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The role of fecal microbiota transplants in the management of inflammatory bowel disease

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Boston University
THE ROLE OF FECAL MICROBIOTA TRANSPLANTS IN THE
MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

by

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SEJAL MAHESH THAKER

ABSTRACT

Recent advances have increased the understanding that dysbiosis of the gut microbiome may be a significant contributor to the pathophysiology of ulcerative colitis. Because of this, the use of fecal microbiota transplants (FMT) has become more popular as a potential supplemental treatment option for patients suffering from this disease. Research has shown a possible benefit of FMT in conjunction with varying conventional therapies for patients with mild to moderate disease severity. However, there are scarce publications that have investigated the benefit of FMT in conjunction with a single conventional therapy for patients with moderate to severe disease, specifically. The proposed study is a multicenter, double blind, randomized controlled study of FMT, mercaptopurine (6-MP), and prednisone vs 6-MP and prednisone alone in patients with moderate to severe ulcerative colitis. The study subjects will have a baseline evaluation and the treatment trial will last 8 weeks with follow up throughout the study. Investigators will analyze the primary outcome of clinical remission and secondary outcomes of improvement of fecal calprotectin levels, Inflammatory Bowel Disease Questionnaire (IBDQ) score, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in the treatment vs control groups. The data from this study will help to identify if FMT would be an additional safe, efficacious treatment modality to the current medical management of ulcerative colitis.
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LIST OF ABBREVIATIONS

5-ASA .......................................................... Aminosalicylates
6-MP ........................................................... 6-Mercaptopurine
ACG ......................................................... American College of Gastroenterology
AZA ......................................................... Azathioprine
CDI .......................................................... Clostridium Difficile Infection
CRP .......................................................... C-reactive Protein
ESR .......................................................... Erythrocyte Sedimentation Rate
FMT .......................................................... Fecal Microbiota Transplants
GI ............................................................ Gastrointestinal
IBD .......................................................... Inflammatory Bowel Disease
IBDQ .......................................................... Inflammatory Bowel Disease Questionnaire
IgG .......................................................... Immunoglobulin G
IgM .......................................................... Immunoglobulin M
mL ........................................................... Milliliters
MTX ........................................................ Methotrexate
PO ............................................................ By Mouth
QD ........................................................... Once a Day
UC ........................................................... Ulcerative Colitis
INTRODUCTION

Background

Inflammatory bowel disease (IBD) is a set of disorders characterized by chronic inflammation of the intestine that typically presents in the second to forth decade of life. The two major types of IBD are Crohn’s disease and ulcerative colitis (UC), which can be differentiated based on physical exam, endoscopic findings, anatomic distribution of the disease, histologic features, and potentially serologic testing. UC typically presents as diarrhea mixed with blood or mucous, abdominal discomfort, tenesmus, and in more severe situations, evidence of systemic toxicity or toxic megacolon. Endoscopically, ulcerative colitis manifests as mucosal inflammation beginning in the rectum and extending proximally in a continuous fashion. Endoscopic classification is based partly on the extent of involvement. A combination of clinical features and endoscopic scoring is used to classify UC into mild, moderate, and severe disease, usually via the Mayo Score.

In the United States, the incidence of UC is estimated to be 9-12/100,000 cases, with prevalence estimated to be 205-240/100,000 individuals. Genetic, environmental, bacterial and immunologic factors have been implicated as causal risk factors for UC, but there are still many unknowns regarding the etiology and management of this condition. Diet, oral contraceptives, and infections have been suggested to play a role in the development of UC, but none of these associations have been proven. Despite extensive research efforts, UC is a lifelong illness that is currently incurable with pharmacological treatment alone. The goals of therapy are directed towards inducing and maintaining
remission, preventing complications, optimizing the need for surgical intervention and improving quality of life\textsuperscript{4}. Medical treatments of UC focus on modulating or suppressing the immune system given the inflammatory nature of the disease. A combination of aminosalicylates (5-ASA), corticosteroids, immune modulators (6MP, azathioprine, methotrexate), biologic medications (infliximab, adalimumab, golimumab, natalizumab, and vedolizumab), and surgery are used as treatment methods depending on severity of the disease\textsuperscript{2}. Surgery is generally reserved for patients who are either refractory to medical management or who experience severe complications such as bowel perforation, hemorrhage, fulminant disease, a high suspicion of cancer, or systemic complications. In these situations, total colectomy is generally considered curative for patients with ulcerative colitis.

Efforts to develop future treatments for UC have identified several potential targets of intervention. Some research has focused on dysfunction of the intestinal barrier and dysregulation of the immune system\textsuperscript{5}. However, evidence also shows that gut microbial flora significantly contribute to the metabolic, immunologic and homeostatic properties of the intestine\textsuperscript{6}. Studies have shown that an imbalance in intestinal microbiota, known as dysbiosis, may play a role in the pathogenesis of ulcerative colitis\textsuperscript{7}. This has catalyzed further investigation and identification of the organisms which reside in the gut to understand the interactions between the intestinal immune system and the microbes\textsuperscript{8}. Manipulation of the intestinal microbiota has been suggested as a possible therapeutic intervention for UC.
One method of modulating the gut microbiome is through the use of fecal microbiota transplants (FMT). The mechanism of action of FMT is believed to be the restoration of natural intestinal flora through the introduction of beneficial new species from the donor while also supplementing other species present at low populations in the host. FMT was first used as an oral suspension in China during the 4th century to treat food poisoning. Formal known use of this modality in humans did not resurface again until the mid-1900s when it was documented to be effective in a trial to treat children with pseudomembranous colitis. In 1983, the first case of using FMT to treat Clostridium difficile infection (CDI) was confirmed, and since then, there has been increasing interest in the study and use of this therapy with promising results for recurrent CDI. In fact, FMT is now included in clinical practice guidelines developed by the American College of Gastroenterology (ACG) for recurrent or relapsing CDI, moderate CDI that does not respond to standard therapy for a week, or severe CDI with no improvement with therapy over a period of 48 hours.

