

FECAL MICROBIOTA TRANSPLANTATION:  
A CASE STUDY PRESENTATION AND EDUCATIONAL OPPORTUNITY

by  
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## ABSTRACT

Background: *Clostridium difficile* is an infectious disease that is having a direct and drastic impact on patients and healthcare resources. *Clostridium difficile*, an anaerobic, spore-producing, toxin-forming, gram-positive bacillus, has become the leading cause of hospital- and, more recently, community-acquired infections. It is estimated that 250,000 new *Clostridium difficile* infections (CDIs) arise annually. Prior antibiotic use has been recognized as the largest risk factor for acquiring a CDI, and it has been estimated that 90% of CDIs result from patients having previously been on antibiotics. Current antibiotic treatments for *Clostridium difficile* infections are becoming increasingly less effective at treating this infection. A new emerging treatment, Fecal Microbiota Transplantation (FMT) is proving to be an effective treatment option for CDIs. However, the impact these infections and FMT are having on patients isn't well represented within the literature. Methods: This study aimed to understand the patient perspective of having a CDI and choosing to have FMT as a treatment. It also evaluated the knowledge levels of APNs of FMT as a treatment option for CDIs. Results: A total of three patients provided insight related to their experiences of having recurrent CDI's and utilizing FMT as a treatment modality. All three patients report CDIs having a drastic negative impact on their life and wellbeing. Additionally, all three patients report FMT has resolved their CDI. The second part of this study, which looked to evaluate knowledge of APNs of FMT, indicated that 25% of the APNs who attended the presentation had never heard of FMT and, following education, 99% of APNs would recommend FMT as a treatment option for CDIs.

## INTRODUCTION

For decades, *Clostridium difficile* (*C. difficile*), a gram positive, anaerobic, spore-producing, bacteria, has been responsible for antibiotic-associated diarrhea and colitis. *C. difficile* is transmitted via the fecal-oral route and is capable of producing toxins A, B, and a binary toxin. It is these toxins in conjunction with a disruption of the gut microbiota that cause the symptoms associated with *Clostridium difficile* infections (CDIs). The clinical symptoms associated with CDIs can range from diarrhea, fever, leukocytosis, and cramping to pseudomembranous colitis, toxic megacolon, and death.

*C. difficile* is the most common infectious cause of nosocomial diarrhea and has recently surpassed methicillin-resistant *Staphylococcus Aureus* (MRSA) infections as the most common hospital-associated infections (Khanna & Pardi, 2012). In 2013, the near epidemic of *Clostridium difficile* infections (CDIs) triggered the United States Centers for Disease Control and Prevention (CDC) to raise the threat level associated with *C. difficile* to urgent, a status indicating that CDIs pose an immediate threat to public health (Mergenhagen, Wojciechowski, & Paladino, 2014).

There are two types of infections caused by *C. difficile*: community-acquired and hospital-acquired. Community-acquired *C. difficile* is defined by the Infectious Disease Society of America as “onset of CDI symptoms that occur within the community. The symptoms must occur within 48 hours of admission to a hospital and after no hospitalization in the past 12 weeks” (Gupta & Khanna, 2014, p.63). Hospital-acquired involves an infection attained less than twelve weeks from being in the hospital, or one that develops after 48 hours of being admitted to a healthcare facility (Gupta & Khanna,

2014). Infections caused by *C. difficile* have traditionally been acquired by patients in a hospital or long-term-care setting; however, recent data suggest that community-acquired CDIs are on the rise (To & Napolitano, 2014).

### Background

The effects of these infections are staggering. CDIs directly impact the patients who are infected at many levels, such as financially, psychologically, spiritually, and even quality of life. The costs associated with CDI's are enormous and a significant burden is placed on the providers and healthcare institutions treating these infections.

### Patient Impact

Recent research demonstrates that, in healthy American adults, about 3% are colonized with *C. difficile*. This colonization increases to between 20% and 40% of hospitalized patients, and upwards of 70% of patients who reside in long-term-care facilities (Mergenhagen, Wojciechowski, & Paladino, 2014). Nearly one-half of all CDI cases occur in patients younger than 65; but over 90 % of deaths associated with CDIs occur in patients over the age of 65.

An alteration of the normal colon flora often occurs after antibiotic use. This alteration is often caused by the antibiotic diminishing the total number of normal bacteria present in the colon. This diminishment enables other bacteria to flourish and sometimes overgrow, which is the case for *Clostridium difficile* (To & Napolitano, 2014). As many as 31% of patients who received antibiotics were shown to be colonized with *C. difficile* and over one-half of those subsequently developed symptoms of a CDI (To &

Napolitano, 2014). It is estimated that 250,000 new CDI cases occur annually. In 2007, 14,000 patients died from CDIs, with an estimated 90% having previously been on antibiotics (Mergenhausen, Wojciechowski, & Paladino, 2014).

Recently, there has been an increasing emergence of newer, at-risk populations affected by CDIs. Traditionally low risk populations, such as children and community dwellers who lack the associated risk factors, are being infected with CDIs. In one study, it was found that the overall incidence of community-acquired and hospital-acquired CDIs has risen by 5% and 19% respectively over the past seven years (Khanna & Pardi, 2012). As the rise of CDIs continued, so did the number of deaths associated with CDIs. Data taken from U.S. vital records indicate that the number of death certificates with enterocolitis due to *C. difficile* listed as the primary cause of death increased from 793 in 1999 to 7483 in 2008 (Lessa, Gould & McDonald, 2012).

#### Economic Impact of CDIs

It is estimated that the costs associated with CDIs are close to \$1 billion annually. The direct costs associated with CDIs include prolonged hospitalization, drug treatment regimens, and follow-up care. These costs are conservative estimates as they only reflect the direct cost. There is little data that exists to show indirect costs associated with CDIs. Some of the indirect costs include rehabilitation of patients, potential home-care cost, and long-term care.

