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Recurrent *Clostrioides difficile* Infection and Fecal Microbiota Transplantation in the Atlanta Metropolitan Area: 2016-2019

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Recurrent *Clostrioides difficile* Infection and Fecal Microbiota Transplantation in the Atlanta Metropolitan Area: 2016-2019

By

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BS, University of Texas at Austin, 2013
MD, UT Southwestern at Dallas, 2017

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An abstract of A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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Abstract

Recurrent *Clostrioides difficile* Infection and Fecal Microbiota Transplantation in the Atlanta Metropolitan Area: 2016-2019

By Nirja Mehta

Patients with multiple recurrences of *Clostridioides difficile* infection (CDI) have longer hospital stays and lower quality of life. Understanding characteristics of patients with multiple recurrent CDI episodes is important as these patients may benefit from microbiota restoring therapies in addition to standard antibiotics therapy to prevent further CDI recurrence.

Rates of recurrent *Clostridioides difficile* infection and the use of fecal microbiota transplantation (FMT) were studied in the metropolitan Atlanta area between 2016 to 2019 using three community wide databases: the Georgia Emerging Infections Program, the Georgia Hospital Association Discharge Database and the Atlanta Fecal Microbiota Transplantation. These databases were used to determine the number and chronology of recurrent CDI, associated demographic and comorbid conditions with patients with CDI and contextualize CDI and FMTs with regard to hospital admissions.

Among13,852 patients with at least one episode of CDI, 3,038 (22%) had at least one recurrence within 365 days. Patients with co-morbid conditions (i.e., pulmonary disease, renal disease, liver disease and diabetes) and those hospitalized for any reason soon after a CDI episode were more likely to have a recurrence. In this cohort, 250 FMTs were administered. Of patients with three or more episodes of CDI, 12% of patients received a FMT. FMTs were administered disproportionately to white, young women. Patient with co-morbid conditions such as cerebrovascular disease, congestive heart failure, diabetes, renal disease and liver disease were less likely to have received an FMT. FMT receipt was associated with decreased CDI recurrence (OR: 0.6; CI: 0.37-0.95) in a multivariable logistic regression model with propensity matching for likelihood of FMT receipt, compared to antibiotics alone in patients with recurrent CDI.

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Introduction

Recurrent *Clostridioides difficile* infection (rCDI) leads to major negative health and quality of life consequences[1]. CDI is traditionally treated with targeted antibiotics such as vancomycin, metronidazole and fidaxomicin though patients often have recurrence of CDI after these therapies. Recently, increasing use and evidence of the role of supplemental microbiome therapeutics, such as fecal microbiota transplantation (FMT), have resulted in professional society guidelines recommending FMT as a treatment consideration for rCDI [2-4]. Microbiome therapeutics utilize live bacteria or bacterial spores derived from healthy, non-infected patients [5]. This microbiologic material is introduced to the patient's colon, usually via colonoscopy, with the intent to restore the commensal bacteria to the gut microbiome.

Following the first randomized control trial in 2013 demonstrating fewer rCDI episodes with FMT compared to antibiotics alone [6], various institutions including several in metropolitan Atlanta began to offer this therapy. Between 2016 and 2019, at least 250 FMTs were administered to patients living in the eight-county metropolitan Atlanta. However, the outcomes of these patients compared to patients who received standard of care therapy is not well characterized outside of a single academic center study [7].

Microbiome therapy is a new field. FMTs were typically administered using colonoscopy which sometimes lead to barriers to delivery. However, there are now several additional microbiome products undergoing FDA approval with promising results [8, 9] that can be delivered through oral capsules or enemas, which has the potential benefit of improving patient access and acceptability by eliminating the risks and inconvenience of an invasive procedure. By understanding how FMT has been used, the patients who received these products and the outcomes following administration of FMT, we will be able to better inform our practices as we

begin to create protocols for the use of these novel microbiome therapeutics including for diseases other than rCDI.

In this study we aimed to first determine risk factors of rCDI, the most common indication for FMT, in our study population, and second quantify the beneficial outcomes attributable to FMT receipt among patients in our large metropolitan area.

Background

Clostridioides difficile is a gram positive spore forming, toxin producing anaerobe [10]. CDI is the most common healthcare-associated infection [11]. Annually, CDI accounts for an estimated 460,000 infections in the U.S. [12] at an estimated cost of more than $5.4 billion [13].