**Statement of the Problem**

Use of FMT has recently been increasing given that clinical trials have proven it to be effective in treating patients suffering from recurrent, antibiotic resistant Clostridium difficile infections. This has prompted studies to evaluate the efficacy of FMT as a remission inducing therapy for individuals suffering from other intestinal disorders such as UC. The largest study of to date found that 24% of UC patients who received FMT were able to achieve remission compared to 5% in the placebo group (p<0.05). However, this study, similar to many others, allowed patients to continue using their
individualized conventional therapies while receiving FMT, resulting in variations among treatment regimens. Additionally, the majority of studies that have investigated the use of FMT in UC patients have only included individuals who suffer from mild to moderate disease severity. There are few studies that have used a single conventional therapy coupled with FMT to evaluate its efficacy as an adjuvant agent in inducing remission in patients with moderate to severe ulcerative colitis.

**Hypothesis**

Fecal microbiota transplants used in conjunction with 6-mercaptopurine (6-MP) and prednisone will have higher rates of remission for ulcerative colitis in patients with moderate to severe disease previously unresponsive to 5-ASA therapy compared to 6-mercaptopurine and prednisone alone.

**Objectives and specific aims**

Based on the theory that microbial flora contribute to the pathogenesis of ulcerative colitis, the objective of this study is to identify if manipulation of intestinal microbiome can be used to treat ulcerative colitis. Specific aims include:

- To determine if FMT is an effective adjuvant treatment to 6-MP and corticosteroids to induce remission in patients with moderate to severe ulcerative colitis
- To determine if FMT, 6-MP and corticosteroids can improve inflammatory biomarkers in patients with moderate to severe UC from baseline
- To determine if FMT, 6-MP and corticosteroids can improve quality of life measures based on IBDQ score in patients with moderate to severe UC
To help identify where FMT should lie in the traditional treatment algorithms for UC.
REVIEW OF THE LITERATURE

Overview

Ulcerative colitis is diagnosed based on a combination of clinical findings, including patient symptoms, laboratory markers, endoscopic findings, and histology. The onset of UC is gradual and it can progress over time for several weeks. The most common signs and symptoms of ulcerative colitis include cramping abdominal pain, fever, weight loss, and increase in urgency and frequency of defecation with bleeding and passage of mucus in stool. Inflammatory markers, which are elevated in the majority of patients with active UC, such as fecal calprotectin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly monitored to identify disease activity. On endoscopy, notable findings can include mucosal inflammation with erythema, granularity, friability with bleeding, loss of vascular markings, and/or ulceration of the large intestine, progressing from the rectum to the cecum in a continuous fashion. Endoscopic findings can include loss of vascular marking due to edematous mucosa, erythematous appearing mucosa with increased granularity, exudates, erosions, and friability. Because the endoscopic findings can be nonspecific, biopsies of the colon are necessary to demonstrate chronicity of inflammation and exclude other causes of colitis. The most common locations of involvement are the rectum and distal colon because of the contiguous spreading of the disease. Histology of ulcerative colitis reveals inflammation of the inner mucosal lining with crypt abscesses and architectural distortion. Additionally, ulcerative colitis can be associated with a variety of extraintestinal manifestations that involve the eyes, hepatobiliary system, skin, and most
commonly the joints\textsuperscript{11}. Ulcerative colitis can result in potential complications such as gastrointestinal hemorrhage, bowel perforation, toxic megacolon, and colorectal carcinoma.

The pathophysiology of UC is poorly understood; however, studies continue to explore several theories. Among these includes a theory regarding dysregulation of the patient’s immune system towards either normal or dysbiotic commensal bacteria\textsuperscript{5}. The large number of microbes that inhabit the intestine result in continuous interaction between the host cells and bacteria, and the intestinal immune system must carefully balance defense against pathogens and tolerance of symbiotic bacteria. Disruption of host tolerance to non-pathogenic resident bacteria is believed to predispose individuals to ulcerative colitis, and in fact, there have been observations of increased levels of antibodies directed against intestinal bacteria in the mucosa of patient’s with IBD\textsuperscript{5,12}. Additional investigations have identified specific inflammatory cells and cytokines believed to play a central role in the induction and persistence of ulcerative colitis\textsuperscript{13}. Such studies have influenced the development of medical therapies aimed to decrease intestinal inflammation and modulate host immune responses.

