Fecal Microbiota Transplantation in Vulnerable Populations: An Up-and-Coming Treatment for *Clostridium difficile* Infections

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Abstract

Clostridium difficile infections are becoming increasingly difficult to treat as antibiotic resistant strains continue to evolve. As traditional methods of curing these infections become less effective, alternative treatment options are constantly being developed. One such treatment option is fecal microbiota transplantation (FMT), in which fecal matter from a healthy donor is transplanted into an infected patient to reintroduce a healthy gut microbiome. While this treatment has been proven effective in the majority of human populations, vulnerable patients—including children, immunocompromised patients, and patients with mental and physical disabilities—require special consideration before treatment with FMT. The purpose of this review article is to outline the benefits, risk factors, and ethical considerations involved in utilizing FMT in a variety of vulnerable populations.

Keywords: Clostridium difficile, fecal microbiota transplantation, gastrointestinal infections

OVERVIEW

Clostridium difficile (*C. diff*), is a microorganism that has been wreaking havoc in the medical community for many years. *C. diff's* resistance to antibiotics, resilience, and ease of transfer have made it a major concern for infection control, especially in hospital and group home settings. Over 500,000 people contract a *C. diff* infection (CDI) every year, and these infections are responsible for over 15,000 deaths annually. Its impact on gastrointestinal health is dramatic and can severely impact the patient's quality of life. From severe discomfort to death, the suffering caused by *C. diff* infections is a widespread issue with the potential to impact every human population, regardless of age (Bakker and Nieuwdorp, 2017).

C. diff is a gram positive, rod-shaped microbe that thrives in anaerobic environments such as the human gut (Figure 1). It has evenly distributed **peritrichous** flagella, making it highly motile. Additionally, *C. diff* is a sporulating microbe, meaning that it is able to

Peritrichous: uniformly distributed.

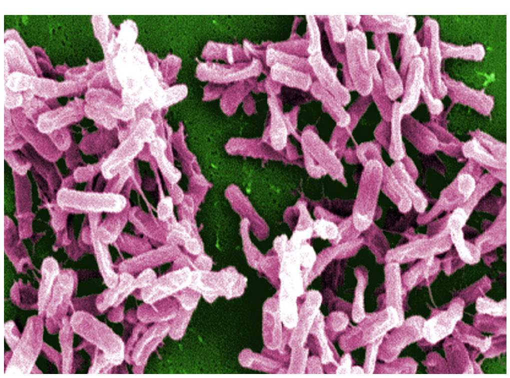

Figure 1: Micrograph showing Clostridium difficile bacteria. Scale bars represent 10 mm. Image taken from Center for Disease Control and Prevention Public Health Image Library.

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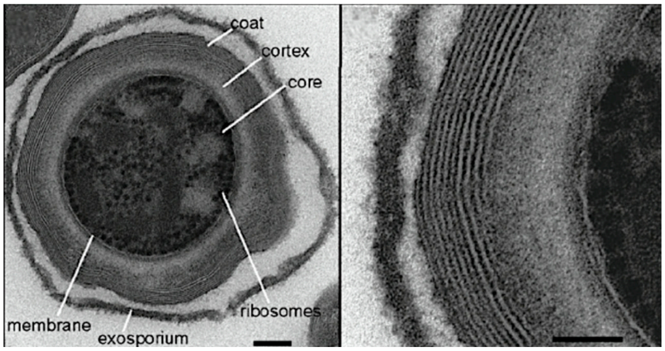

Figure 2: Anatomy of a *C. diff* cell. Left panel:transmission electron micrograph of sectioned *C. diff* spores. Right panel: magnified section of the spore outer wall. Error bars represent 50 nm. Figure slightly modified from Lawley et. al, 2009 and republished with permission of the *Journal of Bacteriology*; permission conveyed through Copyright Clearance Center, Inc.

form a difficult-to-penetrate spore (Figure 2). Its spore allows *C. diff* to hibernate for up to two years when exposed to unfavorable conditions, such as extreme pH or temperature (Crobach et al., 2017).

