A Systematic Review of the Efficacy and Safety of Fecal Microbiota Transplant for *Clostridium difficile* Infection in Immunocompromised Patients

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1. Introduction

*Clostridium difficile* (CD) infection is the leading cause of healthcare-associated diarrheal illness in the United States, affecting nearly 500,000 patients annually [1, 2]. Both incidence and severity of CD infection have increased over the past two decades, and CD infection is now responsible for 29,000 deaths/year within 30 days of diagnosis [1]. Immunocompromised patients, including those receiving immunosuppressant medications or patients with human immunodeficiency virus (HIV) and transplants, seem to be at increased risk of hospitalization and recurrence of CD infection as the immune system is an important defense for both protection and recovery from infection [3–6].

Antibiotics have long been the mainstay of treatment for CD infection. However, 25% of patients suffer recurrence of CD infection within 60 days of antibiotic therapy [7, 8]. FMT has emerged as an effective alternative for the relapsed and...
refractory CD infection patients with reported success rates of 80-90% in clinical trials [9, 10]. Due to safety concerns related to introducing bacterial therapy in immunocompromised patients, those with immunocompromised states have been excluded from most trials, and guidelines currently recommend caution in these patient populations due to the absence of safety and efficacy data [11, 12].

The aim of our study is to conduct a systematic review of the existing literature to collate the evidence for efficacy and safety of FMT in immunocompromised population.

2. Methods

We searched PubMed, EMBASE, and Google Scholar for English language articles published on FMT for treatment of CD infection from inception through May 2017.

These databases were searched using the search terms under 2 broad search themes of "Clostridium difficile" and "fecal microbiota transplantation" and were combined using a Boolean operator AND (see supplementary file 1). For the term "Clostridium difficile", we used a combination of MeSH entry term words Clostridium difficile and C. difficile. For the MeSH term "fecal microbiota transplantation", we used synonyms for fecal microbiota transplantation, intestinal microflora transfer, donor feces infusion, and stool transplant. We made the decision not to include the term "immunocompromised" due to concerns that our search would not capture the patients broadly enough. We instead reviewed all individual articles for descriptions of treated patients who matched our definition of immunocompromised.

We defined a patient as immunocompromised if that patient was receiving immunosuppressive agents (including but not limited to mTOR inhibitors, calcineurin inhibitors, anti-TNF agents, other biologic agents, high dose steroids > 20 mg/day or ≥ 1 mg/kg for > 14 days), patients with human immunodeficiency virus (HIV) infection (regardless of CD4 count), acquired immune deficiency syndrome (AIDS), inherited or primary immunodeficiency syndromes, hematologic malignancy or solid tumor (active with treatment in past 3 months or in remission for less than 5 years), solid organ transplant, and/or bone marrow transplant. We excluded inflammatory bowel disease (IBD) patients that were not receiving immunosuppressant medications. We also excluded patient with chronic medical conditions such as chronic liver disease, chronic kidney disease, and autoimmune conditions not on immunosuppressant. We included patients of all age groups.

Our outcomes of interest were clinical resolution of diarrhea, bacteriologic resolution, treatment failure, adverse events, and mortality. Clinical or bacteriologic resolution was defined as absence of diarrhea or need for further CDI treatment after FMT within the study or follow-up period clinically or with C. difficile toxin testing, respectively. Treatment failure was defined as nonresponse or recurrence of diarrhea with or without positive C. difficile toxin. We defined post-FMT death as any death within 30 days of FMT.

We reviewed all study types with original data published in English language. The reference lists of included articles and chosen articles were manually hand-searched for additional articles. Our eligibility criteria for inclusion were as follows: (1) studies of any type on human subjects with a full published manuscript who met at least one of our definitions for immunocompromised, (2) received fecal transplant via any method for a laboratory-confirmed, symptomatic CD infection, and (3) any of the outcomes of interest was reported in the manuscript. We included patients who received FMT in inpatient, outpatient, or home setting. We excluded studies that evaluated FMT for non-CD illness. We excluded conference abstracts to avoid duplication of our study population with a subsequent full publication. We excluded studies that did not report on any of our outcomes or had mixed population of immunocompromised and immunocompetent patients that did not report outcomes of immunocompromised population separately.