The pathogenesis of CDI is largely attributed to gut dysbiosis which is defined as a disequilibrium of naturally occurring microbiota in the gut microbiome. While gut colonization with *C. difficile* is common, meaning the bacteria is present but not causing disease, progression to pathogenic infection is driven by several complex processes including the influence of other microbiota in the environment.

C. difficile is introduced through oral ingestion of spores, which germinate in response to exposure to bile acids in the colon. The bacteria can then produce the toxin that leads to infection [14]. This process is influenced by other organisms in the surrounding microenvironment of the gastrointestinal tract. Several commensal bacteria in the gut hydrolyze primary bile acids which can decrease the potency of signals promoting germination [15]. Other bacterial metabolites such as short chain fatty acids produced by some taxa of bacteria found in gut acidify the environment to make conditions less favorable for proliferation [16]. Other bacteria directly produce antimicrobial peptides which directly target *C. difficile.* Viruses such as bacteriophages inhibit proliferation of CDI [17], whereas some fungal species may augment proliferation[18].

These complex interactions between the existing microbiome and *C. difficile* can lead either to a microbiome which protects against CDI infection, known as a "resistant microbiome." A resistant microbiome is a consortium of bacteria which prevents *C. difficile* from proliferating and causing disease. Conversely, a "susceptible microbiome" is one in which in which *C. difficile* is able to grow and result in disease [15]. Disruption and decreased abundance of various taxa of commensal bacteria is thought to result in increased microbiome susceptibility to CDI [19].

Likelihood of recurrence increases with each sequential episode of CDI. The rates of recurrence after a first episode is approximately 20% [20]. Approximately 35-40% of patients will go on to have a third episode after their second episode and approximately 45-50% of patients will go on to have recurrence after each episode following episode three [21]. Increasing rates of recurrence following each episode has been attributed to worsening gut dysbiosis with each subsequent episode of CDI.

Patients who develop rCDI have increased length of stay in the hospital and report lower quality of life due to infection [1, 22]. rCDI costs an excess of >$24,000 per patient given hospitalization and treatment costs [22].

Various studies report different significant clinical and demographic risk factors for recurrent CDI, however some of the most commonly cited risk factors include older age, healthcare-onset CDI, gastric acid suppression, recent hospitalization, recent IV antibiotic use, renal disease and inflammatory bowel disease [21, 23, 24]. Changes in the gut microbiome can be traced to several of these risk factors. As humans age, common changes in the gut microbiome have been linked to reduced immune function and increased susceptibility to disease [25]. Because gastric acid can damage spores, gastric acid suppression can increase susceptibility to disease in the colon. Renal disease may be associated with gut dysbiosis; additionally, these patients are both

immunosuppressed and have frequent healthcare exposure which may result in increased exposure to *C. difficile* and CDI. [26, 27]. Patients with inflammatory bowel disease are known to have dysbiosis due to chronic inflammation and epithelial damage [28].

The use of antibiotics increases risk of CDI. This is because in addition to the organism causing acute infection (ie pneumonia, urinary tract infection, etc), antibiotics also will incidentally damage the gut microbiome by killing commensal bacteria in the gut which prevent the pathogenesis of CDI. It is important to note that the mainstay of therapy for CDI is administration of relatively narrow spectrum antibiotics which are active against *C. difficile*, including fidaxomicin, vancomycin and metronidazole [3]. However, even these antibiotics, in addition to targeting *Clostridioides difficile*, may further exacerbate gut dysbiosis by killing other commensal bacteria [29]. FMT interrupts this cycle of worsening dysbiosis by replenishing commensal bacteria to a damaged microbiome and creating a resistant microbiome [30].

FMT has been used for hundreds of years for gastrointestinal ailments. The first written account of administration of FMT can be traced to a Chinese text from 400 AD. FMT was first used for pseudomembranous colitis (prior to the discovery *C. difficile* as the causative organism for this clinical entity) in 1958 with good outcomes in the four patients who received this therapy. The first randomized control trial for FMT was completed in the Netherlands in 2013 by van Nood who noted a 81% rate of resolution of CDI in patients after a first infusion of FMT, with a 100% resolution rate after a second infusion for those without initial resolution. Patients randomized to the vancomycin group alone were found to have a 31% resolution rate at ten weeks [6]. These results were so significant that the study was stopped after an interim analysis.

Since that time, multiple randomized and observational studies have demonstrated the efficacy of FMT for rCDI compared to antibiotics alone. When compared to vancomycin alone in a large meta-analysis, single administration FMT had an anticipated absolute effect of 72%

compared to 35% of vancomycin alone in preventing recurrent CDI at eight weeks. For patients with repeat FMT administration, FMT had a 93% anticipated absolute effect [30]. Route of FMT administration has also been evaluated with increased efficacy of colonoscopy over oral route of administration for a single dose, though these modalities appear to have similar results following multiple administrations [30].