There are a multitude of medical agents aimed at immune responses which are used to improve quality of life, induce remission and prevent relapse in individuals with UC. Current therapies are individualized to each patient based on location, extent and severity of disease. A step-up approach for medical therapy has been used to effectively treat patients\textsuperscript{14}. The medications traditionally used include 5-aminosalicylic acid (5-ASA), corticosteroids, immune modulators, and biologics\textsuperscript{2}.
5-ASA agents are among the first to be used to manage UC. They are available for administration through oral forms and topical methods. The exact mechanism of action is unclear but they are believed to act in an anti-inflammatory fashion. Studies have shown that this agent improves symptoms within 2-4 weeks of initiating treatment, and they are effective for inducing remission in mild-to-moderately-active UC\(^2\). This makes it the first medication of choice in the step up approach for patients with this disease severity. Additionally, studies have proven that continuing 5-ASA therapy while in remission aids in the prevention of relapse\(^2\). Randomized controlled trials have shown that adverse effects are not increased compared to placebo although rare adverse events such as interstitial nephritis, pancreatitis, pericarditis and hepatitis have been documented\(^2\).

Corticosteroids are anti-inflammatory agents typically reserved for acute UC flares. This medication can be administered orally, parenterally, and topically. The molecules interact with glucocorticoid receptors, resulting in an inhibitory effect\(^2\). This reduces the expression of adhesion molecules and the attraction of inflammatory cells to a specific site. Additionally, corticosteroids diminish the expression of inflammatory cytokines and stimulate cell death of lymphocytes\(^2\). Randomized controlled trials have shown that corticosteroids are effective at inducing remission in active UC\(^2\). However, because this medication can be involved in a large amount of physiological processes, it is associated with a variety of adverse effects including increased risk of infection, psychiatric illnesses, Cushing’s disease, hyperglycemia, and osteoporosis. Therefore, the risks make this an undesirable long term therapy, and its use is primarily reserved for
inducing remission rather than maintenance. As such, patients requiring corticosteroids to induce a remission must also be started on another medical agent to help maintain the remission.

The next level of the step-up approach includes the immune modulating therapies 6-mercaptopurine (6-MP), azathioprine (AZA), and methotrexate which work to alter the number or function of immune cells. These are used for patients who do not respond to 5-ASA agents or for those with moderate-severe disease severity. Studies have shown that AZA and 6-MP are more effective than placebo for maintenance of remission, but most evidence shows no statistically significant benefit of AZA/6-MP as an induction agent. This may be because ASA/6-MP require 3-6 months of administration before they are effective. Therefore, these medications are often started with corticosteroids or biologic agents (which can induce remission) during acute flares to serve as an eventual maintenance regimen.

The final layer of the step-up approach includes the biologic agents which are monoclonal antibodies targeted against tumor necrosis factor alpha and integrin, key components of the immune activity in UC. Medications in this class currently include infliximab, adalimumab, golimumab, natalizumab, and vedolizumab. The ACT 1 and ACT 2 trials for infliximab and CHARM trial for adalimumab have showed that these agents are effective at inducing and maintaining remission in patients with moderate-to-severely active UC. Once remission has been achieved, life-long therapy is required in attempt to prevent relapse. Although effective, these medications result in varying degrees of immunosuppression and cause patients to be vulnerable to infectious
complications. Patients taking these therapies also have an increased risk of developing non-Hodgkins lymphoma, other malignancies and infusion reactions. Because these biologic therapies are presently the final pharmaceutical approach to management of UC before surgical intervention, it would be beneficial to determine if another medical therapy can be used in conjunction with standard therapies to induce remission.

**Figure 1: Traditional Step Up Treatment Approach adopted from Hanauer SB**

Intestinal dysbiosis and reduced gut biodiversity has been thought to contribute to the etiology of UC. Over the last 15 years, there have been advances in DNA sequencing that have allowed scientists to explore the 40% of microbes living in the gut that have not been cultured. Using these techniques, studies have shown that healthy humans have an intestinal microbiome dominated primarily by four bacterial phyla: Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria. This has resulted in the use of culturing techniques and molecular analysis to gain further understanding of specific alterations of the GI microbiota in patients with UC. One study using broad range PCR analysis, demonstrated a decrease in the number of commensal bacteria, specifically those of the phyla Firmicutes and Bacteroidetes in patients with UC compared to healthy control subjects.
Studies such as this have been important to understand that dysbiosis may contribute to UC; however because the microbial composition of the gut differs greatly between individuals depending on environmental and genetic factors, it is difficult to identify a single causative organism to target for therapy\textsuperscript{12}. Therefore, techniques to modulate the gut microbiome as a whole have been explored via the use of fecal microbial transplants.

FMT derives commensal bacterial from stool samples of healthy donors and introduces them in patients with enteric bacterial imbalances. The transplanted bacteria exert their therapeutic benefit by colonizing the recipient gut and outcompeting pathogenic bacteria for nutrients. Successful treatment for patients develops a more diverse population of microflora and restores gut bacteria that may have been present in low numbers\textsuperscript{21}.

The successful use of FMT for CDI has prompted the ACG to create guidelines for the selection of FMT donors \textsuperscript{6}. Laboratory tests are performed to test for specific pathogens in both the stool and serum of potential donors to assure that they are free of transmissible disease. Additionally, a portion of the exclusion criteria requires that donors do not have any medical history of autoimmune disorders, intrinsic GI illnesses, or oncologic diagnoses\textsuperscript{6}.