Studying *C. diff* in a laboratory setting has proven to be difficult because the bacteria is nearly impossible to grow in culture. In fact, the "difficile" portion of its name stems from the Latin word for "difficult" because it is challenging to grow. There are several different strains of *C. diff*, and certain strains have much higher toxicity levels than others (Crobach et al., 2017). Most notably, the strain known as NAP1 is 20 times more toxic than other strains of *C. diff*. Although all toxin-producing strains of *C. diff* are capable of causing **colitis**, strains that have higher **virulence factors** cause more severe symptoms (Kosai et al., 2017). Not all strains are capable of producing toxins, and only toxin-causing bacteria are capable of causing disease in humans (McConnie and Kastl, 2017). There are three types of toxins that can be produced by *C. diff*, known as Toxin A, Toxin B, and binary toxin. Binary toxin alone cannot cause disease; however, when binary toxin is present alongside Toxin A and Toxin B, the resulting infections can be life-threatening (McConnie and Kastl, 2017). The multiple strains—and the fact that new strains are constantly evolving—contribute yet another factor making it difficult to study the effects of *C. diff* in humans.

Colitis: inflammation of the lining of the colon.

Virulence factors: substances released by a microorganism that can cause injury to the host.

***Clostridium difficile* Infections**

The spread of CDIs has become increasingly difficult for healthcare professionals to control. Nearly 50% of CDIs result from healthcare exposure, such as nursing homes and hospitals (Figure 3). The only household cleaner proven to penetrate *C. diff*'s difficult-to-penetrate outer spore is bleach, and since most cleaning products, hand sanitizers, and germicides are alcohol-based and do not contain bleach, *C. diff* is extremely difficult to remove from the environment. Its ability to survive on a variety of surfaces for long periods of time allows *C. diff* to be spread easily, allowing it to be spread from patient-to-patient in healthcare settings (Salazar et al., 2017).

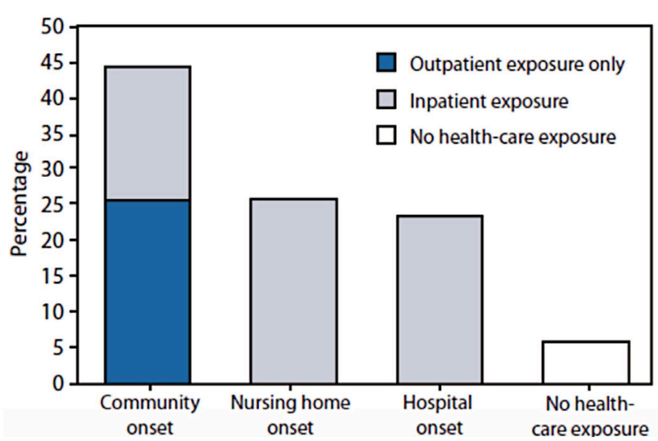

Figure 3: Percentage of CDI cases by inpatient or outpatient status. Status at the time of stool collection and type/location of exposure. Data collected by the United States Emerging Infections Program in 2010 (N=10,342). Figure from McDonald et. al, 2012.

Table 1: Risk of developing CDI after exposure to common antibiotics.

Low Risk	Medium Risk	High Risk
Metronidazole	Ampicillin	Clindamycin
Trimethoprim	Amoxicillin	Cephalosporins
Rifampicin	Macrolides	Fluoroquinolones
Vancomycin	Tetracyclines	Co-amoxiclav

Toxic megacolon: an acute form of colonic distension characterized by a very dilated colon, abdominal pain, bloating, and fever.

CDIs take place in the gastrointestinal tract and can cause a wide range of complications, including bowel perforation, **toxic megacolon**, kidney failure, and dehydration. Symptoms of a CDI include chronic diarrhea, abdominal cramping and pain, fever, nausea, dehydration, and blood or pus in the stool. These symptoms vary in severity, but nearly all lead to intense patient discomfort. Additionally, the infections are often recurrent, meaning that patients who have had a CDI in the past are more likely to get one again (Cohen et al., 2016). Only about 3% of healthy adults have *C. diff* present in their normal gut microbiome without symptoms; the other 97% of the population will experience symptoms upon contracting *C. diff* (Bakker and Nieuwdorp, 2017).