A recently developed statistical model has shown that indirect costs of CDIs are 40% higher than direct costs in terms of loss in productivity. This model also showed that the range of cost per case of CDI is between \$2000 and \$72,000. This wide range of costs

accounts for the varying comorbidities of each patient. Each patient is unique, and these costs reflect the uniqueness in the previous comorbidities and condition many of the patients have prior to acquiring a CDI. Despite the potential severity of the CDI, the majority of the costs associated with CDIs occur at the initial infection with median costs of \$7511 (CI, \$6868–\$8210), \$8485 (CI, \$7562–\$9427) and \$9539 (CI, \$8342–\$10 994) for a 6-, 10-, and 14-day CDI-attributable additional LOS, respectively (McGlone, Bailey, Zimmer, Popovich, Tian, Ufberg, Muder & Lee, 2012).

#### Impact on Providers and Healthcare Institutions

With costs of upwards of \$1billion annually, it is no doubt providers and healthcare institutions are fiscally affected by CDIs. CDIs are a common complication associated with hospitalization. Overall, 8% of all patients diagnosed with hospital-acquired CDIs suffer other medical complications such as dehydration, sepsis, bowel perforation, and occasionally some operative interventions. All of these complications place an increased burden on providers and healthcare institutions caring for these patients. Furthermore, the increased mortality and morbidity associated with CDIs pose a threat to the reputation of those treating patients with these infections. Part of the problem in treating CDIs is that the current treatment options are failing, and providers are being left with patients still having a serious gastrointestinal infection. The lack of provider knowledge in the long term management of CDIs compounds the problem, leading to prolonged treatment regimens for CDIs.

## Epidemiology

In 1935, *C. difficile*, a gram-positive, spore-forming, anaerobic bacillus was found in healthy newborns. *C. difficile* was initially named *B. difficilis* due to the difficulty researchers had in growing it outside of anaerobic broth cultures. *C. difficile* was also thought to be normal flora of the newborns, as it was isolated with such frequency. Crude samples of this newly discovered *C. difficile* were taken and injected into laboratory animals, which proved that *C. difficile* produced toxins (Hall and O'Toole, 1935). Initially, the toxins produced by *Clostridium difficile* were not considered pathogenic in humans. However, in 1978, the link was discovered between *C. difficile* toxins and pseudomembranous colitis, proving *C. difficile* to be pathogenic in humans. This linked *C. difficile* to the capability of causing diarrhea, colitis, and even death (Bartlett, Change, Gurwith, Gorbach & Onderdonk, 1978).

After this link was identified, it was found that most of the infections during the 1970s to late 1990s were associated with the use of clindamycin, which was given routinely for dental infections and systemic bacterial infections. Recent advances in technology and research have shown that most of the current antibiotics used today are associated with an increased risk for developing CDIs. Technology, specifically PCR and advanced gene typing, has enabled researchers to implicate many of the current antibiotics used in causing alterations in the gut flora and have enabled researchers to identify specific strains of *C. difficile*. The most common antibiotics implicated in causing CDIs include clindamycin, fluoroquinolones, and third-generation cephalosporins (Owens, Donskey, Gaynes, Loo, & Muto, 2008).

Over the past five years, several CDI outbreaks have been linked to a strain of *C. difficile* that had not been previously recognized. This emerging strain is known as the “J-Strain,” which is now known to be associated with significant outbreaks of CDIs in the United States during the early 1990s and in Canada in the early 2000s. This strain was responsible for an increase in hospitalized patients acquiring toxic megacolon and requiring colectomies. It also has an increased risk of treatment failure, along with a significantly higher mortality and relapse rate, as compared to other strains of *C. difficile* (Cookson, 2007; Mergenhagen et al., 2014). In Montreal, Quebec, from 2004-2005, approximately 82% of the estimated 14,000 new cases of *C. difficile* were isolated to be this new and severe “J-Strain” (Cookson, 2007). In 2006, this new strain had spread rapidly to seven other provinces within Canada with estimates of 13 cases of the new “J-Strain” that were expected per 1000 hospital admissions (Cookson, 2007). Between the years 1996 and 2003, isolates taken from stool of patients infected with *C. difficile* showed the “J-Strain” present in six different outbreaks within the United States. Both Canada’s and the United States’ research found recent fluoroquinolone use and the use of cephalosporins were significant risk factors for acquiring this new strain of *C. difficile* (Cookson, 2007).

#### Current Treatment for CDIs

The current first-line treatment recommendation for patients with CDIs is prompt discontinuation of the antibiotic. After cessation of the antibiotic, the patient is thought to be treated; however, up to 35% of patients treated with these antibiotics have a recurrent infection of *C. difficile*. It is estimated that up to 65% of these patients who experience a

recurrence of *C. difficile* will develop a chronic recurrence of *C. difficile*. General practice guidelines recommend a tapered or pulsed regimen of vancomycin and flagyl for the first or second recurrent CDI. These recurrent infections often result in poor outcomes; thus the investigation for alternative treatment options has emerged (Gough, Shaikh, & Manges, 2011).

Flagyl is the first-line recommended antimicrobial therapy for treating CDIs even though the United States Food and Drug Administration (FDA) has not officially approved it for this purpose. Flagyl is a low-price medication and is generally used to treat mild-to-moderate CDIs. Vancomycin has demonstrated greater effectiveness in treating CDIs and is considered a first-line choice for more severe infections (Cohen, Gerding, Johnson, Kelly, Loo, McDonald, & Wilcox 2010).

In 2011, the FDA approved Fidaxomicin, a macrolide, for the treatment of CDI. Much of the research has shown it to be equally as effective as flagyl and vancomycin. The main drawback with this new macrolide is the cost to the patient, as it is considerably more expensive compared to other treatment options. Current costs for the antibiotics and other treatments for CDIs are:

Figure 1: Cost of treating CDIs

Flagyl	\$18-\$25
Vancomycin	\$1400-\$1950
Fidaxomicin	\$3550
Fecal Microbiota Transplantation (FMT)	\$500-\$1000
* Each of the costs listed are per treatment course which for all is at a minimum of 10 days (Mergenhagen et al., 2014).	

