

Review

## What Role does the Gastrointestinal Tract Microbiota Play in the Infection and Treatment of *Clostridium difficile*?

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### Abstract

*Clostridium difficile* is a spore-forming bacterium responsible for antibiotic-associated diarrhoea and *Clostridium difficile* infections at a great cost to the National Health Service. The human gastrointestinal tract microbiota provides a varied ecosystem supplying robust foundations for human health. In the past decade increased understanding of the gastrointestinal tract microbial makeup and its role in disease states, has prompted research endeavouring to assess the microbiota as a target for therapeutic intervention. One of the treatments widely researched within this field is Fecal Microbiota Transplantation, which is implemented with the curative aim of restoring this complex microbial eco-system.

### Introduction

Initially isolated from the stool of healthy neonates, *Clostridium difficile* is a gram-positive, spore-forming, obligate anaerobic bacillus [1]. Found within the mammalian gastrointestinal tract (GIT), it has the ability to create toxin-mediated *Clostridium difficile* infections (CDI), with symptoms ranging from mild diarrhoea to pseudomembranous colitis and death [2]. Data from the US and Europe has revealed that the incidence of CDI has surpassed that of MRSA, making it the most prevalent health-care associated infection [3]. Unfortunately, in 27% of CDI cases, current standard treatments, including metronidazole and vancomycin, do not effectively treat infection or prevent recurrence [4]. This is widely due to antibiotics triggering alterations and impairment to the human GIT microbiota [5]. Faecal microbiota transplant (FMT) is a highly cost-effective alternative therapy showing promise in the treatment of CDI [6]. This review aims to assess the contribution of the GIT microbiota in CDI and its treatment. This will be done by explaining the composition of the GIT microbiome, how this contributes to the germination of *Clostridium difficile* and evaluating the advantages and setbacks of implementing FMT on a wider scale.

### Methods

Literature was identified through searches on the electronic database PubMed, from 2010 to 2022. The key words searched

for included: '*Clostridium difficile*', 'CDI', 'GIT microbiota', 'faecal microbiota transplant', and 'FMT.' See figure 1 for the inclusion and exclusion criteria.

### Discussion

#### The gastrointestinal tract microbiota

The GIT microbiota is an exceptionally complex ecosystem, comprised of thousands of bacteria species. In healthy adults, this is dominated by the phyla Bacteroidetes and Firmicutes. These bacteria play a crucial role in host metabolism, nutrition function, maturation of the immune system and protection against pathogens. Various factors throughout a person's life influence the composition of their GIT microbiota, including: diet, geography, antibiotic use and disease [7]. Disturbance to the GIT microbiota, known as intestinal dysbiosis, can significantly impact the structure and function of its bacteria. Such changes to the indigenous microbial composition disrupt colonisation resistance, favouring infection, and germination of *Clostridium difficile* [8].

Susceptibility to CDI is strongly associated with antibiotic use, due to their influence on the GIT microbiota, with cephalosporins, penicillin and fluoroquinolones implicated [9]. Different studies have assessed such effects of antibiotics describing the microbial composition of patients with CDI, observing similar results in relation to a reduction in species richness. In