CDIs often take place after use of standard antibiotics, such as amoxicillin, clindamycin, and cephalosporins because these medications tend to kill off a significant portion of the normal gut microbiome (Patron et al., 2017). Certain antibiotics carry a higher risk of CDIs than others (Table 1), but every antibiotic has the potential to significantly impact the composition of the gut microbiome. Without the normal gut microbes present to keep *C. diff* in check, it is able to multiply and essentially take over the environment, thus causing infection.

CDIs are notoriously hard to treat, and treatments are becoming more difficult every day due to increasing levels of antibiotic resistance. Current treatments include the use of strong antibiotics, such as Vancomycin and Flagyl, which are becoming less effective over time. Overuse of antibiotics is a major factor contributing to emerging strains of antibiotic-resistant *C. diff*. When a patient takes an antibiotic, the antibiotic-susceptible strains of *C. diff* are killed off, leaving the antibiotic-resistant strains behind. These difficult-to-treat strains can then be spread from patient-to-patient, causing an outbreak in a healthcare setting, severely impacting both the hospital staff and the patients.

Due to the ever-present problem of antibiotic resistance, researchers and healthcare professionals have been forced to seek out other treatment methods. A vaccine against CDIs is currently being developed, but has not yet been proven effective in humans (Bakker and Nieuwdorp, 2017). An up-and-coming treatment option is fecal microbiota transplantation

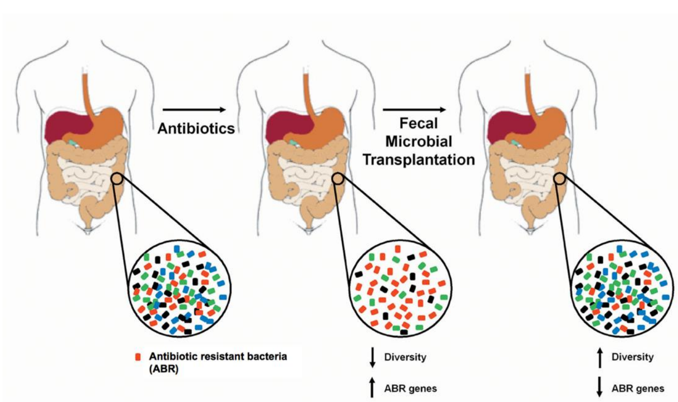

Figure 4: Diversity of the gut microbiome. The normal gut microbiome naturally contains some antibiotic resistant bacteria that can survive treatment with antibiotics. The subsequent decrease in microbial diversity in the gut leaves the patient vulnerable to CDIs. Treatment with FMT increases microbial diversity. Figure from Millan et. al, 2016.

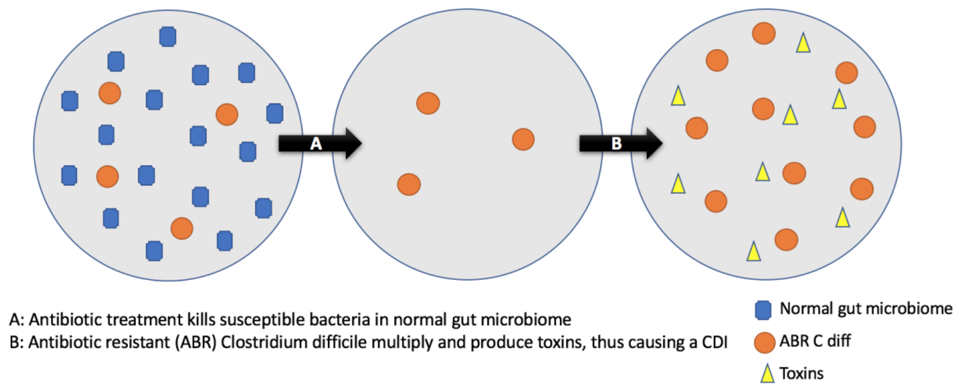

Figure 5: Effect of Antibiotics on gut microbiome. Treatment with antibiotics kills a significant portion of the normal gut microbiome (A), decreasing diversity and allowing antibiotic resistant *Clostridium difficile* to flourish, and thus, produce toxins (B). These toxins then lead to CDI.