Another adjunctive option is probiotics, which have been thought to be helpful in the prevention of CDIs. Probiotics are live bacteria, usually in the form of a pill, which do not cause infections in humans. Probiotics are low-cost and are theorized to introduce healthy bacteria into the lower gastrointestinal (GI) tract of humans. The efficacy of probiotics for CDIs is controversial as there is limited data supporting their use. A recent double-blind placebo trial showed no benefit from taking probiotics in CDI prevention (Allen, Wareham, Wang, Bradley, Hutchings, Harris, & Mack, 2013). This study found no significant reduction in diarrhea associated with antibiotic use, or diarrhea associated with CDI. They also found no secondary reduction in hospital length of stay (LOS), quality of life, diarrhea severity, or abdominal symptom frequency. The quantities of probiotics a patient must take in order to show benefit far exceed what is currently recommended (Allen, Wareham, Wang, Bradley, Hutchings, Harris, & Mack, 2013).

An emerging and promising treatment for recurrent CDIs is Fecal Microbiota Transplantation or FMT. FMT has been shown to treat recurrent CDIs with a success rate of 89% after a single treatment, and 92% overall success rate according to Gough, Shaikh, & Manges (2011).

Fecal Microbiota Transplantation (FMT) is a process by which fecal matter, usually taken from a family member or close relative to the patient, is collected and introduced into the GI tract of the patient. Prior to the instillation, regardless of the method of introduction, the feces is screened for any infectious agents. After it is collected, the fecal material is sent to a laboratory where it is processed into a suspension. The suspension can then be instilled either via a nasogastric tube or by an enema. The

nasogastric-tube method involves a small tube being passed from the nose of the patient into the small bowel in order to instill the fecal material properly. The enema method of instillation involves the patient receiving the fecal solution as a retention enema in which the fluid is introduced into their rectum and the patient must retain the fluid for two hours. Another relatively new way of instilling donor fecal matter into the gastrointestinal tract of the patient is by pill, where the patient swallows a gelatinous capsule containing donor stool. The donor stool is collected, screened, frozen, and put into pill form for the patient to take more easily.

FMT has actually been used as a treatment for illnesses affecting the GI tract dating back hundreds of years. The consumption of fecal material is common in the animal kingdom and has been practiced for centuries in veterinary medicine. Human use of FMT was first documented by early Chinese medicine and was used as a therapeutic agent for many ailments such as upset stomach, nausea, food poisoning, and vomiting. Additionally, in early European times, there was a widespread belief in the medical application of fecal material. A German physician, Franz Christian Paullini, made an observation in animals that fecal consumption was common, and published a book in 1696 on the medical uses of human and animal feces (Ley, Hamady, Lozupone, Turnbaugh, Ramey, Bircher, & Gordon, 2008; Lehrer, 2013).

In the 20<sup>th</sup> century, Ben Eisman was the first to perform fecal transplantation on four patients with pseudomembranous colitis. It was recognized that antibiotics were causing this potentially fatal syndrome by diminishing the normal native gut flora. It was the hope that standardization and implementation of FMT would happen following this

study; but soon after the successful treatment of those patients, vancomycin was identified as an effective treatment for pseudomembranous colitis. Despite this, FMT continued to be used anecdotally worldwide, mostly for the treatment of recurrent CDIs (Eiseman, Silen, Bascom, & Kauvar, 1958).

### Aim

This project had two objectives: to understand the impact CDIs have on patients and to assess APN knowledge of FMT before and after a formal educational offering. The first objective is something not found currently in the literature and is an integral part in promoting and adopting FMT as a potential first-line treatment for CDI's. Secondly, the education component of this project aimed at increasing overall awareness of FMT and its effectiveness for treating CDIs.

### Theoretical Framework

The theory that guided this project was Jean Watson's Theory of Transpersonal Caring. This theory places an emphasis on the caring human relationship (Alligood, 2013). Nursing and caring are almost synonymous as they exist codependently with each other. Nurses stand as professionals trained to take care of our patients through compassion, effective communication, and *being* there for our patients and their families. Watson's theory requires the nurse or practitioner to have an instilled and deeply spiritual connection within themselves and with the patient (Lachman, 2012). The basis of Watson's theory was the main guiding light for the capstone project. Nursing as a profession is responsible for "caring" for the human and fostering a caring relationship.

Everything done for this capstone project always began with this question: Does exploration into this topic potentially help foster and enhance a caring/healing environment and relationship for the patient? These infections are having profound impacts on our patients and an exploration into this topic will not only shed light on the impact these infections are having on our patients, but will show that FMT is an effective option for our patients in treating these arduous infections.