For effective administration, stool is homogenized in either water, milk, or normal saline using a mixing tool\textsuperscript{6}. It is then filtered to remove large, undesirable particles and either infused directly into the patient, or further processed into capsules. The solution is administered to the patient via upper endoscopy, nasogastric tube, colonoscopy, rectal
tube, enema, or swallowed in the recently developed pill form. Currently, studies comparing the most effective method of administration are limited and there is no formal agreement regarding the best mode of installation.

Studies that have identified dysbiosis as a contributing factor to the pathophysiology of UC suggest that FMT may be a beneficial adjuvant treatment for patients suffering from acute disease flairs. Addressing immune dysregulation towards commensal bacteria and dysbiosis simultaneously may be useful to induce remission in patients with moderate to severe UC. This would add another potential therapy to the step up approach.

**Existing research**

Ongoing investigations continue to reveal that FMT may be able to correct dysbiosis and restore a more natural enteric microbiome. One study observed alterations in the structure and composition of microbiota in feces before and after using FMT to treat CDI. Molecular analysis and metagenomics were used to compare the microbiota from the host (pre and post FMT) fecal samples to that of their respective donors. The primary goal was to identify changes in the host fecal microbiome after FMT to discover if this modality is efficacious at restoring more natural gut colonization. The investigators found that the microbiome following FMT had significant changes with restoration of diversity and structure. The data suggests that the fecal microbiome of hosts after FMT administration more closely resemble that of each donor, highlighting the importance of a healthy donor. Although the sample population of the study was small, it was reported that the findings are supported by observations of similar previous
These research efforts are crucial to understand that FMT can be an effective agent to alter the gut microbiome in a favorable fashion.

Researchers have been using investigations of FMT for CDI as guidance to test the efficacy for FMT for UC. In 1989, Bennet and Brinkman were the first to report the use of FMT for UC\(^2\). Bennet self-administered fecal retention enemas which induced remission of his own UC, and 6 months after the intervention he continued to be free of symptoms without medications\(^2\). Shortly thereafter, another investigator published a case series that featured 6 patients who had diagnoses of UC for at least 5 years and had failed the maximum medical interventions at the time\(^2\). A combination of pretreatment antibiotics and 5 days of fecal retention enemas resulted in remission for all 6 patients\(^2\).

More recently, a systematic review and meta-analysis was performed to evaluate studies which used FMT as a primary therapeutic agent in IBD patients. All of the studies included in the review allowed patients to continue their conventional medication regimens and defined clinical remission as the primary outcome. Subgroup meta-analysis the patients who suffered from UC demonstrated that about 24.1\% of the patients who received FMT in conjunction with individual conventional therapies achieved clinical remission and there was a low risk for heterogeneity\(^2\). The study provided a comprehensive overview of the treatment success of FMT as an adjuvant for inducing remission in UC patients but was limited by publication bias due to the inclusion of case studies in the analysis\(^2\). Additionally, the review was limited by the small number patients and lack of controlled trials, highlighting the need for more robust investigation.
Nonetheless, the findings suggest that altering gut microbial flora may be a promising treatment for UC.

The largest randomized controlled trial for FMT in any disease has shown the potential of FMT to be an effective treatment option in patients with UC. In the study, FMT or water was administered via sigmoidoscopy and retention enema once a week for 6 weeks and the primary outcome was remission at week 7. Patients taking concomitant treatments were permitted to continue these throughout the trial as long as the doses were stable for a specified time period. The trial resulted in statistically significant findings with 24% of the participants in the FMT group achieving remission at the end of the experiment compared to 5% in the placebo group\textsuperscript{10}. The remission rate of 24% was notably similar to the remission rate found in the subgroup meta-analysis performed by Coleman and Rubin (24.1%). The study however did not target patients with a specific disease severity. Although the mean Mayo score of the patients who received FMT was calculated, there was no analysis comparing FMT remission and response rates of patients with mild to moderate disease vs. those with moderate to severe disease. More randomized controlled trials such as this are necessary to further reveal the benefit of FMT in UC patients.

Managing UC from two contributing processes simultaneously may be more effective than targeting them individually. Maoyyedi et al. showed trends towards individuals taking immunosuppressant agents to have an increased benefit from FMT compared to those not on immunosuppressant therapy\textsuperscript{10}. At 12 month follow up, 8 of 9 of the patients that received FMT and achieved remission remained in remission \textsuperscript{10}. These
findings support the idea that combination therapy of FMT with conventional immunosuppressive therapies may be beneficial to induce remission in patients with UC compared to FMT alone.

Beneficial changes of the intestinal microbiota after FMT have been reported in patients with UC. In randomized controlled trials, analysis of the microbiome outcomes showed that there was more diversity and statistically significant changes in the composition of the microbiota in the treatment groups vs. the placebo groups \(^{10,25}\). The investigators of these trials identified that the microbiota of individuals who responded to the FMT was distinct from that of the nonresponders \(^{25}\). Interestingly in one of the studies, the majority of individuals that achieved clinical remission all received FMT from the same donor \(^{25}\). Analysis showed that responders had microbiota more similar to the specific donor than non-responders, but this was found to not be statistically significant. This suggests that response effect may be dependent on the donor and restoration of a more natural gut colonization may play a significant role in the management of UC.

