only one had a failure to treatment (7%). Patient 9 received two enemas and did not experience any effect at any of these at the time of the enema. (Table 2)
<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Treatment</th>
<th>Immediate effect</th>
<th>Effect today</th>
<th>Diarrhea after</th>
<th>Antibiotics after</th>
<th>Effect of Antibiots</th>
<th>Unspecified because</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>female</td>
<td>51</td>
<td>2010-03-02</td>
<td>Success</td>
<td>Cured</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>female</td>
<td>83</td>
<td>2010-11-25</td>
<td>Success</td>
<td>Unspecified</td>
<td>No</td>
<td>Yes (eczema)</td>
<td>None</td>
<td>Still loose stool</td>
</tr>
<tr>
<td>3</td>
<td>female</td>
<td>71</td>
<td>2010-11-30</td>
<td>Patient did not participate</td>
<td>in the follow-up</td>
<td>Yes (antibiotics)</td>
<td>Yes (Urinary tract infection) + vancomycin</td>
<td>Diarrhea due to AB. Vancomycin -&gt; resolution</td>
<td>Treated with vancomycin after enema. Diarrhea due to relapse?</td>
</tr>
<tr>
<td>4</td>
<td>female</td>
<td>65</td>
<td>2012-02-07</td>
<td>Success</td>
<td>Unspecified</td>
<td>Yes (antibiotics)</td>
<td>Yes (Urinary tract infection) + vancomycin</td>
<td>Diarrhea due to AB. Vancomycin -&gt; resolution</td>
<td>Treated with vancomycin after enema. Diarrhea due to relapse?</td>
</tr>
<tr>
<td>5</td>
<td>female</td>
<td>21</td>
<td>2012-07-17</td>
<td>Success</td>
<td>Cured</td>
<td>Yes (calici)</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>female</td>
<td>85</td>
<td>2012-11-27</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>male</td>
<td>94</td>
<td>2012-12-10</td>
<td>Success</td>
<td>Cured</td>
<td>Yes (transient)</td>
<td>No</td>
<td></td>
<td>Still loose stool</td>
</tr>
<tr>
<td>8</td>
<td>female</td>
<td>85</td>
<td>2012-12-18</td>
<td>Success</td>
<td>Cured</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>female</td>
<td>22</td>
<td>2013-11-28</td>
<td>Failure</td>
<td>Relapse</td>
<td>Yes (relapse)</td>
<td>Yes (vancomycin because relapse)</td>
<td>Vancomycin after enema, resolution. Now, no AB because of pregnancy. No symptoms at followup</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>female</td>
<td>86</td>
<td>2013-12-11</td>
<td>Success</td>
<td>Cured</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>female</td>
<td>67</td>
<td>2013-07-03</td>
<td>Success</td>
<td>Cured</td>
<td>Yes (antibiotics)</td>
<td>Yes (erysipelas)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>female</td>
<td>45</td>
<td>2013-04-09</td>
<td>Success</td>
<td>Cured</td>
<td>Yes (transient)</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>male</td>
<td>32</td>
<td>2013-11-11</td>
<td>Unspecified</td>
<td>Relapse</td>
<td>Yes (relapse)</td>
<td>Yes (vancomycin because relapse)</td>
<td>Resolution of symptoms due to vancomycin</td>
<td>Uncertain of recurrence or new infection</td>
</tr>
<tr>
<td>14</td>
<td>male</td>
<td>88</td>
<td>2014-03-13</td>
<td>Unspecified</td>
<td>Cured</td>
<td>No</td>
<td>Yes (vancomycin between enemas)</td>
<td></td>
<td>Enema+ vancomycin+ enema.</td>
</tr>
<tr>
<td>15</td>
<td>female</td>
<td>86</td>
<td>2014-03-18</td>
<td>Success</td>
<td>Cured</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Effect at follow-up**

Furthermore, the patients were asked to answer if the effect from the enema still was present. The time that had passed since the enema and the follow-up ranged between four years for patient 1 and three weeks for patient 14.