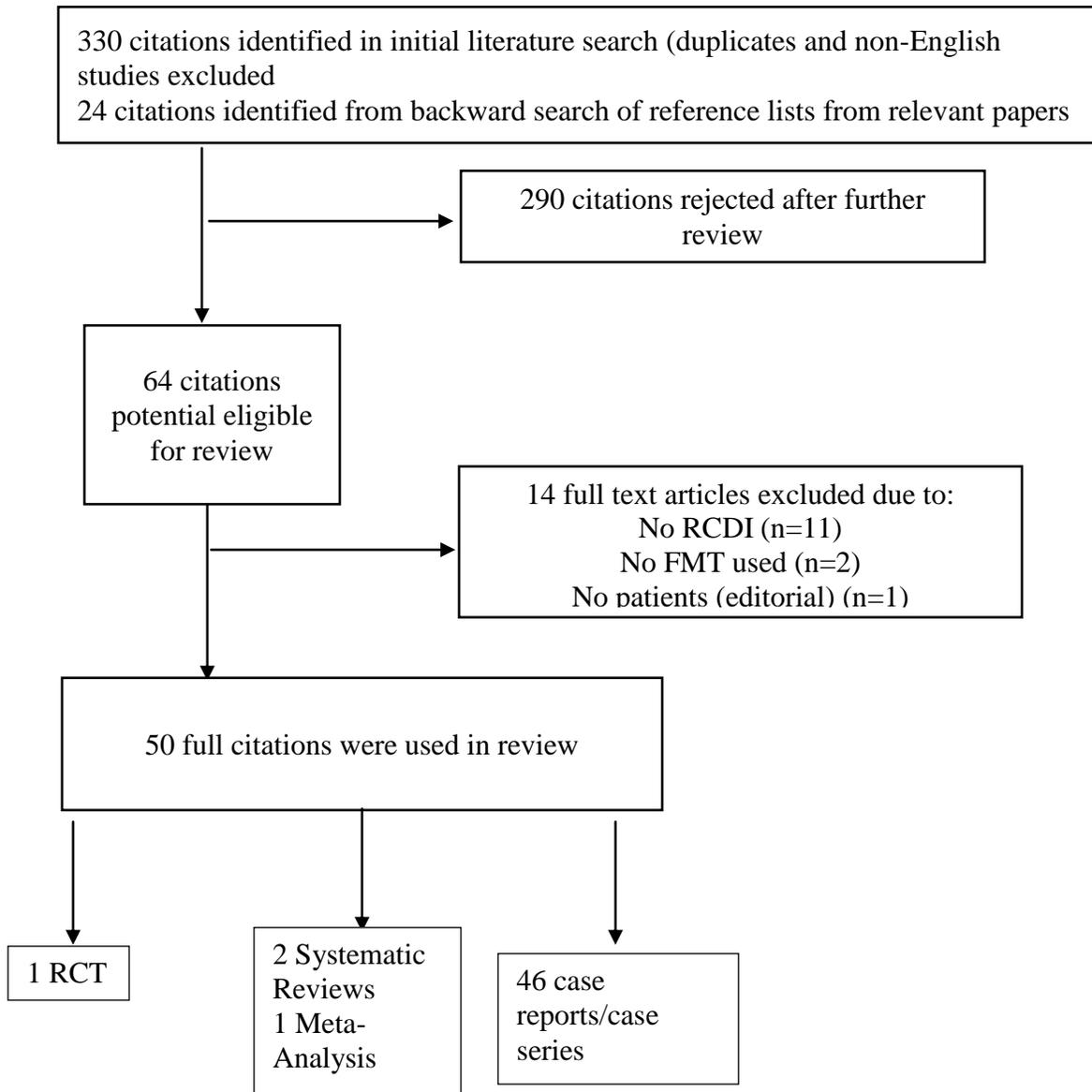
Jean Watson's theory was chosen for three reasons. The first reason was the nature of this theory. Jean Watson's theory is logical and cuts to the core of what the nursing profession is about: caring and the human interaction. Caring was chosen by Watson instead of "curing" to delineate the nursing profession from medicine and other health professions (Alligood, 2013). The theory was an obvious choice because of Watson's emphasis on caring and how vital it is to patient and human interaction. The second reason for selection of this theory was that it is more about *being*, rather than doing, and thus it is relatively simplistic in nature. This simplicity and *being* are easily applicable to any nursing realm. So much of what nursing does today is doing, and the importance of *being* has fallen by the wayside. *Being* is an essential and vital component in establishing rapport and fostering a healing human relationship. The third and final reason for this theory selection was its intended lack of concrete instructions on applying this theory. This theory allows for the nursing professional to be flexible, adaptable, and individual when attempting to achieve, foster, and gain an authentic caring-healing relationship (Alligood, 2013).

## LITERATURE REVIEW

A review of literature was done specifically looking for English-language publications using the following databases: Cochrane (for all years), CINAHL (for all years), Medline (from 1950 to present), PubMed (for all years), Joanne Briggs EBP Database (for all years), and Biomed central (for all years). This search aimed to identify observational, randomized control trial, meta-analyses, and systematic reviews relating to the topic of this project. Search terms were used as free text or keywords only and no relevant medical subject headings were recognized in the databases searched. Search terms included: fecal microbiota transplant, fecal transplant, recurrent *Clostridium difficile*, feces transplant, human microbiome, alternative *Clostridium difficile* infections, CDI case report, and fecal microbiome.

The research questions/aims that were used in this project, along with inclusion and exclusion criteria, were developed by using the Patient, Intervention, Comparison, Outcome (PICO) format (Polit & Beck, 2008). The inclusion criteria for patients were that they be over the age of 18 with recurrent *Clostridium difficile* infections. The intervention inclusion criteria included those patients over the age of 18 with recurrent *Clostridium difficile* infections treated with FMT. Alternative treatment modalities (antibiotics) were used as the comparison. Each outcome associated with the use of FMT was also used as inclusion criteria. The electronic search identified a total of 345 sources, of which 54 articles met the criteria for inclusion for this project.

Figure 2: Flow Diagram of Literature Review



### Current Best Evidence

Few quality studies have been completed to support this topic. To date, only 54 articles have been published that looked specifically at implementing and analyzing the effects of FMT. Some of the current and latest evidence written includes a systematic review by Gough, Shaikh, & Manges (2011) who analyzed 27 articles regarding FMT

and its effectiveness. This review reported a cure rate of 92% that included 89% after one FMT instillation and 92% cure rate after a second instillation.

Another study by Youngster, Sauk, Pindar, Wilson, Kaplan, Smith, & Hobmann (2014) demonstrated similar results. The study done by Youngster et al. (2014) was an open-label, randomized control trial evaluating the efficacy of FMT in treating recurrent CDI. This is one of only two randomized control trials regarding FMT. This study had two groups, of which one group received FMT via a nasogastric tube (N=10) and the other via an enema containing donor fecal material (N=10). This study's aim was to evaluate the effectiveness of FMT at resolving the main symptom of CDIs; diarrhea. In both arms of the study, 14 out of 20 total patients (70%) were cured after one instillation of donor feces. The group that received FMT via enema had an 80% cure rate (8 out of 10) and the second group who received FMT via nasogastric tube had a 60% cure rate (6 out of 10). Five patients required an additional donor fecal instillation. Four of the five were cured following this second instillation providing an overall cure rate of 90%. Authors concluded that FMT delivered via nasogastric tube was as effective as enema administration.