A reasonable concern regarding the use of FMT in patients with UC is the safety of the intervention, especially regarding patients taking immune suppressing medications. A prospective, open-label, uncontrolled study explored this concern after administering FMT to children and young adults with UC \(^{26}\). Administration of FMT was via retention enema daily for a period of 5 days and during this time, subjects continued taking their individualized conventional medications. Seven of the 9 subjects showed clinical improvement and 3 out of 9 subjects achieved clinical remission within 1 week of FMT \(^{26}\).
The majority of the adverse events were mild (see Table 1) and there were no serious adverse events noted\textsuperscript{26}. Overall, the study found that adverse effects were manageable, self-limiting and acceptable to the subjects\textsuperscript{26}. In addition to showing potential efficacy of FMT at inducing remission in patients with UC, the study also discovered it was a safe treatment while on other conventional medications.

**Table 1. Subject Reported Symptoms adopted from Kunde et al. \textsuperscript{26}**

<table>
<thead>
<tr>
<th>Reported Symptoms</th>
<th>Reported Severity</th>
<th>Number of Subjects Overall</th>
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<tbody>
<tr>
<td>Bloating/Flatulence</td>
<td>Mild to Moderate</td>
<td>9</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Mild</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Mild to Moderate</td>
<td>6</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>Mild</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Mild to Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>Mild to Moderate</td>
<td>2</td>
</tr>
</tbody>
</table>

More studies are indicated to evaluate the safest and most efficacious mode of installation; however, the current data suggests that FMT is a safe and tolerable intervention for patients with UC.

Infrequent use of FMT may also be due to the assumed unappealing nature of the intervention. There have been a limited number of studies that have used surveys to evaluate the patient perception of FMT. One publication has shown that patients are willing to consider FMT as a therapy, and would choose the intervention if recommended by a physician\textsuperscript{27}. The study did support the assumption that FMT is an unappealing treatment modality; however, survey participants have expressed willingness to accept it regardless of this. The findings also suggest that the support, advice and education provided by a healthcare provider plays an important role in the acceptance of FMT. A weakness of this study is that the participants were naïve of GI illnesses and therefore did
not provide perspective of individuals suffering from a enteric disease processes\textsuperscript{27}. Additionally, the small sample size decreases the generalizability of the study.

Another study aimed to identify interest in and concerns about FMT for patients with UC. Ninety-five participants from the University of Chicago IBD Center completed the survey. Interestingly, the majority of the patients reported either excellent or good/satisfactory medical management of their UC at the time the survey was administered. Even so, 46\% stated they would be willing to receive FMT and 43\% were “unsure”\textsuperscript{28}. The data shows that the vast majority of patients are willing to accept or willing to consider FMT despite having excellent or satisfactory medical management of their disease. Subgroup analysis revealed that patients who had been hospitalized for their UC were more willing to receive FMT, indicating that disease severity may play a role in decision making. Weaknesses of the study include the small sample size and that recruitment was from a single medical center which decreases the generalizability of the results\textsuperscript{28}.

Focus groups are a beneficial method to identify perceptions and interest in FMT. Studies have revealed that if there was careful donor screening and adequate research supporting the safety and efficacy of FMT, the adult patients and parents of children suffering from the disease would consider accepting FMT as a treatment for UC\textsuperscript{29}. Most importantly, the study highlights that participants believed the potential benefits of FMT greatly outweigh the unappealing factors associated with the intervention.

Patient interest in FMT is not the only opinion that is included in the adoption of this treatment method. Although there is enthusiasm for the future of FMT, the majority
of gastroenterologists have limited access to or experience with the intervention. Studies have aimed to investigate the experience and perceptions that gastroenterologists have regarding FMT. The majority of clinicians in a particular study reported that they had referred patients for FMT in the past and would refer their UC patients if it was easily available. The biggest concern reported by the gastroenterologists was lack of evidence regarding the efficacy of FMT for UC. Despite the minimal short term data and lack of long term data, the majority did not report reservations about the safety of FMT. This stresses the importance of amplifying research regarding the efficacy of FMT for UC patients.

These preliminary studies have shown that FMT appears to be a safe, practical, and efficacious for the treatment of UC, likely through restoration of the gut microbiome to a less immunogenic state. There is also a favorable perception of FMT by patients and providers alike, but all agree that more data is needed to verify its benefit and clarify its place in existing treatment algorithms for UC. The purpose of the proposed research trial, below, is therefore to address these issues, limiting the study only to patients with moderate to severe UC who are naïve to treatment with biologic agents.
METHODS

Study design

This will be a multicenter, randomized controlled study of FMT, 6-MP and prednisone vs 6-MP and prednisone alone in patients with moderate to severe ulcerative colitis.

Study population and sampling

The patients will be recruited over a period of 12 months from the outpatient gastroenterology clinics of 6 major academic institutions throughout Boston: Boston Medical Center, Brigham and Women’s Hospital, Lahey Medical Center, Tufts Medical Center, Beth Israel Deaconess Medical Center and Massachusetts General Hospital.

Inclusion and exclusion criteria can be found in Table 2. Disease severity will be evaluated using the Mayo score which takes into consideration stool pattern, rectal bleeding, endoscopic findings, and global evaluation by a health care provider. Based on these factors, UC is classified as inactive, mild, moderate, severe or fulminant.

