Ulster Med J 2017;**86(2):**108-110

Case Report

Faecal Microbiota Transplantation for Clostridium Difficile – a local perspective

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Accepted: 18th August 2016
Provenance: externally peer-reviewed.

ABSTRACT:

Clostridium Difficile represents one of the major challenges of the antimicrobial era with associated significant morbidity. Treatment options are limited to a number of specific antibiotics with significant failure rates. Faecal Microbiota Transplantation has been recognised as a possible treatment option when standard therapy fails.

We report a local case of Clostridium Difficile Infection ultimately requiring Faecal Microbiota Transplantation with good success. While no formal service providing the treatment is available within Northern Ireland it is a feasible treatment option for Clostridium Difficile Infection.

INTRODUCTION:

Clostridium Difficile (CD) is an anaerobic, gram-positive spore-forming bacillus. It can be identified in the bowel flora of 3% of the healthy adult UK population[1]. When the normal balance of bowel flora is altered, CD can precipitate life threatening inflammation of the intestine by the nature of the toxin produced by the bacteria. Antibiotic usage has been identified as a potent trigger for Clostridium Difficile Infection (CDI) disrupting the natural balance of gut flora.

CDI is defined as diarrhoea with a positive stool test for CD toxin. The clinical spectrum of CDI can vary from asymptomatic carriage to life threatening disease. Populations at particular risk include children under 2 years of age, patients over 65 years of age or immunocompromised patients[1]. The clinical impact of CDI is significant as evidenced by the outbreak in 2007-8 within hospitals in Northern Ireland[2].

CDI is on the decline in the UK as a result of appropriate antibiotic protocols[1]. While standard antibiotic therapies, including metronidazole and vancomycin, are used successfully in the majority of cases a significant number of patients developed resistant infection. Despite initially successful treatment, recurrence of CDI occurs in 15-20% of patients[3]**.** In these situations, there is growing recognition that Faecal Microbiota Transplant (FMT) is a viable alternative option.

CASE:

A 77-year-old lady female was admitted to the general medical take at Craigavon Area Hospital following a fall which was attributed to a catheter associated urinary infection. She had an extensive medical history including rheumatoid arthritis (on long term steroids), chronic kidney disease (Stage III), bilateral total hip replacements, hypertension and diverticulosis. Previously, in 2008, she had developed CDI which was successfully treated with oral metronidazole and vancomycin. Her health issues, prior to admission, related to recurrent catheter related infections, with various antibiotic regimes used in the community. She lived independently in a fold, mobilising with a rollator.

The initial working diagnosis was presumed catheter associated urinary sepsis. Initial antibiotic therapy was Tazocin and then Gentamicin – subsequent urine culture was negative. On further review it became apparent that diarrhoea (Bristol Stool chart – type 7) was present prior to admission. Testing of stool samples revealed CDI. Enzyme immunoassay testing identified Glutamate Dehydrogenase (GDH) and Toxin A/B positivity with polymerase chain reaction confirming presence of toxigenic CDI.

Appropriate infection control measures were established while Tazocin and Gentamicin were stopped. Assessment of severity indicated severe disease with on-going pyrexia and constitutional upset. Computed tomography (CT) of the chest, abdomen and pelvis showed significant mural thickening of the caecum and ascending colon.

Subsequent antimicrobial therapy was coordinated with regular microbiology input. As per local trust policy, Metronidazole (500mg 8-hourly) and Vancomycin (125mg 6-hourly) were initially commenced. However by day 8, with on-going diarrhoea and pyrexia, there was felt to be no meaningful response. Fidoximicin (200mg 12-hourly) was commenced while IV Immunoglobulin 400mg/kg was administered as well. With ongoing symptoms Rifampicin (300mg 12-hourly) was

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later added and a second dose of IV Immunoglobulin 400mg/kg was administered. The patient received a total of 12 days of Fidoximicin with 8 days of Rifampicin.

By this stage, clinical assessment indicated on-going active infection with persistent abdominal distension and diarrhoea. The patient's nutritional state was declining due to systemic illness and reduced oral intake. Following multidisciplinary discussion consideration was given towards FMT. As there is no current provision for this treatment option in Northern Ireland it was facilitated through a service based at Ysbyty Gwynedd Hospital, Bangor, North Wales with the patient requiring transfer by the air ambulance service. Antibiotics were stopped for 24 hours prior to FMT which was performed via naso-jejunal approach. After observation for 2 days the patient returned to Northern Ireland for further care.