(FMT), during which fecal matter from a healthy patient is transferred to a patient with a CDI (Bakker and Nieuwdorp, 2017). The goal of FMT is to introduce a new, healthy community of microbes to the infected environment, thus reducing the concentration of *C. diff* present and eventually curing the CDI (Figure 4). Restoration of a healthy microbiome also has the ability to prevent future infections. Reintroducing microbial diversity after antibiotic use is extremely important because the risk of CDI is inversely correlated with the number of microbial species present in the gut (Khanna et al., 2017). In other words, as the number of microbial species decreases, the risk of CDI increases (Figure 5). There are many benefits to using FMT as a treatment for CDIs: it is non-invasive, safe, effective, and it is relatively easy to find fecal donors. Additionally, FMT is becoming extremely cost-effective; however, many healthcare professionals worry about the commercialization of FMT, which could potentially make it less available to certain populations (Ma et al., 2017a). Several studies have shown that frozen fecal samples are as effective as fresh fecal samples, which makes transportation and storage of samples easier, and thus, reduces cost.

Vulnerable populations

Although FMT is safe and effective in the majority of populations, there are still many concerns surrounding the procedure, both ethical and medical (Ma et al., 2017a). However, effectiveness of FMT varies among different groups of patients. The concerns vary depending on the particular population, but some of the most severely impacted populations are known as vulnerable populations.

Vulnerable patients are groups of people who require special consideration before performing any medical procedure, and FMT is no exception. Vulnerable patients are defined as any people who have decreased ability to provide informed consent, as well as those who are unable to anticipate, resist, or cope with the effects of a treatment. This category of patients includes, but is not limited to, those with chronic mental disabilities, physical disabilities, chronic illnesses, and patients who are **immunocompromised**. One of the primary concerns surrounding vulnerable patients is their decreased ability to provide active and informed consent to medical procedures. While FMT is generally a low-risk procedure, it is important to consider both the physical and mental effects of treatment, and it is especially important for vulnerable patients. This review will cover the biological and ethical considerations of FMT in children, patients with mental disabilities, and patients with physical disabilities and chronic illnesses.

Immuno-compromised: having an impaired immune system.

FMT in Children

Young children are at significant risk for developing CDIs due to frequent illness. Their presence at schools, daycares, playgrounds, and similar environments exposes young children to a wide variety of viruses and bacteria. Unlike adults, who typically experience higher rates of CDI when in an inpatient setting, between 71 and 75% of pediatric CDIs are community-acquired (Chen et al., 2017). Most children develop dozens of illnesses each year, and although most are mild, many require treatment with antibiotics. Because these antibiotics are capable of killing a wide range of microbes, they can significantly disrupt the gut microbiome, increasing the chances of contracting a CDI. FMT is a viable treatment option because it can reintroduce a healthy balance of microbes. Since, FMT is a non-invasive, fast, and effective treatment, it is an excellent option for children, who are often less tolerant of long-term treatment methods.

In general, children do not experience differing levels of effectiveness of FMT than their adult counterparts. FMT can be performed without general anesthetic by using a **nasogastric tube**, and therefore eliminates anesthesia-associated risks, such as irregular heart rate, breathing problems, or allergic reactions to the anesthetic itself (Kronman et al, 2015). Since these are common concerns when dealing with pediatric patients, FMTs ability to be performed without anesthesia makes it a suitable treatment option for children.

Nasogastric tube: A tube that passes through the nose, nasopharynx, and esophagus into the stomach.

A child's gut microbiome is different than an adult's, and adult microbiomes change throughout the course of their lives (Figure 6). Because of this, it is important to consider whether or not the fecal donor should be similar in age to the recipient. Most fecal transplants are performed using adult fecal matter. It is not known if there are lasting

