Review

Faecal microbiota transplantation should replace antibiotic treatment of recurrent *Clostridioides difficile* infection

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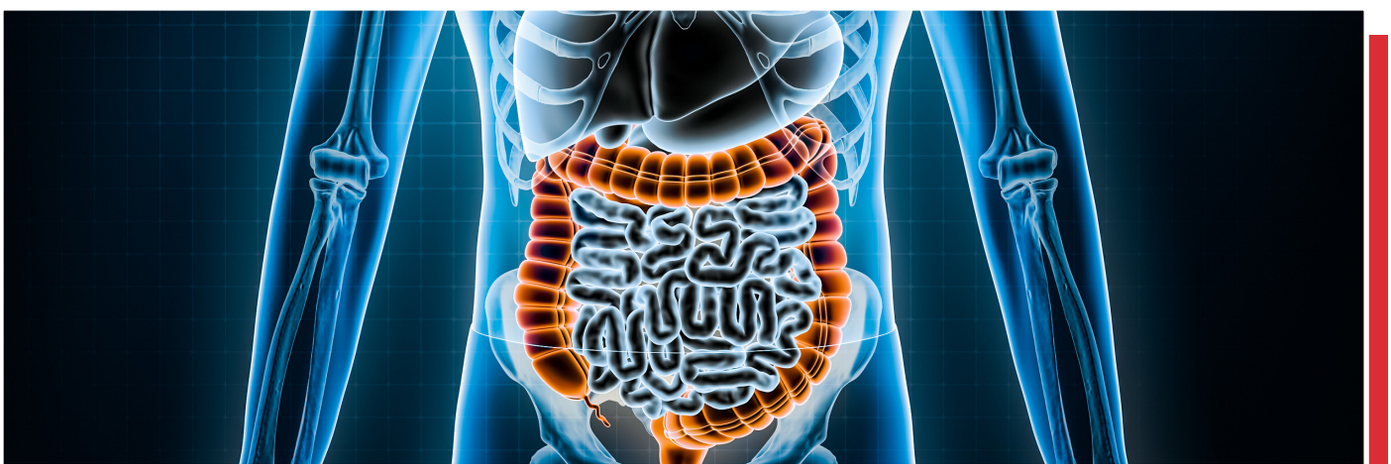

Abstract

Clostridioides difficile infection is a common cause of antibiotic associated diarrhoea in healthcare settings. It is a highly transmissible infection and there is growing concern about its resistance to antibiotics. Faecal microbiota transplantation (FMT) is only offered as a last resort for those with recurrent infections. FMT has been shown to have a high success rate in treating recurrent *C. difficile* infections and there is evidence to suggest that it is also more cost-effective than using antibiotics. There are advancements on how we can deliver FMT in healthcare with research into frozen capsules. There are some concerns around safety and standardisation of FMT but with the growing research surrounding our gut microbiota we can understand how to optimise this treatment method. This article aims to establish the potential use of FMT to treat recurrent *C. difficile* as a first-line treatment instead of antibiotics and how future research could optimise the delivery of FMT.

Abbreviations

CDI – Clostridioides difficile infection
cFMT – capsule based faecal microbiota transplantation
FMT – faecal microbiota transplantation
NICE – National Institute for Health and Care Excellence
rCDI – recurrent Clostridioides difficile infection

Introduction

Clostridioides difficile is a Gram positive, spore-forming anaerobe that is a common cause of antibiotic associated diarrhoea in both healthcare settings and the community. *C. difficile* has both non-toxigenic strains and toxigenic strains where only the latter causes disease.[1] In healthy individuals the gut microbiota exists in a delicate balance and is thought to protect against *C. difficile* infection (CDI). The microbiota is comprised of many types of microorganisms that have co-evolved with the host to be mutually beneficial. The composition of microorganisms is determined by many factors such as diet and antibiotic use. Antibiotics can cause dysbiosis of the gut microbiota and this is why there is a strong association between antibiotic use and CDI.