Table 2: Inclusion and Exclusion Criteria for Recipient Patients

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
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<tbody>
<tr>
<td>1. All patients will be over the age of 18 and be able to provide informed consent.</td>
<td>1. Any patients with severe systemic illness.</td>
</tr>
<tr>
<td>2. All patients will have a histological diagnosis of UC.</td>
<td>2. Any patients who have used antibiotics or probiotics within 4 weeks of starting trial.</td>
</tr>
<tr>
<td>3. All patients will have a Mayo score of 6-12 indicating moderate-to-severe disease severity³.</td>
<td>3. Patients with any concurrent infection.</td>
</tr>
<tr>
<td>4. All patients will have refractory disease while on standard doses of 5-ASA.</td>
<td>4. Any patients who are pregnant.</td>
</tr>
<tr>
<td>5. All patients will have been on a stable dose of 5-ASA for 2-4 weeks.</td>
<td>5. Patients who have received any immune modulating therapies.</td>
</tr>
<tr>
<td></td>
<td>6. Patients who have received any biologic medications.</td>
</tr>
<tr>
<td></td>
<td>7. Patients who have previously received any corticosteroids.</td>
</tr>
</tbody>
</table>
Patients who have an undetectable thiopurine methyltransferase genotype.

Patients who are receiving treatment for tuberculosis.

The estimated sample size will be 84 patients with active UC using sample size calculations that assume a 70% remission rate in the FMT arm and 46% remission rate in the placebo arm given 90% power and 5% significance.

**Treatment**

The eligible study population will be randomized 1:1 using computer generated randomization based on a complete list of patients from all of the participating medical centers. Group A will include 50% of the recruited patients and they will receive FMT, 6-mercaptopurine (50mg PO QD) and prednisone taper (see Table 3). Group B will include 50% of the recruited patients and they will receive placebo, 6-mercaptopurine (50mg PO QD) and prednisone taper (see Table 3).

**Table 3: Prednisone Taper Regimen**

<table>
<thead>
<tr>
<th>Number of Days</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>40 mg</td>
</tr>
<tr>
<td>7</td>
<td>30 mg</td>
</tr>
<tr>
<td>7</td>
<td>20 mg</td>
</tr>
<tr>
<td>7</td>
<td>10 mg</td>
</tr>
<tr>
<td>7</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

FMT donor screening, collection and processing will be performed per the Open Biome protocol for lower delivery microbiota preparation. Patients from both groups will undergo colonoscopies with biopsies on the first day they initiate their 6-MP regimen to assess baseline disease prior to starting therapy. At this time, Group A will receive
250mL of FMT via the colonoscopy according to the protocols established at each institution. Group B will receive 250mL of water via colonoscopy following the same methods in Table 2. Group A will then take 6-mercaptopurine 50mg PO QD, Prednisone taper and Open Biome FMT capsule G3 (10 capsules once a week) for 8 weeks. Group B will take 6-mercaptopurine 50mg PO QD, Prednisone taper and placebo capsules (10 capsules once a week) for 8 weeks.

**Study variables and measures**

The primary outcome will be clinical remission of UC by week 8, defined as a Mayo score of <3 and endoscopic Mayo score of =031. Secondary outcome will be fecal calprotectin value of <50 which indicates absence of significant intestinal inflammation. Additional secondary outcomes will be improvement in Inflammatory Bowel Disease Questionnaire (IBDQ) score and the serum inflammatory biomarkers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

**Recruitment**

Patients with moderate to severe UC who meet the inclusion and exclusion criteria will be recruited from the outpatient gastroenterology clinics of Boston Medical Center, Brigham and Women’s Hospital, Lahey Medical Center, Tufts Medical Center, Beth Israel Deaconess Medical Center and Massachusetts General Hospital. Each institution will be responsible for generating a list of eligible patients who receive gastroenterology care at their facility. Candidates will initially be informed of the study one week prior to a scheduled outpatient visit with their gastroenterologist. At the time of the visit, the investigators will meet with the patients to provide further details about the trial including
risks and benefits. Individuals who choose to be enrolled will sign a consent form to be registered for the study.

**Data collection**

Prior to starting therapy, each patient will undergo a complete physical exam and medical history. A stool and blood sample will be collected and analyzed for specific markers detailed in Table 4. Additionally, patients will take an Inflammatory Bowel Disease Questionnaire survey to obtain a baseline score.

**Table 4: Baseline Stool and Blood Testing**

<table>
<thead>
<tr>
<th>Stool Studies</th>
<th>Blood Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fecal Calprotectin</td>
<td>1. Complete Blood Count</td>
</tr>
<tr>
<td>2. Clostridium difficile</td>
<td>2. ESR</td>
</tr>
<tr>
<td>3. Salmonella</td>
<td>3. CRP</td>
</tr>
<tr>
<td>4. Shigella</td>
<td>4. Thiopurine Methyltransferase Genotype</td>
</tr>
<tr>
<td>5. Campylobacter</td>
<td>5. Human Immunodeficiency Virus IgG (types 1 and 2)</td>
</tr>
<tr>
<td>7. Ova and Parasites</td>
<td>7. Hepatitis A IgG and IgM</td>
</tr>
<tr>
<td></td>
<td>8. Hepatitis B surface antigen, surface antibody, and core antibody</td>
</tr>
<tr>
<td></td>
<td>9. Hepatitis C IgG and IgM.</td>
</tr>
</tbody>
</table>

Patients will receive a phone call at weeks 1, 2, and 5 after the start of treatment to assess for adverse events (see Appendix 1).