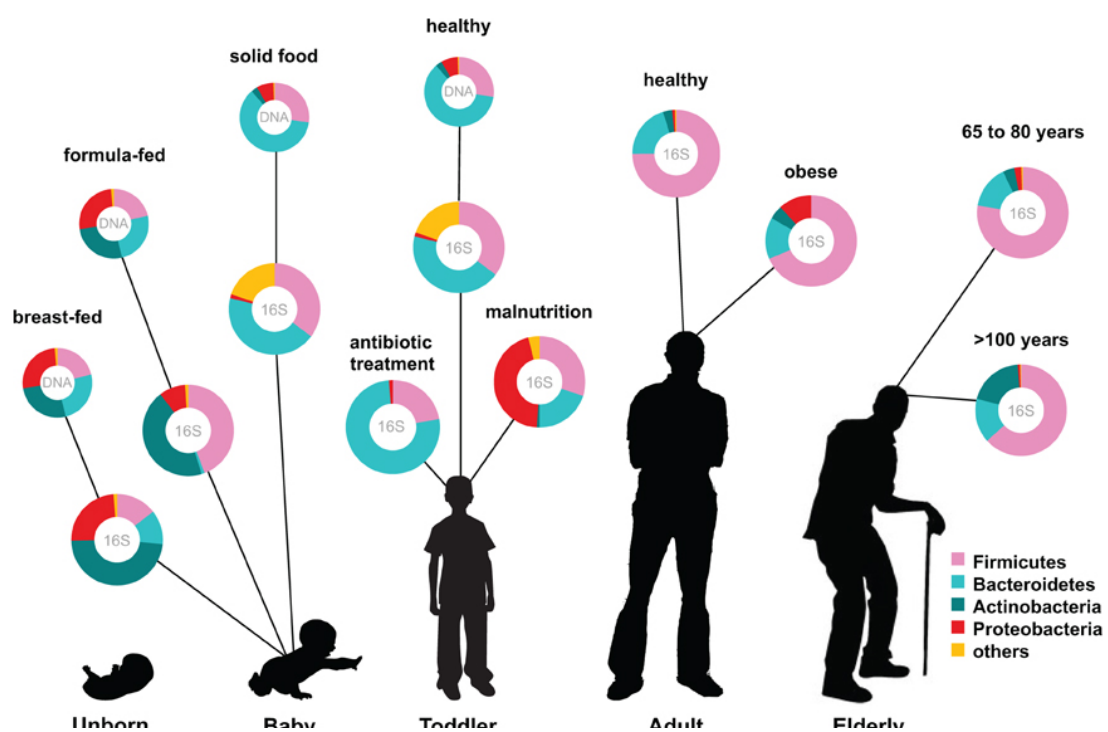

Figure 6: Gut microbiome composition varies depending on life stage. As a person ages, his or her microbiome will continue to change. Diet and age play key roles in determining the characteristics of an individual's gut microbiome. Figure modified from *Ottman et al., 2012.*

consequences to introducing an adult microbiome to pediatric patients. More research is needed to determine whether or not age-specific transplants are necessary, and if so, what are the benefits and risks of performing FMT with donations obtained from different age groups. This is especially important because there is evidence for age-dependent developmental factors (McConnie and Kastl, 2017). Children are typically not used as donors, but further studies of their gut microbiomes may show that pediatric donors are necessary. Infants have been shown to carry high levels of both toxin-causing and harmless *C. diff* strains, yet they are resistant to the associated toxins and do not develop symptoms (McConnie and Kastl, 2017). Because of this, stool obtained from infants should not be used for transplantation into children or adults with CDIs to prevent transfer of virulent *C. diff*.

The usefulness of FMT in the pediatric population is seldom negated, yet ethical concerns often hinder children from receiving this method of treatment. Studies show that FMT is safe for children of all ages, yet many healthcare professionals take additional precautions in regard to FMT in children and often try other treatment methods first (Ma et al., 2017b). One of the main concerns regarding FMT in children is their lack of ability to consent to the procedure. Young children rarely understand the biological mechanisms surrounding their medical treatments, yet many may understand the basics of fecal transfer. Children may feel afraid, disgusted, or both. Because of these feelings, many medical professionals worry about emotionally traumatizing young children. Due to the stigma surrounding FMT, children may feel less dignified after the procedure; nearly 51% of clinicians express concerns for pediatric patient dignity (Ma et al., 2017b). Because there are so many special considerations for young children undergoing FMT, it is extremely important for guardians and healthcare professionals to make well-informed decisions regarding both physical and mental health (McConnie and Kastl, 2017).