After a number of days the patient's bowel habit returned to normal with resolution of abdominal distension. Her oral intake gradually improved with markers of nutritional status showing improvement. The patient required transfer to a rehabilitation unit for further multi-disciplinary input prior to discharge home. There has been no recurrence of CDI to date.

DISCUSSION:

FMT was first described in the 1950s as a possible treatment option for pseudomembranous colitis. The process involves the transfer of faecal material (approximately 30-50g) from the intestinal tract of a healthy donor. Possible routes of administration to the recipient include naso-jejunal tube, colonoscopy or rectal enema. The desired aim is restoration of the normal microbiota flora within the recipient's intestinal tract. While the exact mechanism is unclear, the restored microbiota suppresses Clostridium Difficile colonisation and promotes an immunological response, facilitating eradication of the CD[3].

While standard therapies for CDI, including metrondiazole and vancomycin, are successful in most cases they have a deleterious effect on the post infection microbiota characterised by lower-than-expected diversity of the subsequent microbiota. This has the effect of reducing resistance to repeat colonisation by CD explaining the 15-20% risk of reinfection after the first episode of CDI[4].

In recent years FMT has been increasingly recognised as a viable alternative treatment option for CDI. A recent meta-analysis of non-randomised observational data reported resolution rates of 245 out 273 patients - resolution rate 89.1% (95% CI 84.0% to 93.3%; 11 studies)[3]. Commonly reported side effects related to FMT include transient diarrhoea and abdominal pain relating to colonic irritation lasting less than 48hour[5]. A case series in immunocompromised patients reported a 14% risk of flare of inflammatory bowel disease in patients previously diagnosed with the disease receiving FMT for CDI[6]. Long term complications after altering the gut microbiota with FMT is unknown with long-term follow-up studies required. One case report indicated unintentional weight gain in a recipient after receiving donor faeces from patient with obesity[7].

Within the UK a number of specialist centres now offer FMT as a treatment option for treatment resistant or recurrent CDI although no such option is available in Northern Ireland. NICE guidance from 2014 recommend FMT be reserved for treatment of CDI that is either recurrent or resistant to standard antimicrobial therapy.[5]

Faecal donors are usually selected from a banked donor stool system. Screening of stool samples is under taken, including CD toxin and enteric pathogens including Salmonella, Campylobacter, Giardia, Norovirus and Cryptosoridium. Screening serology tests comprise HIV, HTLV, Hepatitis A/B/C/E, syphilis and strongyloides.[8] Exclusion criteria for donors include gastrointestinal disease (such as inflammatory bowel syndrome, irritable bowel disease, gastrointestinal malignancy or active diarrhoea), immunosuppression, recent antibiotic use (within 3 months) and obesity (BMI>30).[8] Donor faeces can be administered fresh or stored in frozen formulation for later use[1]. Prior to performing FMT, it is recommended antibiotics should be stopped for 24 hours.

Proposed indications for FMT include the following[9]

1) Recurrent or relapsing CDI (A. at least 3 of episodes Mild/moderate CDI and failure of 6-8 week trial of vancomycin or B. 2 episodes of severe CDI requiring hospitalisation),

2) Moderate CDI not responding to standard therapy after 1 week,

3) Severe CDI with no response to treatment after 48hours

A number of obstacles exist in relation to FMT which includes the following[10]. Recruitment of donors and screening of donor faeces entail certain costs particularly for storage and transport of material. Infection control issues particularly in the endoscopy suite are obvious practical concerns. Concerns regarding risk of transmission of viral or bacterial infections potentially missed during screening. The aesthetic nature of the procedure is a significant consideration of patients. Cost-effectiveness studies have not been performed.

There is growing interest in what role FMT may play in other conditions particularly Inflammatory Bowel Disease (IBD)[11]. Research is also looking at how processing of donor faeces could affect outcomes and address safety concerns. Route and form of administration may also evolve with time particularly in relation to encapsulated oral administration.

Currently FMT would not be seen as a standard treatment option for CDI in Northern Ireland. However the growing evidence base suggests it is becoming a more viable option. Certainly in this case it proved invaluable. How the utilisation of FMT changes over time will be interesting to watch.

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