The second randomized-control-trial study using FMT was done by Van Nood, Vrieze, Nieuwdrop, Fuentes, Zoetendal, de Vos & Speelman (2013), comparing donor feces infusions on three different groups of patients. One group received a four-day, four-times-a-day vancomycin regimen followed by bowel lavage. The second group of patients received the standard, 14-day course of vancomycin. The final group received 14

days of vancomycin and a bowel lavage. The primary endpoint for this study was cure without a relapse within 10 weeks of treatment.

Patients were randomly allocated at a 1:1:1 ratio to three treatment options: (1) donor feces infusion, who were given vancomycin (500mg orally four times per day for 4 days) and had a bowel lavage (4 liters of macorgol solution) done four days prior to instillation of donor feces, (N=16); (2) a standard, 14-day vancomycin (500mg orally four times per day, N= 13), and (3) 14-day vancomycin (500mg orally four times per day) with bowel lavage on day four (N=13). A total of 43 patients were included in this study. Of the 16 patients in the infusion group, 13 (81%) were considered cured after the first donor fecal lavage. The second group's infection resolutions occurred in 4 out of the 13 (31%). The final group had only 3 out of 13 (29%) that demonstrated resolution of the CDI. The authors reported donor fecal lavage was statistically superior as compared to the other two groups in this study. Donor fecal lavage in this study showed an 81% cure rate with first-time lavage for patients with CDIs.

## METHODOLOGY

Design

A qualitative-observational design in the form of an exploratory (pilot) case study was chosen for this project. This method was chosen due to a desire to derive an up-close and in-depth understanding of three cases occurring in a real-world context. This in-depth examination aimed to elicit invaluable understanding on the direct impact CDIs are having on patients and their quality of life. Furthermore, an exploratory case study enabled the researcher to examine a phenomenon with numerous variables and to develop a framework for which future analysis can take place (Yin, 2013).

The intent of this project was to explicitly explore and describe the patient experience of having CDIs and electing to have fecal microbiota transplantation. This project also looked at evaluating current knowledge of APNs as it relates to CDIs and FMT. This project had two objectives: to understand the patient experience of those who elect to have fecal microbiota transplantation (FMT), and to educate healthcare providers, specifically APNs, in the use of FMT as a potential treatment option for CDIs.

In order to evaluate the impact of CDIs, patients who received FMT that chose to participate were asked a series of questions after their FMT at a local gastroenterologist's office. A questionnaire was constructed to ensure uniformity and validity of questions asked to each participant. This questionnaire was utilized during the interview of the participants in this project. The patient questionnaire consisted of some basic

demographic questions, along with five basic questions constructed to assess the impact CDIs had on patients who elected to have FMT (see Appendix A).

In addition to an in-depth investigation into Fecal Microbiota Transplantation, the second aim of this project was to assess the level of knowledge of nurse practitioners, as providers, of FMT for the treatment of recurrent CDIs. A large gap exists in the literature related to providers' knowledge. There are no studies to date that look directly at APN's knowledge of FMT and its use for recurrent *Clostridium difficile*. Thus, the education component of this project consisted of a presentation at an annual APN Pharmacology conference in Helena, Montana. It was a 60-minute presentation to approximately 35 APNs from across the state of Montana. A pre/post-test was done during the presentation to ascertain the baseline knowledge of APNs on FMT, its availability, effectiveness, and overall attitude towards this treatment option for CDIs.

The pre-test was done to first assess the initial knowledge of APNs on the given content. A post-test was done to ensure that knowledge was retained by APNs and to evaluate the effectiveness of the presentation. The post-test was created based on the information included within the PowerPoint presentation. It included six questions to assess baseline and basic knowledge of APNs in relation to current recommended treatment for CDIs and basic knowledge regarding *C. difficile* (see Appendix B).

### Ethical Considerations

According to Polit & Beck (2008), any research carried out using human subjects must be done with care and must be exercised as such to ensure that the rights of the

subjects are protected. This project uses three board principles according to which standard ethical research is done: beneficence, respect for human dignity, and justice.

Beneficence is an imposed duty of the researcher to do no harm to human subjects. Any human research must be done with the intent to benefit the participants. This case study emulated this ethical standard. A clear explanation of the role the researcher plays in the study was given to all participants, and verbal understanding was ensured.

The respect for human dignity is the ethical consideration that allows participants full disclosure and the right to self-determination (Polit & Beck, 2008). For this case study, only participants who voluntarily agreed to participate were considered. Participants were encouraged to ask any questions regarding the procedure and specifics about FMT. Additionally, all participants were informed that the researcher was neutral in this process and was unable to share his/her opinion in order to maintain fairness and decrease the potential for bias. The participants were given the option to withdraw at any point during this study with no penalty or repercussions.

Justice is the third ethical principle used to guide this study. Justice ensures the right to privacy, and the right to fair and just treatment. Care was taken in conducting this study to include all patients as potential participants. Patients participating in this study were chosen at random and voluntarily decided to participate.

Approval from the Institutional Review Board (IRB) for Montana State University, as well as the St. Vincent Health Care System, was obtained prior to initiation of the study.

### Time-Setting and Sample

This project was conducted from January 1, 2016 to June 30, 2016. This timeframe enabled recruitment of patients. It also included time to present at the state APN conference.

The setting for this project was in a large city in Montana at a local nonprofit hospital. A local gastroenterologist who performs FMT supported this project and allowed access to the patient population for potential participants. This gastroenterologist has been doing FMT at this facility in Montana for the past two years, and has done close to 75 FMT procedures on patients with recurrent CDIs.