In the environment, *C. difficile* exists in spore form where it can survive most environmental insults and is resistant to many disinfectants. The spores can persist on surfaces for up to 12 months making it very difficult to eradicate them[2] thus leading to relatively easy transmission to other patients. Once ingested, the spores reach the jejunum where they will begin to germinate due to the high concentration of bile, before passing into the caecum where they can become metabolically active.[2] When metabolically active, if a toxigenic strain is present, this is where they will begin to produce their toxins which will disrupt the epithelial barrier and cause diarrhoea. In the healthy gut, the microbiota can protect against colonisation and growth of *C. difficile* by metabolising bile salts. However, when antibiotics have disrupted this microbiota the bile salts can increase in concentration creating a favourable environment for *C. difficile* to proliferate.[2] CDI can range from mild disease through to causing life-threatening conditions such as pseudomembranous colitis, sepsis and in some cases, this can lead to death.[3]

CDI is a notifiable disease in the UK with all toxin positive samples needing to be reported for any patient over the age of two years.[4] In the financial year 2021/22 Public Health England reported 14,249 cases both in healthcare and community settings.[5] These case rates have remained relatively stable in the UK and a similar pattern has also been seen across Europe. This is thought to be as a result of *C. difficile* infection control, detection and surveillance guidelines introduced by the World Health Organization in 2010.[6] The current National

Institute for Health and Care Excellence (NICE) guidelines outline that the first line of treatment is vancomycin, which can be progressed to fidaxomicin if treatment is unsuccessful. For life-threatening cases vancomycin can be given in combination with metronidazole.[7]

Emerging antibiotic resistance is a cause for concern in healthcare and there is reported non-susceptibility to first line antibiotics for *C. difficile*. Research into resistance to antibiotics is vital and a meta-analysis conducted in 2020 found that only 1% of *C. difficile* isolates were resistant to vancomycin and metronidazole.[8] However, another meta-analysis in 2022 found that the average resistance of *C. difficile* isolates to vancomycin and metronidazole in hospitalised patients worldwide were 3% and 5%, respectively.[9] Although only small, this increase in resistance over a two-year period is a cause for concern. *C. difficile* is currently being referred to as being non-susceptible to vancomycin, which under the European Committee for the Study of Antimicrobial Susceptibility definitions would put it into the intermediate category. This means that the bacteria can be inhibited but may require higher doses of antibiotic and the therapeutic effect is uncertain. Resistance is defined as when there is a high chance of therapeutic failure.[10] Resistance to vancomycin for vancomycin resistant enterococci was determined to be at 32µg/ml of the antibiotic.[11] *C. difficile* isolates from infected patients have been found to be non-susceptible to vancomycin at a concentration of 32µg/ml[11] leading to concern of possible resistance despite mechanisms yet to be known. In addition to this, both vancomycin and metronidazole are only effective against the germinated, metabolically active *C. difficile* as they target cell wall synthesis and DNA, respectively.[2] This therefore could be contributing to the significant percentage of patients that will suffer from recurrent infections because spores are remaining and these may eventually germinate.

A recurrence is defined by NICE as having a CDI infection more than 12 weeks after symptoms have resolved and a relapse is as an episode within 12 weeks of symptom resolution.[7] However, amongst the literature, recurrent CDI (rCDI) is typically defined as a relapse of the previous infection by the same strain or reinfection by a different strain within 8 weeks.[12] This could indicate the need for a potential review of NICE guidelines definitions which will ultimately alter patient treatment pathways. This is because despite research highlighting the importance of a healthy gut microbiota in helping to prevent the growth of *C. difficile*, faecal microbiota transplants to restore the patient's microbiota are not recommended unless a patient is having a recurrent episode and have already had two or more previous episodes.[13] It has been found that 35% of patients experience rCDI6 and that once you have one recurrence, the risk of further recurrences increases.[12] It is therefore not only important to try and successfully treat a first CDI but also prevent rCDI to improve patient outcomes.

It is already widely understood in the literature the importance of the healthy gut microbiome in protecting against CDI and hence the use of faecal microbiota transplantation (FMT) in some cases of rCDI. FMT involves collection of faeces from a healthy donor with no history of malignant or autoimmune diseases and is screened for infectious pathogens. The sample is then prepared by mixing with water or saline and can then be administered to the patient in a variety of methods.[14] Currently the most popular methods of administration are via nasogastric tube or colonoscopy. In one study of 16 patients, duodenal infusion via a nasogastric tube was found to resolve a rCDI in 81% of patients after the first infusion. Of those needing a second infusion only one person still showed symptoms.[15] This was a huge success compared with the standard vancomycin regimen only resolving 31% of the rCDI cases in this study.[15] Most studies are done on a small number of cases but when these studies are combined the overall success rate of FMT for resolving rCDI is about 90%.[14] It should therefore be considered as an earlier treatment option rather than waiting for antibiotic therapy to fail three times.