Patients will have a gastroenterology clinic visit at week 4 for a complete physical exam, and to provide stool and blood samples. They will also complete IBDQ at this visit. Patients will have colonoscopies with biopsies performed at week 8 to endoscopically evaluate disease response to treatment. At this time, they will again
undergo a complete physical exam and provide stool and blood samples. Patients will have a follow up clinic visit at week 12 (4 weeks after therapy completion) for a final physical exam, stool and blood collection and IBDQ.

**Data analysis**

A Pearson’s chi squared test will be used to analyze the primary outcome: patients in clinical remission at the end of the study. Absolute risk and relative risk for remission will be calculated between groups as well as number needed to treat. Quantitative variables such as Mayo score, fecal calprotectin, IBDQ score, ESR and CRP will be statistically analyzed using SAS 9.3 (Cary, NC). Appropriate means, standard deviations, and ranges will be calculated. Continuous data will be analyzed using student’s t-tests and linear regression. Descriptive statistics will be used to characterize patients by demographic features such as age and ethnicity. Pearson’s correlation coefficient will be use to assess correlations between gender, smoking status and extent of disease. Multivariate analysis, specifically multiple logistic regression analysis, will be used to adjust for possible confounders. Stratified analysis will be used to control the effect of any baseline factors that are determined to be confounders.

**Timeline and resources**

**Table 5: Study Timeline**

<table>
<thead>
<tr>
<th>Fall 2016</th>
<th>IRB Submission and Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2017-January 2018</td>
<td>Patient Recruitment</td>
</tr>
<tr>
<td></td>
<td>Treatment Intervention</td>
</tr>
<tr>
<td>Spring 2018</td>
<td>Data Analysis</td>
</tr>
</tbody>
</table>
The primary investigator and co-investigators at each medical center will perform project oversight, data collection and data entry. A statistician will perform analysis of the data.

**Institutional Review Board**

The protocol of the study will be submitted for full IRB review to the Boston University Medical Campus IRB under INSPIR II criteria, and to the corresponding IRBs of the participating institutions.
CONCLUSION

Discussion

This study does have notable limitations. First, the recruited subjects will all likely be from Northeast region of the United States. This would limit the generalizability of the study to other parts of the country given the gut flora from donors and patients would be from one geographical area. Secondly, because the study calls for individuals with a specific disease severity, it will not be generalizable to those who do not fit the targeted category. Furthermore, the sample size of the study is relatively small. Finally, there are no studies that have evaluated the most efficacious mode of delivery and dose of FMT; therefore, these factors may need to be adjusted to have increased response rates.

Additionally, the study does have anticipated obstacles. The treatment plan requires adherence to large numbers of oral medications as well as close follow up with frequent clinic visits and telephone calls. This can be very time consuming and unfavorable to subjects which may result in participants exiting the study. If this does prove to be a significant barrier, it will be important to simplify the treatment regimen and educate subjects on the importance of close follow-up.

Summary

The step up approach for the medical management of ulcerative colitis has been widely accepted by gastroenterologists. However current therapies rely on targeting the immune system from the side of the host, rather than the intestinal triggers of inflammation. Advancing research has revealed that intestinal dysbiosis may also contribute to UC and this can be corrected to restore a more natural gut microbiome with the use of FMT.
Using a treatment modality that addresses both immune dysregulation towards commensal bacteria and dysbiosis may be a beneficial addition to the step up approach.

Research has showed that FMT has the potential to be an efficacious adjuvant treatment for patients with UC. However, current FMT studies have inconsistent combination treatment regimens in the subjects. Moreover, sub-analysis of these studies have shown increased remission in patients taking FMT and immunomodulating therapies compared to those taking other medications, but this has not been specifically investigated.

The proposed study will use a combination of FMT, 6-MP and corticosteroids to evaluate if this is an efficacious regimen for inducing remission in patients with moderate to severe UC. This project will help to identify if correcting dysbiosis and modulating the immune system is beneficial for patients suffering from acute disease flairs. Furthermore, this study can provide information that would increase options for both UC patients and gastroenterologists when choosing treatment plans.

**Clinical and/or public health significance**

Patients who suffer from UC that is refractory to medical management commonly require surgical intervention to prevent serious complications. Although curative, a total colectomy is an invasive, life changing intervention. By identifying if FMT is an effective adjuvant, an additional component can be added to the step up approach for managing UC. Ultimately, this could prolong or eliminate the necessity for surgery. The goal is to provide healthcare providers and patients with another effective regimen to medically manage such a complicated illness.
APPENDIX

Appendix 1:

Phone Call Survey

1. Have you been experiencing bloating or flatulence?  
   Yes  No

2. Have been experiencing abdominal pain?  
   Yes  No

3. Have you been experiencing diarrhea?  
   Yes  No

4. Have you been experiencing hematochezia?  
   Yes  No

5. Have you been experiencing fatigue?  
   Yes  No

6. Have you been experiencing fevers?  
   Yes  No

7. Have you required any trips to the emergency department or to your primary care provider?  
   Yes  No
## LIST OF JOURNAL ABBREVIATIONS