Inclusion criteria for this case study were: (1) adult patients, (2) English-speaking, (3) a chart diagnosis of recurrent *Clostridium difficile* infection, (4) no previous treatments using FMT, (5) live within a 50-mile radius of the healthcare center, (6) no previous antibiotic use one week prior to FMT. Exclusion criteria for this study included: (1) anyone under the age of 18, (2) non-English-speaking participants, (3) a CDI infection with < 2 reoccurrences, (4) previous FMT, (5) previous antibiotic use.

## RESULTS

Patient Experience

A total of three participants agreed to participate in this study. Each participant was given a label: 1, 2, & 3 respectively. Participant 2 was female and patients 1 and 3 were both male. The average age of the participants was 63 years old. All three participants reported two previous reoccurrences of a *Clostridium difficile* infection. Participants 2 and 3 reported having taken both vancomycin and flagyl for their first CDI infection, and a tapered/pulse dose of vancomycin for close to six months for their second reoccurrence to only have their infection reoccur one month after finishing their vancomycin regimen. Participant 1 reported being on vancomycin as a treatment for his first CDI, which was unsuccessful at treating his CDI, and had a reoccurrence of his CDI two months after finishing the vancomycin treatment regimen. All of the participants reported feeling quite apprehensive and unsure about consuming donor fecal material to treat their CDI, but knew this was the only remaining option. All three of the patients have tried and exhausted the traditional standard treatment regimens to treat and cure their CDIs.

There were a few insightful themes from the experiences of these three participants. All three reported a significant impact that CDIs had on their daily living and quality of life. They also reported experiencing difficulty mentally, physically, and feeling helpless in carrying out daily activities. In addition, participants 1 and 2 reported they had a very difficult time concentrating at work or on tasks at home. Also, they

mentioned that so much of their time and energy were focused on knowing where the nearest bathroom was in case they had to immediately have a bowel movement.

Participant 3 reported that the largest impact the infection had was on his day-to-day life and reported intermittent feelings of hopelessness. This patient reported not taking trips any further than an hour from his house due to fear of not having access to a rest room.

They all reported numerous occasions where they wondered if they would have this infection for many more months, years, or even for the rest of their lives.

Additionally, participants 1 and 2 reported having thoughts of dying from this infection. A common theme throughout all of the participants' experiences was that they all reported the impact of this infection was far beyond what they had expected. One patient reported that having recurrent CDIs was the most difficult thing he had ever gone through.

Participants 2 and 3 had knowledge of FMT prior to choosing this method of treatment; participant 1 had only heard of FMT from her primary-care doctor after two failed attempts at treating her infection. Both participants 2 and 3 reported doing some "research" on the internet about FMT and its effectiveness. Participant 1 mentioned a lack of understanding why FMT isn't an option for a first-line treatment since "it appears quite safe and effective." Finally, all three of the participants reported adamantly that they would recommend FMT as a treatment option for CDIs.

### Education Component

The education component of this study was conducted during the state APN Pharmacology conference. The educational offering consisted of a pre-test followed by a

60-minute PowerPoint presentation. Participants were then given a post-test to measure the effectiveness of the educational PowerPoint. The PowerPoint included background information regarding CDIs and their drastic impact on patients. It also discussed the current recommended treatment options and their success rate, in addition to FMT as a viable option for treating CDIs.

A total of thirty-two (N=32) APNs from across the state of Montana, from both rural and urban settings, participated in the educational offering. A pre-test was conducted prior to the presentation to evaluate APN's current knowledge of *Clostridium difficile* and to assess their knowledge about FMT as it related to treating *Clostridium difficile*. The pre-test indicated that 45% of the APNs had heard of FMT as a treatment option for recurrent *Clostridium difficile* infections. Furthermore, during the pre-test, 45% said that they would recommend FMT as a treatment option for their patients. The APNs were also asked about the current treatment guidelines for treating recurrent *Clostridium difficile* infections. Only 79% during the pre-test were able to identify the correct treatments for recurrent *Clostridium difficile* infections. Finally, when asked if anyone had patients who received FMT, only 5% said they had patients who have received FMT for treating a recurrent CDI, or were the providers who made the referral for further treatment.

Following the presentation, a post-test was conducted with the same questions that were asked during the pre-test. Results from the post-test indicated 98% of the APNs reported that, after the presentation, they would recommend FMT as a treatment option to their patients. Additionally, 99% of them answered all of the questions correctly. An

open-forum-type discussion followed the post-test. Many APNs voiced their opinions and interest in this new and upcoming treatment option. A few of the APNs who had never heard of FMT mentioned their lack of knowledge relating to this treatment option and can see the significant impact this treatment can have for patients.

## DISCUSSION

This project offered a unique perspective to understanding the patient experience as it related to having *Clostridium difficile* infections. The knowledge attained from the patients who have this life changing infection is powerful. It gives insight to know that these infections are having profound impacts on them emotionally, spiritually, and psychologically, aside from the already-known physical impact. In addition, the information acquired has a few implications for practice. The first impact is that we now have a brief view into what our patients are going through when they acquire this infection. This enables providers to have the ability to understand with more clarity what patients are experiencing. A second impact (and a powerful insight into what is potentially holding FMT back) is the perception of FMT. The patients in this study all mentioned the initial reaction and subsequent reactions after hearing what FMT actually is and what the procedure entails. All three of the participants in this study reported feeling apprehension and fear of the unknown as an initial reaction. This insight impacts FMT in that we now know this is a potential barrier for many patients. In knowing this barrier, we can change the way we approach promoting FMT. Patients also can be educated better and provided with clearer, more understandable information. It also opens the door for new research, such as ways to break the main barrier of FMT adoption: the “ick” factor, and to research further the perspective of patients who will be receiving donor feces.

The educational component of this project also added substantial information and provided necessary understanding of APNs’ views and knowledge of this new treatment.