The majority of studies evaluate outcomes of FMT at eight weeks, but a longer follow up period is valuable to better understand sustained responses beyond two months. We were able to find only seven studies which evaluated a follow up period of one year or longer. In these studies, primary cure rates (resolution of symptoms for at least 48 hrs) ranged from 82-100% and lack of recurrence (throughout the follow up period) ranged from 75-100% [31].

Mamo et al evaluated long term outcomes of FMT conducted at Emory University by following 137 FMT recipients for a median time of 22 months. This group found that, 82% of patients had no recurrence following FMT[7].

The overall goal of our study was to evaluate the real-world usage and outcomes of FMT in the Atlanta Metropolitan area, beyond a single institution, in order to inform protocol design for pill and enema based microbiome therapeutics nearing FDA approval. To evaluate sustained response, patient data was evaluated for 365 days after FMT to evaluate for recurrence.

Methods

Study Aims

This study aimed to 1) characterize rCDI in the Atlanta Metropolitan area by demographic and clinical information; 2) describe the use of FMT for rCDI in this study period and 3) estimate the attributable outcome of FMT. We hypothesized that older patients with recent hospitalization and multiple comorbid conditions would have higher rates of rCDI. We

expected patients with multiple rCDI episodes (more than 3 episodes in one year) to be significantly more likely to receive an FMT. Finally, we did expect to see a protective effect of FMT use against future rCDI.

Study Population

This study included patients over the age of 18 who were residents of Georgia Health District 3 (HD3), comprising eight counties in the Atlanta metropolitan area (Cobb, Douglas, Fulton, Clayton, Gwinnett, Newton, Rockdale, and Dekalb) between 2016 and 2019. An episode of CDI was defined as a positive laboratory assay in a resident without a prior positive test in previous 14 days. Patients with two episodes of CDI within 365 days were classified as having a one episode of rCDI. Patients with more than two episodes of CDI within 365 days were classified as having multiple episodes of rCDI. FMT recipients were defined as patients who received at least one FMT between 2016 and 2019. A final cohort was selected for the main analysis consisting of residents who at least one episode of rCDI during this study period and had at least one overnight hospitalization in an acute care hospital in the state of Georgia between 2016 and 2019.

Data Sources

Three data sources were used to complete this work. The Georgia Emerging Infections Program (EIP) conducts active laboratory-based population-based CDI surveillance which receives reports of all positive test results for *C. difficile* from laboratories caring for patients residing in HD3. *C. difficile* tests include: glutamate dehydrogenase (GDH), Toxin A/B EIA, *C. difficile* culture, nucleic acid amplification test and cell culture cytotoxic assay. All cases of incident and recurrent CDI were included in this dataset. Ascertainment of episodes spanned 2015-2020, to allow for one year of lead time prior to the diagnosis and one year of follow up

time around the planned study period of 2016-2019. Data collected includes the date and modality of testing. Information about demographics including age, gender and race were abstracted from the EIP database. This data, including race, was abstracted from the medical record and was not self-reported.

The Georgia Discharge Data System is maintained by the Georgia Hospital Association. This database records all acute care overnight hospitalizations with related dates of admission and discharge and up to 10 associated ICD-10 codes. Comorbidity information was assigned to each patient by compiling all ICD-10 codes associated with any hospitalization during this study period for each patient. The R comoRbidity package was applied to this data to evaluate whether patients had recorded ICD-10 codes which could be assigned to one of 17 possible comorbid conditions according to the Charlston Comorbidity index (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatoid disease, peptic ulcer disease, mild liver disease, diabetes without complications, diabetes with complications, hemiplegia, renal disease, cancer, moderate to severe liver disease, metastatic cancer, HIV/AIDS). Variables for inflammatory bowel disease and dialysis were created using known ICD-10 codes: K50.9, K51.9, K52.3, K52.9 and Z99.2, respectively.

We created the Atlanta FMT database by combining the list of all FMTs completed at two institutions which we estimate encompassed 90% of FMTs carried out in the Atlanta Metropolitan area during this study period based on expert knowledge and distribution of FMT product to area institutions from a large biobank. If one patient underwent FMT twice in eight weeks, the date attributed to FMT was the second date as this would be considered a single therapy with multiple doses in keeping with prior studies with similar definitions [32]. All

outcomes were determined following the date of the second episode. If a patient had two FMT episodes which were greater than eight weeks apart, only the first FMT episode was analyzed.