Three reviewers (YF, SV, and OS) independently screened titles and abstracts and excluded irrelevant studies. Full manuscript review was conducted by three investigators (YF, SV, and OS) to determine inclusion eligibility. Disagreement on inclusion was adjudicated by a third investigator (AD). Data extraction was performed by 3 investigators (GS, AJ, and SV) and reviewed for accuracy by a third investigator (OS).

We extracted data on patient’s characteristics including age, gender, number of CD infections prior to FMT, interventions prior to FMT, time from index CD infection diagnosis to FMT, method of diagnosis of index CD infection, and reasons for immune compromise. We collected study characteristics including study type, location, clinical setting, and duration of study including length of follow-up period. We also extracted FMT treatment data, including delivery method (upper GI infusion, capsule ingestion, colonoscopic infusion, or enema), number of treatments, whether fresh or frozen stool was administered, treatment dose infused, stool donor relationship (related or unrelated), pretransplant bowel preparation, and pretransplant use of antibiotics. Outcome data collected included resolution of clinical symptoms, treatment failure after single FMT, all-cause mortality within 30 days, number of relapses, and need for additional FMT prior to resolution. We also categorized adverse events including colectomy, CD/FMT-related deaths, new hospitalizations, life-threatening events, need for surgery, infection complications, IBD flares, and time from infection to adverse event. A CD/FMT-related adverse event was defined as any complication or new event occurring within 30 days of first FMT. Duplicate patient entries were identified and removed. Authors were contacted for clarification on data where necessary.

We assessed study quality using questions from the NIH quality assessment tool for case series studies. We conducted quality assessment only on studies with at least five patients in original study population (Supplementary file 2) [57].

We did pooled studies and calculated resolution and adverse event rates with 95% confidence interval using STATA version 13 (College Station, TX). We set statistical significance at p ≤ 0.05. Some studies reported adverse events but had missing data for efficacy. Given the importance of adverse event outcomes in immunocompromised patients, we conducted separate efficacy and safety analyses.
There were no randomized controlled trials and study heterogeneity between the nonrandomized trials precluded performing a meta-analysis on our included studies.

3. Results

We identified 44 studies which met inclusion criteria describing 303 patients (Figure 1) [13–56]. Forty-three were single cases or case series and one was a retrospective cohort study, and no randomized designs were identified (Table 1). Of those studies reporting gender, 62% were females and 38% were males. The mean age was 57.3 years (range: 2-88 years). The most common reason for the immunocompromised state was use of immunosuppressant medication (77.2%). Other reasons for being immunocompromised included solid organ transplant (18.2%), active malignancy including lymphoma or leukemia (16.2%), hematopoietic stem cell transplant (2.5%), and HIV/AIDS (2.1%). There was more than one immunocompromising condition in 19.9% of patients.

Patient averaged about 2.5 episodes of CD prior to first FMT. Most patients (73.7%) had received other treatments for CD infection, mainly antibiotics, before FMT, with many (48.6%) receiving 2 or more CD infection treatments prior to FMT. Treatments other than antibiotics prior to FMT included probiotics, intravenous immunoglobulin, and surgery. For patients that received antibiotics prior to FMT, antibiotics were stopped on average about 1.5 days (range: 0-3, SD: 0.55 days) prior to FMT procedure.