The most importance piece gleaned was the lack of awareness and misunderstanding about FMT among APNs. This lack of awareness provides the supporting data that we must continue to promote and educate APNs on FMT. Further education offerings, podcasts, webinars, or FMT handouts are all ways to further increase APNs' knowledge regarding FMT and promote its use or referral to appropriate care. Though much information was gathered from this project, there is still more work to be done and there are still many challenges facing FMT as a recommended treatment.

### Challenges for FMT

The largest challenge for FMT to date is regulatory. According to the United State Food and Drug Administration (FDA), human feces is considered a drug. The FDA defines a drug as anything used to diagnose, cure, treat or prevent disease. Human feces is not like most drugs; it comes from healthy volunteers, and contains varied and complex mixtures of microbes and human cells. Blood, cartilage, bone, skin and egg cells are all currently regulated by the FDA as human tissues or similar categories (Sachs & Edelstein, 2015). There are rigorous protocols, meticulous record keeping, and screening for the transplanting of these aforementioned tissues into humans. This is not the case currently for FMT.

It is frequently debated on how best to regulate human feces. Human fecal material is still considered by the FDA as a drug. However, many practitioners, patients, and lawmakers have argued against this current classification. There have been three alternative proposed options for the reclassification of fecal material.

The first option would be to consider feces as a biologic. Reclassifying feces to a biologic would enable feces to still maintain the need for extensive safety evaluations, but would decrease the oversight associated with the classification of an investigational drug. The only problem with reclassifying to a biologic is the decreased ability to regulate purity and potency of individual samples of fecal material. The complexity of human stool is remarkable. It is a conglomeration of trillions of microbes and metabolites of which the full characteristics have never been fully recognized. In addition, the composition of human stool can be highly variable and often changes for each individual on a day-to-day basis. (Edelstein, Kassam, Daw, Smith, & Kelly, 2015).

Another option is to classify feces as tissue. Fecal material used in FMT has been referred to in the literature as a “virtual organ” that is integral to the host physiology. This reference comes from the fact that the gut microbiota is made up within the first few years of life and the symbiotic relationship that the microbiota has with the host is analogous to that of an organ or skin. Furthermore, the complexity of the microbiota that makes up the GI tract is beyond comprehension. Edelstein, Kassam, Daw, Smith, & Kelly, 2015).

Since the function of the microbiota, and the potential for highly variable samples of stool given by one person, and the potential risk of infectious diseases, it is logical to consider feces as a human cell, tissue, or cellular-based product (HCT/P). This category is currently where bone, skin, corneas, tendons, heart valves, semen and other “human tissues” are categorized. Regulating feces under this classification is appealing because of the perceived balance struck between access and oversight/regulation. This balance is

found by imposing strict regulatory statutes during the screening, preparation, and storage of the material, while limiting the regulatory issues and without restriction on physicians or providers of the stool. This classification would still enforce strict screening and testing of potential donors and require a robust record keeping of all stool/fecal material used and its screening results. According to the FDA, a tissue cannot be classified by anything “secreted or extracted” from the human body. Given this definition, human fecal material would not classify since it is secreted and/or extracted (Edelstein, Kassam, Daw, Smith, & Kelly, 2015).

A final option for fecal material in terms of regulation could be classifying feces in the same category as what human blood is considered. This classification offers a compelling model/foundation for regulation of human fecal material. Both blood and feces require extensive donor screening protocols and require very specific exclusion criteria for donor selection. They both also require strict storage and handling standards. Blood, technically, by definition is considered a biologic, but due to safety and regulatory restrictions, blood is considered under its own regulatory category, of which some argue FMT should be as well. (Edelstein, Kassam, Daw, Smith, & Kelly, 2015).

The regulatory side of FMT is still a large and significant hurdle for FMT. However, the safety of FMT has been well documented and has never been called into question. In 2015, a meta-analysis identified 16 case series with a total of 526 patients who had CDI and received FMT. Of those 526 patients, there were no documented adverse events or infectious diseases acquired by the recipients of the donor stool (Edelstein, Kassam, Daw, Smith, & Kelly, 2015).

The current landscape for FMT is still somewhat unclear. In 2015, the FDA still considered FMT as a biologic and an investigational drug (IND), for which an IND application is required. The basis for this categorical assignment is based on the fact that fecal material is to be used in the diagnosis, cure, mitigation, treatment, and/or prevention of disease or is intended to have an impact on the function of the human body (Edelstein, Kassam, Daw, Smith, & Kelly, 2015). Furthermore, the FDA cites that the lack of a high quality, large, random-control trial (RCT) to evaluate and demonstrate the safety and effectiveness requires the FDA to view fecal material used in FMT as an “unapproved” product and, therefore, an investigational drug. The FDA is not currently enforcing the IND application for physicians who are doing FMT to treat recurrent CDIs that are unresponsive to traditional treatments. In addition, the FDA is only requiring that these physicians have patients sign an informed consent ensuring they understand the fecal material used is considered an IND.

Another obvious challenge for FMT is the unappealing aesthetics of this treatment. Humans have a natural aversion to fecal material (Petrof & Khoruts, 2014, p. 6). The preparation of these “fecal slurries” requires biosafety level-two containment, which means protective gear of laboratory personnel, a devoted space to work, and appropriate storage are required for mixing of the fecal material, which can produce significant amounts of aerosolized particles. These particles can lead to significant respiratory exposure and potential complications; thus the biosafety level-two containment is a necessity (Petrof & Khoruts, 2014). All of these safety protocols and equipment can pose a significant aesthetic appeal for the physicians and laboratory

personal responsible for preparation of the fecal material needed for treatment as well as delivery of the treatment.

There appears to be a belief of patients and physicians that the aversion to FMT is due to the lack of appealing aesthetics associated with FMT. Little data are available to support this belief. A survey study done by Zipursky, Sidorsky, Freedman, Sidorsky, & Kirkland (2012) posed two hypothetical scenarios to assess patient perceptions of FMT and their willingness to consider FMT as a treatment. Respondents in this study were given two separate hypothetical scenarios in which they were instructed to envision they had a recurrent CDI.