FMT in Patients with Mental Disabilities

Patients with severe disabilities—both mental and physical—are at a significant disadvantage when undergoing any type of medical procedure. Because those with severe mental disabilities often have their medical decisions made by a third party, they have less control over what happens to their body. The concerns regarding FMT in patients with mental disorders are purely ethical rather than biological. Although those with mental disabilities aren't at a significantly higher risk for contracting CDIs than their neurotypical counterparts, their treatment requires special consideration due to their lack of ability to consent; some patients may be entirely unable to make medical decisions on their own behalf. Patients with severe mental disabilities may be misled or manipulated into treatments that they may not otherwise consent to, which is a major ethical concern. Treatment with FMT may prove to be a positive experience for this population because of its speed and effectiveness, as well as the relative lack of potential complications despite their unique circumstances.

FMT in Patients with Physical Disabilities and Chronic Illnesses

Unlike patients with mental disabilities, many patients with physical disabilities and chronic illnesses are at an increased risk for contracting a CDI. This is especially true of patients who are hospitalized frequently. Healthcare settings are notorious for contributing to onset of CDIs; exposure to healthcare environments significantly increases the risk of developing a CDI simply because these environments have higher concentrations of antibiotic-resistant *C. diff*. Nearly 95% of adult CDIs occur after presence in a healthcare facility. Of these infections, approximately two-thirds are relapses or re-infections (Gomez et al., 2017). FMT has the potential to reduce the number of relapses and re-infections by replenishing the gut microbiome (Bakker and Nieuwdorp, 2017).

FMT has been proven to decrease CDI-associated mortality rates in the elderly and the disabled (Alrabaa et al., 2017; Cheng and Fischer, 2017). Additionally, several studies have shown that FMT is safe in patients who have undergone major surgery, are immunocompromised, or have chronic gastrointestinal problems (Alrabaa et al., 2017; Khanna et al., 2017; Meighani et al., 2017; Weingarden and Vaughn, 2017). Notably, patients who have undergone major surgery in their gastrointestinal tract or have received organ transplants—such as **ileostomies**, intestinal transplants, and insertion of ileostomy or colostomy bags—typically do not experience surgery-related consequences upon treatment with FMT. In fact, FMT can reduce the occurrence of venous **thromboembolisms**, especially in patients with **Crohn's disease** and irritable bowel syndrome (Bhandari et al, 2017).

Ileostomy: removal of the large intestine and diversion of the ileum to a surgical opening in the abdominal wall.

Thromboembolism: obstruction of a blood vessel by a blood clot that originated at another site in the circulatory system.

Crohn's disease: a chronic inflammatory disease of the colon and ileum that often leads to ulcers.

Because the safety and benefits of FMT in patients with physical disabilities and chronic illnesses are so concrete, there are fewer ethical concerns associated with treating these populations. However, many clinicians still worry about patient dignity after receiving FMT. As more and more people learn about the benefits of FMT, the stigma surrounding the procedure will fade, and thus, patients will experience less shame and loss of dignity following treatment.

CONCLUSION

Although FMT is a promising treatment option, there are still many concerns regarding treatment of CDIs in vulnerable populations. From ethics to efficacy, each population has a unique set of obstacles to overcome. Because there is no one-size-fits-all treatment option, researchers and healthcare professionals are constantly searching for new, innovative, and effective treatment methods. FMT is one of the best up-and-coming treatments for CDIs. In the case of treating patients with most disabilities, the benefits from performing FMT far outweigh the risks.

The primary concern regarding FMT in vulnerable populations is patient dignity. As research surrounding CDIs continues, FMT alternatives are being designed and tested. An oral transplantation method is being tested and a vaccine is in development, thus providing alternatives to the traditional method of transplantation directly into the colon. Having a variety of treatment options and making FMT more widely available will significantly benefit vulnerable patients by providing a treatment option that is as low-risk, dignified, and beneficial to their specific situation as possible. As the understanding of the treatment increases, doors are opening for FMT to be useful in a wide variety of gastrointestinal treatments beyond CDIs.

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