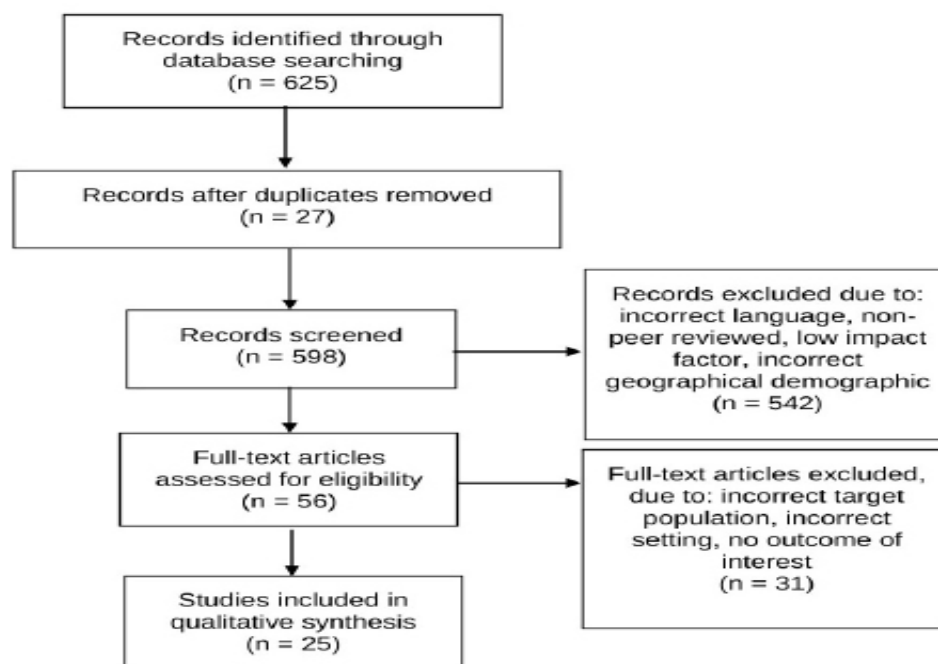


Figure 1. The inclusion and exclusion criteria for the literature selected

contrast to healthy controls, patients with CDI showed an increase in Firmicutes and Proteobacteria phyla and a decrease in Bacteroidetes phylum disrupting normal function of the microbiota. The data from these studies is highly significant, not only due to their similar reproducible results, but also because they are published in peer review journals with a high impact factor [10,11]

#### Bile-acid mediated germination

Bile-acids are the end products of cholesterol metabolism in the liver, they play a pivotal role in mediating *Clostridium difficile* spore germination [12]. In humans, there are two main primary bile-acids: cholic acid and chenodeoxycholic acid. The majority of cholic acid and chenodeoxycholic acid secreted into the gut is reabsorbed by the liver, however some bile-acids evade hepatic recirculation. These enter the large intestine where the microbiota act upon them, altering their composition [13]. In patients with an altered GIT microbiota the numbers of bacteria producing hydrolytic enzymes are reduced triggering a reduction in the secondary bile-acids responsible for the inhibition of vegetative cell growth. Simultaneously, the volume of cholic acid and chenodeoxycholic acid will dramatically rise, stimulating spore germination, resulting in CDI. Additionally, depletion of the GIT microbiota produces an excess supply of nutrients supporting germination of *Clostridium difficile* [7]. In two studies, administration of antibiotics resulted in a shift within the bile acid pool thereby increasing spore germination. Both studies utilised a Murine model, showing replicable results [14].

#### Conventional treatment of CDI

Currently, the mainstay in the treatment of CDI is oral metronidazole or vancomycin for 10-14 days, in the instance of mild or moderate disease, alongside cessation of the antibiotic

therapy which may have predisposed the patient to infection. In patients suffering with severe CDI, oral vancomycin ( $\pm$  IV metronidazole) or oral fidaxomicin are recommended. Between 20% and 30% of patients with CDI fail these initial treatments and of these up to 60% experience a second CDI [16]. The majority of recurrences arise due to the original strain rather than re-infection with an alternate strain [17]. However, resistance to vancomycin and metronidazole are not deemed a factor in recurrence, instead it is thought that these antibiotics contribute to a continued dysbiosis, disturbing the body's natural colonisation resistance [18]. Rising instance of health care associated infections in the United Kingdom are estimated to cost the National Health Service £1 billion annually [19], placing the trial and implementation of alternative treatments high on the agenda.

#### Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) involves the infusion of faecal suspension garnered from a healthy donor, with the curative aim of restoring a healthy gut microbiota in a patient with CDI [17]. The rationale underpinning this procedure is based upon re-establishing the specific commensal species within the GIT, depleted by antibiotic treatments. This will allow them to resume normal functioning, suppressing pathogen proliferation. In particular FMT aims to re-instate Butyrate-producing bacteria which are depleted in CDI. Butyrate - a short-chain fatty acid - is crucial in energy production, intestinal epithelial cell homeostasis, immune function and normal microbial growth. This is significant as recurrent CDI is strongly associated with a reduction in Butyrate-producing bacteria. Re-implanting strains of Butyrate-producing bacteria via FMT can restore normal microbial biodiversity and metabolic function. Furthermore, FMT significantly increases the amount of secondary bile acids, restoring short-chain fatty acid production leading to greater inhibition of

vegetative cell growth [20].

The optimum method of administration has not yet been determined. However, one pooled analysis indicated that use of gastroscopy, nasogastric tube, or nasojejunal tube are marginally less efficacious when compared with rectal tube/enema and colonoscopy. Colonoscopic application was shown to have a moderately greater curative effect than nasogastric application; however this was not statistically significant (93% vs 85%) [21].