The first scenario described the common symptoms associated with CDIs and information regarding two separate treatment options: (1) another course of antibiotics alone (with a 65% chance of cure) or (2) antibiotics followed by a treatment called “floral reconstitution” (FR) (with a 90% chance of cure). Respondents were asked to select their treatment preference. Those choosing option 1 were asked to indicate the reason for their choice. In scenario 2, respondents were presented with the same clinical situation and the same treatment options, but were given more detailed information about FR... They were asked again to select their preferred treatment and, if they chose antibiotics alone, to identify a reason for that choice (Zipursky, Sidorsky, Freedman, Sidorsky, & Kirkland 2012, p. 1653).

This study found 94% of the participants would willingly choose FMT along with antibiotics for the treatment of a recurrent CDI. There were many reasons listed, but the majority of the patients said that the effectiveness of FMT was the main reason they would choose FMT and the very low risk of having a recurrence after receiving FMT. The data from this study demonstrate an openness and willingness of patients to receive FMT, despite the unappealing aesthetics.

### Limitations

This project had two limitations to discuss. The first and most obvious is the small number of patients included in the case study. This study was a qualitative examination of the patient experience and documented three patients who have had FMT for treating their CDI.

In qualitative research the term “saturation” is often used to understand the ideal sample size. According to Mason (2010), there often comes a point in qualitative research where an increase in patient sample size does not change the results. A case study often has 15-20 interviewees. Ideally, this project could have had at least ten total participants, but with FMT still a considerably new treatment option, there exist few patients who have actually received the procedure or who are willing to participate in research. The use of FMT for CDIs is steadily growing, but currently, the lack of access and the number of providers doing the procedure are significant barriers.

The second limitation is the pre/post-test design for the education session. It is well understood that there stands to exist a test-retest bias. Since the participants had already seen the questions and knew what they were asking the second time around, it is plausible to assume that the increase in percentage of participants answering the post-test questions correctly were merely due to familiarity with the questions as opposed to actual knowledge retention.

### Suggestions for Future Research

There is a significant amount of work and research yet to be done in the realm of FMT and CDI's. Currently, there has not been a well conducted random-control trial (RCT) done to compare FMT against the current recommended treatment options. FMT hasn't been fully adopted by the medical community. A well-constructed and conducted RCT would hopefully prove the effectiveness and efficacy of FMT and that it stands to be a viable and cost effective way to treat CDI's. In addition, an RCT would add significant weight to the already existing supporting literature for FMT. Many opponents of FMT say the lack of "quality" research is a significant barrier for them to fully adopt and accept FMT as a treatment option and, therefore, recommend it as a first line treatment.

This project demonstrated that the impact these infections are having on patients is profound. However, much more work can be done to evaluate and understand further the impact that these infections are having on our patients.

### Conclusion

The impact CDIs are having on patients, healthcare, and the economy is overwhelming as demonstrated by the nearly one half million new CDI infections occurring in 2011 in the U.S (Pakyz, Moczygemba, VanderWielen, & Edmond, 2016). Additionally, current treatment options are becoming increasingly less effective. It is imperative that alternative ways are explored in order to treat these deadly infections. Fecal microbiota transplantation stands as a demonstrated, effective treatment option.

There currently exists limited research on the direct impact these infections are having on patients' lives. This, coupled with the fact that the rates of these infections continue to rise, as well as the CDC raising the threat level associated with these infections, other "nontraditional" options should be considered in order to stem the devastating impact these infections are causing.

Furthermore, no data exist on APN knowledge of CDI treatment options. This project aimed to examine the impact CDI infections have on patients, and also educate APNs to increase their overall knowledge and awareness of this treatment option. Many APNs have an awareness of FMT, but this study indicated that at least 25% had never heard of this form of treatment. This is alarming, and further efforts must be made to ensure that the awareness of FMT is being addressed in order to adopt and use FMT as a viable treatment option for CDIs.

FMT faces some challenges yet before it becomes a mainstay treatment option for CDIs. However, it stands to be a viable, effective, and efficient treatment option for these infections.

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APPENDICES

APPENDIX A

PATIENT QUESTIONNAIRE

Date of Fecal Transplant:

Date of Questionnaire

Gender:

Age:

Follow-up Questions

1. How has having this infection impacted your life?
2. Do you feel like this infection has affected others in your life?  
If yes, how do you feel it what way do you feel it has affected others?
3. How many recurrences have you had prior to doing the fecal transplantation?
4. Did you have any hesitancy in having this procedure?
5. Would you recommend this treatment to other patients with the similar medical condition?

APPENDIX B

FECAL MICROBIOTA TRANSPLANTATION: AN  
EXPLORATION OF THE PATIENT EXPERIENCE

Fecal Microbiota Transplantation: an exploration of the patient experience.

Pre/Post Test Questions for presentation

1. What is the current recommended first-line treatment for a mild to moderate clostridium difficile infection?
  - a. Flagyl
  - b. Ceftriaxone
  - c. Piperacillin
  - d. Fluoroquinolone
2. When is fecal microbiota transplantation indicated to be used as an alternative treatment for recurrent clostridium difficile infections?
  - a. 1<sup>st</sup> reoccurrence
  - b. 2<sup>nd</sup> reoccurrence
  - c. Never; it isn't a recommended treatment.
3. How many toxins does clostridium difficile produce?
  - a. None
  - b. One
  - c. Five
  - d. Three
4. What the name of a new drug recently approved by the FDA to treat recurrent clostridium difficile infections?
  - a. Flagyl
  - b. Vancomycin
  - c. Fidaxomicin
  - d. None of the above
5. Would you recommend FMT as a treatment for your patients with recurrent clostridium difficile?
  - a. Yes
  - b. No
  - c. Not sure
6. How comfortable would you feel caring for a patient who received Fecal Microbiota Transplantation?
  - a. Not comfortable at all
  - b. Somewhat comfortable
  - c. Very comfortable