Colonoscopy was the route of delivery of FMT in 76% of patients, while 21% had stool transplanted via ingestion of capsules or other upper gastrointestinal route (nasal tubes or endoscopy). Retention enema was performed in 7.6 % of patients. Most patients (95%) received fresh stool, while...
### Table 1: Summary of included articles.

| Author, Year | Article type | N patients included | Immunocompromised | FMT delivery | N transplant | Stool (g or volume (mL per transplant) | Donor relationship | AE |
|--------------|--------------|---------------------|-------------------|--------------|--------------|----------------------------------------|--------------------|----|
| Aas, 2003 [13] | Case series | 1 | Leukemia | NG Tube | 1 | 30 g/25 ml | NR | No |
| Aratari, 2015 [14] | Case report | 1 | IBD on IS | Colonoscopy | 1 | 150 g | UR | No |
| Bilal, 2015 [15] | Case report | 1 | Liver and kidney transplant on tacrolimus | Colonoscopy | 1 | 180 mL | R | No |
| Blackburn, 2015 [16] | Case report | 1 | Leukemia | Colonoscopy | 1 | NR | NR | No |
| de Castro, 2015 [17] | Case Report | 1 | ALL s/p HSCT | Upper Endoscopy | 1 | NR | NR | No |
| Duplessis, 2015 [18] | Case report | 1 | CD on IS | Upper Endoscopy | 1 | 75 g/200 mL | R | No |
| Ehlermann, 2015 [19] | Case report | 1 | Heart transplant | Upper Endoscopy | 1 | 100 mL | R | No |
| Elopre, 2015 [20] | Case series | 2 | AIDS, DM + AIDS | Upper Endoscopy | 1 | 30 g/25 ml | R | No |
| Fischer, 2015 [21] | Cohort | 101 | Multiple defined | Colonoscopy | 1 | NR | NR | NR |
| Friedman-Moraco, 2014 [22] | Case series | 2 | SOT | Upper Endoscopy and Colonoscopy | 2 | 30 g/80-325 mL | R | Yes |
| Garborg, 2015 [23] | Case series | 1 | AML | Upper Endoscopy | 1 | 50-100 g/200 mL | R | No |
| Gathe, 2016 [24] | Case report | 1 | HIV | Colonoscopy, Enema and Nasogastric tube | 4 | NR | R | No |
| Gutierrez-Delgado, 2016 [25] | Case series | 1 | Acute leukemia | Colonoscopy | 2 | NR | UR | No |
| Gweon, 2015 [26] | Case report | 1 | Thyroid cancer | Colonoscopy and Upper Endoscopy | 1 | 75 g | UR | No |
| Hirsch, 2015 [27] | Case series | 5 | Lymphoma, AML, Renal cell CA, IS | Oral (ingested) | 1-4 | 2.3 g (6-22 capsules) | UR | Yes |
| Hourigan, 2015 [28] | Case series | 3 | IBD on IS | Colonoscopy | 1 | 92 g | R | No |
| Kelly, 2014 [29] | Case series | 46 | IS, SOT, Severe/end stage chronic disease, Cancer, HIV | Colonoscopy | 1-2 | NR | NR | Yes |
| Khoruts, 2016 [30] | Case series | 38 | SOT, IS | Colonoscopy | 1 | NR | NR | NR |
| Kromman, 2014 [31] | Case series | 3 | IBD on IS | NG Tube | 1 | 30-60 mL | R | No |
| Laszlo, 2016 [32] | Case series | 1 | UC on IS | Colonoscopy | 1 | 150 mL | R | Yes |
| Lee, 2014 [33] | Case report | 1 | Liver transplant | Upper Endoscopy | 2 | NR | R | Yes |
| Lee CH, 2014 [34] | Case series | 3 | Renal transplant | Enema | 1-4 | 100 mL | UR | No |
| Loke, 2016 [35] | Case report | 1 | Specific Antibody Deficiency (SAD) | Colonoscopy | 1 | 50 g/500 mL | R | NR |
### Table 1: Continued.