In addition to the evidence showing FMT is more efficacious than antibiotic therapy. Its cost-effectiveness has also been evaluated and the results are promising. It has shown that treatment with vancomycin could cost £17,279 per patient whilst FMT via nasogastric tube costs £8877 per patient and colonoscopy £11,716 per patient.[16] This suggests that by switching from antibiotics to FMT the NHS would not only improve patient recovery outcomes but also save a huge sum of money.

Evidence for FMT for treating rCDI is growing and in future could replace treatment with antibiotics but it is important to address the challenges of FMT as a treatment. One such challenge is clinical practicality as stool samples delivered via colonoscopy or nasogastric tube have to be fresh[2] and these procedures are invasive for the patient. A method that is currently being tested to improve administration is capsule based FMT (cFMT) where the donor stool is frozen or freeze dried into a capsule that is swallowed as a pill.[17] A meta-analysis comparing the efficacy of FMT delivered by different routes found that the cure rate of rCDI via frozen capsules was 92.1% which was not significantly different to the cure rate via colonoscopy.[18] These findings are promising for a more practical delivery and there have been suggestions that this could even be used in an outpatient setting to treat rCDI due to the ease of administration.[17] This in turn would reduce the need for hospitalisation and free up bed space and resources which would have been otherwise used for the invasive FMT treatments. Furthermore, cFMT would be equally as practical as antibiotic therapy if not more practical as vancomycin is administered orally and if metronidazole is given this requires intravenous administration.[7]

The adverse effects from FMT are not well evaluated but the most common is abdominal pain.[19] A systematic review found that this was more common when FMT was delivered via the upper gastrointestinal tract e.g. nasogastric tube (29.9%) compared to delivery via the lower gastrointestinal tract e.g. colonoscopy or enema (13%).[19] Of the reported severe adverse effects, only one death was definitely caused by FMT due to aspiration during sedation for the colonoscopy.[19] This could be prevented by the less invasive method of cFMT as it avoids procedural complications[19] and other studies have found a low rate of adverse events which were not definitely attributed to cFMT.[20] The systematic review into adverse effects of FMT recognised that adverse effects such as abdominal pain and bloating are subjective and that other health conditions could impact on the reporting of such effects.[19] With further research into the use of FMT and cFMT adverse effects will become better classified and understood so that serious adverse events can be avoided.

Another major concern of FMT is that stool samples are not standardised and that there is a potential risk of transmission of pathogens. Screening of donors helps to minimise the risks by first conducting an interview about their medical history, drug use, infectious diseases and dietary habits. This is then followed up by blood and stool screening to check the health of the donor and for presence of any infectious pathogens including antibiotic resistant bacteria.[21] Despite thorough screening, there have been some reported pathogen infections following FMT,[12] so further research needs to be conducted to optimise the screening process to ensure safety for all recipients.

However, there is also an argument that FMT should not be standardised and should be treated in the same way as solid organ donation, where a donor should be matched to a recipient.[21] It has been suggested there could be 'super donors', who have a high microbial gut diversity and this has been linked to successful outcomes of FMT, compared to donors with a low microbial gut diversity.[22] In addition to this, research has found that the donor microbial content is more likely to establish in the recipient if they also have that species of bacteria within their microbiome. This led to the suggestion that success of FMT may also be based on compatibility between the donor and recipient microbiome.[23] The current evidence only comes from small-scale studies and so more evidence is needed in this but so far supports the idea that donor-recipient matching will contribute to FMT success and help standardise patient responses.

Overall, FMT is not only more successful at treating rCDI in comparison

to antibiotics but is also more cost-effective and should therefore be considered as a gold-standard treatment moving forward. The increasing antibiotic non-susceptibility and resistance poses a huge problem for the NHS in treating infections, yet FMT is not currently being utilised enough to stop rCDI due to failure of antibiotics. There are concerns with FMT's safety due to the invasive nature of delivery but with the development of the capsule delivery this could help reduce the number of adverse effects and improve patient experience. There should also be further research conducted into understanding FMT and the relationship between donor and recipient to maximise success rate and begin to standardise the therapy.

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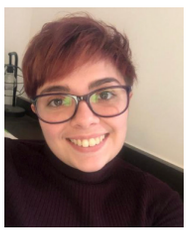

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I'm Niamh and I study medicine at Peninsula Medical School in Plymouth. I have a passion for microbiome research and antimicrobial resistance so this research put two of my favourite topics together. I look forward to one day being a part of delivering these new treatments to patients contributing to the fight against antimicrobial resistance.