The patients were asked about if they had taken any course of antibiotics after the enemas, as well as they were asked if they had experienced any periods of diarrhea after the FT. If so, they were asked if the diarrhea was due to a relapse of CDI, due to use of antibiotics or because of other reasons.

The results showed that out of the 14 patient contacted, 6 patients had been treated with antibiotics after the enema.

Patient number 2 was treated with antibiotics, but this had no effect on the patient’s bowel habits. However, since the patient had loose stool at the time of the follow-up, she was placed in the unspecified group. Patient number 14 took a course of vancomycin between his two enemas. The second enema was successful and the patient has not taken any antibiotics afterwards. He was symptom-free at the time of the follow-up and was placed in the cured category.

Out of the 14, 4 patients had periods of diarrhea that was associated with use of antibiotics or relapse of CDI. Two patients (9 and 13) had a diagnosed relapse of CDI and received treatment with vancomycin for this. These two patients both suffered from ulcerous colitis and both were treated in late 2013. Patient 13 had a relapse of CDI after the FT and has since that been treated with vancomycin. Therefore he was categorized as relapsed. Patient number 9 did not receive any effect of her FT’s and continued to take vancomycin after her treatment, which caused her to be symptom free. At the time of the follow-up, the patient had stopped her treatment with vancomycin due to pregnancy and reported that she was without diarrhea so far. However, since she had no effect of the FT, she was placed in the relapsed category.

The other two patients (4 and 11) both experienced diarrhea after a course of antibiotics taken after the FT, however these were not proven to be relapse of CDI. One of these patients, number 4, took a course of vancomycin at the same time as antibiotics for a urinary tract infection, and continued to take vancomycin after the other antibiotics course had stopped. She experienced a resolution of diarrhea after this treatment and had by the time of the follow-up no symptoms. However, she was categorized as unspecified due to use of vancomycin. The other patient, number 11, had an episode of diarrhea when taking a course of antibiotics. However, the patient had a resolution of symptoms when the course was finished and had by the time of the follow-up no symptoms from her bowel. She was placed
in the cured category. Furthermore, there were 3 patients who reported periods of diarrhea that was not associated with C. Difficile or use of antibiotics. These periods were transient and when passed the patients returned to their prior state. Therefore, these patients were considered cured from their CDI.

There were 7 patients who reported no form of diarrhea after the treatment and these patients had ever since their treatment been cured from their CDI. Five of these patients were placed in the cured category and two were placed in the unspecified category due to loose stool.

At the time of the follow-up, two patients had suffered relapse of CDI (14%). Three patients were categorized as unspecified 21%. Therefore, the overall cure rate at the time of the follow-up as was 9 of 14 patients 64%.

**Patients who had deceased**

There were six patients who died before this follow-up was performed. From their journals data concerning cause of death was obtained. This was done to rule out the possibility of CDI or pseudomembranous colitis as a cause of death. Five of the six patients died from other causes than CDI. Patients 19 and 21 died when hospitalized for CDI or suspected CDI.

However, patient 19 tested negative for CDI and later on died of other causes. Patient 21 had positive test for CDI when hospitalized, but later on suffered from a sepsis, as well as having other medical conditions, making it difficult to rule out CDI as cause of death. (Table 3)

**Table 3. Deceased patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Uppsala County</th>
<th>Gender</th>
<th>Age (death)</th>
<th>Time for enema</th>
<th>Cause of Death</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>female</td>
<td>90</td>
<td>2011</td>
<td>Dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>female</td>
<td>74</td>
<td>2012</td>
<td>Other than CDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 X</td>
<td>male</td>
<td>90</td>
<td>2012</td>
<td>Cerebral hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>female</td>
<td>69</td>
<td>2012</td>
<td>Liverfailure, renal failure</td>
<td>Hospitalized for suspected CDI, however tests were negative</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>female</td>
<td>85</td>
<td>2013</td>
<td>Other than CDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>male</td>
<td>70</td>
<td>2013</td>
<td>Sepsis, hypothermia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Discussion

This follow-up was done to investigate the quality of treatment with a fecal transplant for recurrent CDI. The patients who were treated had all suffered at least one relapse of CDI, due to failure of standard treatment with metronidazole or vancomycin. The main problem in treating CDI is the high rate of recurrence and for some of these patients the infection can become chronic. [19] Treatment with FT is believed to restore the patient’s disrupted microbiota, which plays a major role in the pathophysiology of CDI. [6]