<table>
<thead>
<tr>
<th>Journal Abbreviation</th>
<th>Full Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am J Gastroenterology</td>
<td>American Journal of Gastroenterology</td>
</tr>
<tr>
<td>BMJ</td>
<td>British Medical Journal</td>
</tr>
<tr>
<td>Best Pract Res Clin Gastroenterol</td>
<td>Best Practice and Research: Clinical Gastroenterology</td>
</tr>
<tr>
<td>Clin Infect Dis Off Publ Infect Dis Soc Am</td>
<td>Clinical Infectious Disease: Official Publication of Infectious Diseases Society of America</td>
</tr>
<tr>
<td>Clin Microbiol Rev</td>
<td>Clinical Microbiology Reviews</td>
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<tr>
<td>Cochrane Database Syst Rev</td>
<td>Cochrane Database of Systematic Reviews</td>
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<td>Curr Opin Cell Biol</td>
<td>Current Opinion in Cell Biology</td>
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<td>EMBO Journal</td>
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<td>FASEB J</td>
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<td>Genome Biology</td>
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<td>Inflamm Bowel Dis</td>
<td>Inflammatory Bowel Disease</td>
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<tr>
<td>J Crohns Colitis</td>
<td>Journal of Crohn's and Colitis</td>
</tr>
<tr>
<td>J Pediatr Gastroenterol Nutr</td>
<td>Journal of Pediatric Gastroenterology and Nutrition</td>
</tr>
<tr>
<td>JAMA</td>
<td>The Journal of the American Medical Association</td>
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<tr>
<td>Mayo Clin Proc</td>
<td>Mayo Clinic Proceedings</td>
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<tr>
<td>Mol Cell Biol</td>
<td>Molecular and Cellular Biology</td>
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<tr>
<td>Nat Rev Gastroenterol Hepatol</td>
<td>Nature Reviews Gastroenterology &amp; Hepatology</td>
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<tr>
<td>Journal</td>
<td>Abbreviation</td>
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<tr>
<td>Nat Rev Immunol</td>
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<td>NEJM</td>
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<td>Pharmacol Ther</td>
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<td>World J Gastroenterol</td>
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REFERENCES


31. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the Non-invasive Components of the Mayo Score to Assess Clinical Response in...
CURRICULUM VITAE

Sejal Mahesh Thaker

Home Address: 478 Massachusetts Ave. Unit 1, Boston, MA 02118
Phone: 805-794-8844
Email: sthaker@bu.edu
Place of Birth: Yonkers, NY 1992

Education and Training

2014 – Present  Physician Assistant Student
                Boston University School of Medicine

2010 – 2014    University of California, Irvine
                Bachelor of Science, Biological Sciences

Honors and Awards

2010 – 2014    Dean’s Honors List (University of California, Irvine)
2011           Mesa Court Leadership and Community Award (University of
                California, Irvine)
2010           Miss California (Homecoming Queen Inc.)
2010           2nd Place Miss America (Homecoming Queen Inc.)
2009           Miss Teen Ventura County International (Intl Pageant, Inc.)
2009           Miss Congeniality (Intl Pageants, Inc.)

Research and Related Activities

2014 – 2016    The Role of Fecal Microbiota Transplants in the Management
                of Inflammatory Bowel Disease
                Physician Assistant Program
                School of Medicine
                Mentor: Sharmeel Wasan, MD
                Boston University
                Literature Review Thesis

2012 – 2014    The Effects of Electro-Acupuncture on Acute and Chronic
                Hypertension
                Department of Medicine
                Mentor: Zhi-Ling Guo, MD
                University of California, Irvine
                Cardiovascular Research Lab
## Work Experience

### 2014 – 2016
- **Shoreline Ambulance**
  - Huntington Beach, CA
  - Responded to emergency medical aid calls and transports for Basic/Advanced Life Support and Critical Care patients in Orange, Los Angeles, and San Bernardino Counties.

## Community Service

<table>
<thead>
<tr>
<th>Year</th>
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<th>Location</th>
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<tbody>
<tr>
<td>2014</td>
<td>Health Fair</td>
<td>Healthcare for the Homeless</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Boston, MA</td>
</tr>
<tr>
<td>2012 – 2013</td>
<td>AIDS Services Foundation</td>
<td>Irvine, CA</td>
</tr>
<tr>
<td>2010 – 2012</td>
<td>Red Cross Club</td>
<td>University of California, Irvine</td>
</tr>
<tr>
<td>2010 – 2011</td>
<td>Hospital Volunteer</td>
<td>UC Irvine Medical Center</td>
</tr>
</tbody>
</table>

## Leadership

### 2014 – 2016
- **Student House of Delegates Representative, Boston University School of Medicine Physician Assistant Program**
  - Program delegate to state and national professional organizations

### 2015
- **American Academy of Physician Assistants Leadership and Advocacy Summit**
  - Lobbied a bill to allow Physician Assistants to provide hospice care to California State Legislators at national meeting

### 2015
- **Massachusetts Academy of Physician Assistants – PA Day on Beacon Hill**

### 2015
- **American Academy of Physician Assistants National Conference**
  - Attended the House of Delegates meeting over 3 days which reviewed and voted on legislations regarding the PA profession and education

*References Available Upon Request*