FMT predominantly utilises stool samples from related donors or intimate partners and screening protocols are requisite for minimising infection transmission. Donor screening is extensive including a full patient history alongside the following lab tests: full blood count, liver function tests, screening for hepatitis A, B and C, human immunodeficiency virus I and II, human T-cell lymphotropic virus, Cytomegalovirus, Epstein-Barr virus, syphilis, stool tests for *Clostridium difficile* toxin A and B, stool microscopy for ova cysts and parasites and selective stool culture [17]. This is a time-consuming process, limiting availability of viable stool samples. However, a recent study demonstrated no substantial difference in the efficacy of CDI treatment via FMT when using fresh versus frozen samples or inpatient identified donors versus standardised banked faecal matter [11]. The use of oral frozen faecal capsules from bank donors in the treatment of CDI, has been trialled with substantial clinical efficacy and resolution of symptoms in 90% of cases. The use of such capsules will streamline the FMT procedure, rendering it more accessible and “palatable” for patients [17].

FMT is the only therapy utilised in the treatment of CDI that restores the biodiversity of the GIT microbiota without extending the perturbation of the normal microbial eco-system. Numerous studies have reinforced the safety and efficacy of FMT in the treatment of CDI, it is particularly advocated for in patients with recurrence of disease following conventional treatment [22]. Additionally, there is extensive research supporting the efficacy of FMT in severe CDI. One study suggested the implementation of FMT in moderate CDI not responding to vancomycin, for at least a week and severe CDI with no response to antibiotics after 48 hours [23].

Another measure of clinical effectiveness is Quality Adjusted Life Years (QALYs), a single figure accounting for the length and quality of life an intervention provides. The QALYs of FMT (0.242) versus conventional treatment (0.235) for CDI have been compared revealing FMT to be more cost-effective at \$1,699 compared with oral vancomycin at \$3,788. The QALY figures utilised in this review were directly sourced from studies and therefore results could reflect altered inputs and presumptions [6].

Despite mounting research supporting implementation of FMT in patients with CDI many clinicians remain concerned that the lack of “palatability” remains an evident barrier, deterring patients from the procedure. Nevertheless, patient acceptance does not seem to be a major factor prohibiting wider use of FMT, this was demonstrated in a small survey of 77 patients. These participants had all recently undergone colonoscopic FMT for recurrent CDI, 53% expressed that they would elect to undergo FMT as their preferred primary treatment in the case of future recurrence [24]. Whilst this survey presents evidence that public perception

of FMT may not impact upon the success of wider application of FMT, it provides insight into the views of a relatively small sample size. This limitation makes it difficult to determine if the outcome is a true reflection of the opinions of the public.

Furthermore, concerns have been raised over the efficacy and safety of performing FMT on patients who are immuno-compromised and are particularly at risk of CDI. While application within this patient group has been utilised, implementation has been limited due to worry due to theoretic potential for bacterial translocation and infection. Though the evidence base regarding the use of FMT in immuno-compromised patients is expanding no clinical trials exist to date. Nonetheless, current literature favours the use of FMT in immuno-compromised patients, with an acceptable adverse effect profile and negligible risk of adverse events [25].

## Conclusion

The GIT microbiota plays a crucial role in CDI making it a valuable target for therapeutic intervention. A healthy, heterogeneous microbial composition offers natural pathogen resistance and inhibition of spore germination aiding in the prevention of CDI. Succeeding antibiotic use, the GIT microbiota is depleted lacking variation, the loss of many secondary bile acids and Butyrate-producing bacteria contributes the ideal environment for *Clostridium difficile* colonisation, germination and infection. The conventional standard of treatment against CDI is ineffectual and often results in secondary infection due to continued dysbiosis. In addition, the burden of health care acquired infections on the National Health Service is rising and therefore finding an alternative treatment with high efficacy and low cost is paramount. FMT provides a promising, cost-effective, alternative therapy and is currently the only available intervention that restores the diversity and species richness of GIT microbiota allowing re-establishment of the patient’s natural colonisation resistance. The use of frozen faecal capsules will streamline this procedure, vastly increasing accessibility. While more research is needed to attain a greater understanding of public perception of these capsules, they offer promise due to their superior “palatability”. In addition, further research needs to be undertaken to assess the efficacy and safety of FMT and the frozen faecal capsules in patients who are immuno-compromised.

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