Earlier studies on FT have shown a high cure rate when it comes to treatment of recurrent CDI. A recent systematic review showed a cure rate of 92% when treating recurrent CDI with a FT. [21] The first randomized trial comparing FT to ordinary vancomycin treatment as well as to treatment with both vancomycin and bowel lavage was recently performed in the Netherlands.[25] This study showed a cure rate of 94% for FT and a cure rate of 31% for ordinary vancomycin treatment. However, the patients in the trial had already suffered from several relapses, making the outcome for treatment with vancomycin lower than one would expect if the CDI had not been a recurrent one. [5,25] Recently a Swedish retrospective follow-up on patients treated with fecal transplant, as well as patients treated with infusion with cultivated enteric bacteria was published. [27] For patients treated with FT the cure rate was 70 % and for patients treated with enteric bacteria the cure rate was 88%.

In our follow-up, the immediate treatment outcome would either be success, failure or unspecified. At the time of the follow-up the patients would be categorized as cured, relapsed or unspecified. Our results showed a cure rate of 64% as well as a treatment failure of 14% by the time of the follow-up. Our cure rate was slightly lower than other studies have reported. However, there are several factors affecting the outcome of this follow-up. Firstly, not all patients who were contacted took part in the follow-up, making the population smaller than it could have been.

Factors that could have been investigated more are administration routes, number of enemas, as well as treatment routines. Three patients in this follow-up received two enemas and a question that remains is if the patients with an unspecified treatment outcome would have benefited from an additional enema. The treatment routines changed for the patients treated after 2013. They received less stool in their transplant than the patients treated before them. However, this did not seem to change the outcome of treatment, since both patients treated in 2014 were cured by the time of the follow-up.
Also, there could have been a different outcome categorization for the patients. The basis for the result was the patients’ own words regarding their bowel habits and we categorized this as either cured or not cured. We defined cure as no CDI or loose stool after the enema, and this caused patients without CDI who still were not entirely recovered to fall out of the cured category. These patients were categorized as unspecified; however, there could have been another way to present the outcome, since these patients still had experienced an improvement from the treatment. If this would have been reported in the follow-up, the outcome would possibly have been different.

Moreover, the patients who reported loose stools by the time of the follow-up could have been tested to make sure it was not a relapse of CDI. These patients were categorized as unspecified since a relapse could not be verified. More accurate investigation would have affected the treatment outcome.

The main weakness of this follow-up was the number of patients contacted. There were only 14 patients who participated in the follow-up, and there could have been more patients investigated had the follow-up stretched further back than 2010.

There are still other questions remaining regarding FT as treatment for recurrent CDI. For example; there are not always donors available for the patients which can be problematic. This could be solved by offering FT’s with cultivated enteric bacteria instead of donated stool. This has been done before and shows good results, with a cure rate at approximately 88%. [27] This could therefore be an option when a donor is not available.

Furthermore, there is an uncertainty towards when it is indicated to do a fecal transplantation. It is recommended when standard treatment fails, and numerous relapses have occurred. The question which remains is if a FT should be performed earlier in treatment, due to the fact that further use of antibiotics like vancomycin or metronidazole disrupts the microbiota even more. This makes the risk for a relapse even higher. [5] The question whether an earlier FT could break the cycle of recurrent CDI remains.

**Conclusion**

Out of the patients treated at the Infections clinic at Örebro University Hospital during the past four years, a retrospective cure rate of 64% was seen in this follow-up. As this follow-up, as well as other studies published earlier, show fecal transplant is a simple and efficient treatment for recurrent Clostridium difficile infection when standard treatment with vancomycin, metronidazole or fidaxomicin has failed.
References


10. Andersson B. Markant ökning av Clostridium Difficile - en av de vanligaste sjukhusbakterierna [Marked increase of Clostridium Difficile-one of the most common hospital bacteria] (In Swedish). Läkartidningen 2009;6(2009-02-03).