| Author, Year       | Article type | N patients included |Immunocompromised | FMT delivery | N transplant | Stool (g or volume per transplant) | Donor relationship | AE |
|--------------------|--------------|---------------------|-------------------|--------------|--------------|-----------------------------------|--------------------|-----|
| Mandalia, 2016 [36]| Case series  | 37                  | HIV, AIDS, malignancy, IS | NR           | 1-3         | NR                                | NR                 | Yes |
| Mattila, 2012 [37] | Case series  | 3                   | Lung transplant    | Colonoscopy  | 1-2         | 100 mL                            | R and UR           | No  |
| Mittal, 2015 [38]  | Case report  | 1                   | Diffuse large B cell non-Hodgkin's lymphoma + UC | Enema        | 2           | NR                                | NR                 | Yes |
| Neemann, 2015 [39] | Case report  | 1                   | ALL ± p HSCT       | Upper Endoscopy | 1 | 30 mL                            | R                  | NR  |
| Ott, 2017 [40]     | Case series  | 3                   | Kidney transplant, HIV, Colon Cancer | Upper Endoscopy | 1 | NR                                | R and UR           | No  |
| Pathak, 2014 [41]  | Case series  | 3                   | Adenocarcinoma left colon, Renal transplant, Cancer | Colonoscopy  | 1 | 6-8 teaspoons, 40-500mL            | R                  | No  |
| Pierog, 2014 [42]  | Case series  | 2                   | IBD on IS          | Colonoscopy  | 1 | 60 mL                              | R                  | Yes |
| Porter, 2014 [43]  | Case report  | 1                   | B cell CLL         | Upper Endoscopy | 6 | 50 g                              | UR                 | NR  |
| Quera, 2013 [44]   | Case report  | 1                   | CD on IS           | Colonoscopy  | 1 | NR                                | NR                 | Yes |
| Ramay, 2015 [45]   | Case report  | 1                   | Heart transplant   | Colonoscopy  | 2 | 250 mL                             | UR                 | No  |
| Ray, 2014 [46]     | Case series  | 2                   | Multiple           | Colonoscopy  | 1 | 60 mL                              | R                  | No  |
| Rubin, 2012 [47]   | Case series  | 15                  | Malignant disease  | Upper Endoscopy | 1 | 30 g/25 ml                     | R                  | No  |
| Russell, 2014 [48] | Case series  | 1                   | UC on IS           | Colonoscopy  | 1 | 30-40 g/250 mL                    | R                  | Yes |
| Schunemann, 2013 [49]| Case report | 1                   | AIDS               | Colonoscopy and Upper Endoscopy | 2 | NR                                | R                  | No  |
| Silverman, 2010 [50]| Case series | 3                   | Lymphoma, liver transplant | Enema        | 1 | 50 mL                              | R                  | Yes |
| Stripling, 2015 [51]| Case report | 1                   | Cardiac, kidney transplant on IS | Upper Endoscopy | 1 | NR                                | R                  | No  |
| Trubiano, 2014 [52]| Case report  | 1                   | Diffuse large B cell lymphoma | Upper Endoscopy | 2 | 260 mL                            | R                  | No  |
| Webb, 2016 [53]    | Case series  | 5                   | HSCT               | NJ tube      | 1 | 25-100 g                          | NR                 | Yes |
| Weinigarden, 2013 [54]| Case series | 1                   | Metastatic Ovarian cancer | Colonoscopy  | 1 | NR                                | UR                 | Yes |
| Yoon, 2010 [55]    | Case series  | 2                   | Colon cancer, Breast cancer | Colonoscopy  | 1 | NR                                | R                  | No  |
| Zainah, 2012 [56]  | Case report  | 1                   | UC on IS           | Colonoscopy  | 1 | 300 mL                            | R                  | No  |

AE= adverse events; ALL= acute lymphocytic leukemia; AML= acute myeloid leukemia; CA= cancer; CD= Crohn’s disease; CLL= chronic lymphocytic leukemia; E= enema; HIV= human immunodeficiency virus; IBD= inflammatory bowel disease; IS= immunosuppressant; HSCT= hematopoietic stem cell transplant; LTE= letter to editor; NG= nasogastric tube; NR= not reported or no separate patient level data on immunocompromised patients; R= related (genetically or household; SOT= solid organ transplant; UC= ulcerative colitis; UG= upper gastrointestinal endoscopy; and UR= unrelated

**= more IC patients but only including those with separate data that we could match to IC status, outcome, and AE

#= article reports where most centers used colonoscopy; possibly some included patients had other route of delivery.
5% utilized commercially prepared products. Among those reporting source of stool, a related donor was employed in 75% of patients.

A total of 234 patients had data on outcome and were included in the efficacy analysis. Of these, 206 (87.7%) had clinical resolution of CD infection after first FMT treatment, while 93% had resolution after 2 or more FMT attempts. Comparing rate of resolution by delivery method, colonoscopy delivered FMT had an 84% success rate, while upper gastrointestinal delivery (via endoscopy, capsule, and nasogastric or nasojejunal tubes) resulted in 92% success rate \( p = 0.202 \). In terms of number of immunocompromising conditions, patients with one condition had a success rate of 93%, while those with two or more immunocompromising conditions were resolved 78% of the time (Odds ratio (OR) 0.24, 95% CI: 0.11-0.51, \( p < 0.0001 \)).

All 303 patients were included in the safety analysis. There were 2 reported deaths. Both deaths were in patients with solid organ transplants. One patient died 13 days after successful FMT, with death due to progressive pneumonia, while the second patient died 1 day after FMT following aspiration pneumonitis during sedation for colonoscopy. Other reported adverse events include 2 colectomies, 5 episodes of bacteremia or infection, 10 subsequent hospitalizations, 7 otherwise unspecified life-threatening complications, and 7 flares of inflammatory bowel disease. Twenty-eight patients had other complications including abdominal pain, irritable bowel syndrome, nausea, fever, and diverticulitis post-FMT procedure. Mean time to adverse event was 26.6 days (range: 0-56, SD: 34.3 days) from FMT (Table 2).

Twenty of the included 43 case reports/studies had at least 5 patients in the original study population. Only 10 studies showed adequate reporting in all of six essential domains of study quality (study objective, case definition, outcome measure definition, FMT procedure, adequacy of follow-up, and donor characteristics), with others missing 1 to 3 of these elements (Supplementary file 2).

### 4. Discussion

Our review identified an 88% success rate after a single FMT and 93% after multiple FMTs in our immunocompromised population, which parallels the 80-90% success rates reported in the general population [9, 10]. Patients with a single immunocompromising factor had a higher rate of treatment success when compared to patients with multiple immunocompromising factors \( p < 0.001 \). In comparison, a retrospective series by Kelly et al. looking at 80 immunocompromised patients with CD infection treated with FMT reported a 78% cure rate following a single FMT and 89% cure rate with multiple FMT [28]. Of these 80 patients, 38 met our inclusion criteria and were included in our analyses. A recent systematic review and meta-analysis by Ianiro et al. found a similar cure rate of 93% after multiple FMT with a 76% cure rate after a single FMT [38]. While Ianiro et al. excluded case reports and case series with less than 10 patients who received FMT for CDI with a minimum of 8 weeks follow-up, our study focused on only immunocompromised patients regardless of the study size given our already limited study population.

Safety concerns were the rationale for excluding immunocompromised patients from clinical trials and expression of caution in guidelines for FMT. We identified just 2 deaths among out 303 patients with 30 days of FMT. Both deaths were reported in a retrospective review by Kelly et al. but we could not directly ascertain whether those deaths were directly related to FMT, to the CD infection or the patient's underlying immunocompromised states. Other deaths in our included studies were either not related to FMT (postcolectomy complications) or occurred beyond 30 days after FMT [23, 37]. Of those reporting rehospitalization following FMT, 8.3% reported this. While fecal transplant has been associated with reactivation of existing immune-mediated disorders or new disorders such as immune thrombocytopenia, rheumatoid arthritis in immunocompetent patients following treatment, this side effect was not identified in our study [59]. It is possible that the underlying immunosuppressed states of our study population may have suppressed any adverse immunologic responses observed in immunocompetent patients.

Our study has the following strengths. It addresses a very specific population with CD infection that has a higher incidence of CD infection with higher risk of recurrence and would ideally benefit from FMT. In addition, we included only patients who met a standard, predetermined definition of immunosuppression. However, our study has some limitations. We reviewed case reports and series, as there were no RCTs that were identified for inclusion. Inclusion of case reports with possibility of publication bias towards positive results might account for the high success rate after a single FMT. Missing data on demographics, method of stool transplantation, volume and amount of stool, and relationships of donor and recipients were common in our review and were also noted in a similar review by Bafeta et al. [60]. One clinical trial had immunocompromised patients that met inclusion criteria but had a mixed population of patients that included immunocompetent patients and did not provide separate data on the included immunocompromised population and therefore could not be included in our study [61]. Our efforts at contacting authors to provide data on immunocompromised patients were unsuccessful. In the absence of clinical trials, overall studies were too heterogeneous precluding a meta-analysis.

### 5. Conclusion

In conclusion, FMT in immunocompromised appears to have comparable efficacy and safety data to those on patients with intact immunity. However, due to heterogeneity of immunosuppression subtype, no solid conclusion can be made about any single specific immunocompromised states or a combination regarding response to FMT. Further randomized trials including these patient populations would be appropriate.

### Disclosure

An abstract of the manuscript was presented at the American College of Gastroenterology (ACG) Annual Scientific Meeting in October 2016 as a poster presentation.
Table 2: Adverse events (AE) in immunocompromised patients with recurrent CD infection treated with FMT.

| Author, Year | Patients with events (N) | Type of AE |
|--------------|--------------------------|------------|
| Friedman-Moraco, 2014 [22] | 1 | Life threatening event: ischemic stroke |
| Hirsch, 2015 [27] | 1 | New Hospitalization |
| | 1 | Life threatening event |
| | 1 | Abdominal pain |
| Kelly, 2014 [29] | 1 | Colectomy |
| | 1 | Death |
| | 1 | Death |
| | 5 | New Hospitalization |
| | 1 | Life threatening event |
| | 3 | Infection: pneumonia, Influenza, Pertussis |
| | 4 | IBD flare |
| | 11 | Others: Hip pain, Nausea, Bloating, Fever, Diarrhea, Abdominal pain, Catheter infection, Self-limited diarrhea, Minor mucosal tear during colonoscopy |
| Laszlo, 2016 [32] | 1 | Others: Mild abdominal pain |
| Lee, 2014 [34] | 1 | New Hospitalization/Life threatening event |
| Mandalia, 2016 [36] | 3 | IBD flare |
| | 1 | Diverticulitis |
| Mittal, 2015 [38] | 1 | New Hospitalization |
| Pierog, 2014 [42] | 1 | Life-threatening event/New Hospitalizations/Surgery |
| Quera, 2013 [44] | 1 | Life threatening event |
| | | Infection: Pan-sensitive E. coli |
| Russell, 2014 [48] | 1 | Colectomy/New Hospitalization/Life threatening events/Surgery |
| Silverman, 2010 [50] | 3 | IBS |
| Webb, 2016 [53] | 5 | Abdominal pain |
| Weingarden, 2013 [54] | 1 | Colectomy |

AE= adverse event; IBS= irritable bowel syndrome.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Oluwaseun Shogbesan contributed to conceptualizing, search, data abstraction, and manuscript writing. Samjeris Victor contributed to search, data abstraction, and manuscript writing. Dilli Ram Poudel contributed to data analysis, conceptualizing, and manuscript writing. Opeyemi Fadahunsi contributed to search. Asad Jehangir contributed to data abstraction. Gbenga Shogbesan contributed to data abstraction and conceptualizing. Anthony Donato contributed to conceptualizing and manuscript writing.

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Supplementary Materials

Supplementary 1. Supplemental File 1: search strategy.  
Supplementary 2. Supplemental File 2: study quality assessment using a modified NIH Quality Assessment Tool.

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