Database Linkage

Episode-level data from the EIP database was converted to patient-level data to quantify the maximum number of episodes each patient in the database had in one year. We chose not to link patients with a single episode of CDI, as FMT administration in this population is rare and given the challenges of merging such large datasets with likely diminishing benefit. The final cohort was created once patients with two or more episodes within one year (one recurrence or more) were linked with the hospital discharge database using patient identifiers. This allowed for linkage of 82% of patients with at least one recurrence to the discharge database. This dataset was then linked to the FMT database to identify FMT recipients and contextualize their FMT in the timeline of their CDI recurrence. Database linkage is detailed in Figure 1.

Analytic Plan

<u>Characterization of the Patients with CDI, by recurrence</u>

Crude annual incidence of recurrent CDI per year and incidence by age group per year was calculated using census data to determine the adult population for the catchment area, both in total and divided into each age group from the National Vital Statistics System for HD3. Median time between the first two episodes was reported comparing patients with a maximum of two episodes per year compared to patients with more than two episodes in one year. A Mann-Whitney-U test was used to compare these two values given lack of normality (data was skewed left). Differences in demographic information between patients with a single or more recurrences were reported. Reported p-values demonstrate global chi squared values. Because an incident case of CDI is defined as a positive laboratory assay, we evaluated the modality of diagnosis

during our study period. The methodology of diagnosis (laboratory assay) of each episode was reported as the total number diagnosed through this methodology per year.

Characterization of the CDI patients receiving FMT

Of the 499 patients in the Atlanta FMT database, 250 were identified in the EIP database. Demographic information of FMT recipients compared to non-FMT recipients was evaluated using univariable logistic regression. This analysis was repeated to include only patients with at least one rCDI episode to focus on the population most appropriate for an FMT. Timing of FMT relative to CDI episode number was determined, number and proportion of patients at each sequential CDI episode receiving FMT was calculated. A chart review was then conducted on patients who received an FMT prior to episode three in the Emory system. The reason for FMT was recorded if available. Patients were considered to have received FMT due to refractory disease if they continued to have diarrhea at the time of FMT despite antibiotic therapy. Patients were considered to receive FMT early if their symptoms resolved prior to FMT. Positive CDI tests reported in the chart outside of the catchment area were also recorded if found.

Episode Level Analysis

Most (82%) patients with one or more recurrences were linked to the hospital discharge database and 76% of FMT recipients who received an FMT after episode 2 were linked. At this point, data was transformed from a patient-level dataset to an episode level dataset, and the sequential episode number and the episode prior to FMT (if applicable) were preserved. These episodes were categorized as being followed by recurrence vs being the terminal episode of CDI in this study period.

Transformation to an episode level dataset allowed for the analysis of variables such as hospitalization prior to and after CDI, the use of antibiotics before and after CDI and the characterization of hospital onset CDI. Hospital onset CDI was defined as CDI diagnosis greater

than three days after the date of admission. Admission prior to CDI was defined as one or more admission dates ≤ 90 days to CDI diagnosis. Readmission following CDI was defined as one or more new admissions within 90 days of CDI diagnosis, but prior to the subsequent episode of CDI. Detailed definitions and data sets of origin can be found in Table 1.

Antibiotic use was estimated using a validated list of ICD codes which predict antibiotic use during a hospitalization[33]. If ICD codes affiliated with antibiotic use were associated with any admission with an admission date ≤ 90 days before CDI, this episode was assigned to have had antibiotics before CDI. A similar approach was used to assign a CDI episode as having antibiotics after CDI.

At the episode level demographic, co-morbidity and episode level characteristics were evaluated comparing episodes associated with a subsequent recurrence to episodes without a subsequent recurrence using univariable analysis and generalized estimating equations to account for repeated observations associated with the same subject. Episodes with subsequent FMT were compared to episodes without subsequent FMT evaluating demographic information, comorbidity information, episode number and episode level characteristics.

Propensity Matched Cohort

Variables from the analysis evaluating statistically significant demographic and comorbid information were included in propensity matching to build a propensity matched cohort. Variables found to have a p-value of <0.05 were included in propensity matching. Variables included in propensity matching included gender, age group, race and diagnosis of cerebrovascular disease, congestive heart failure, renal disease and diabetes. Propensity matching was conducted using proc PSMatch in SAS. A 1:1 match was conducted with the 150 episodes with subsequent FMT to non-FMT control episodes. We conducted exact matching on

episode number because the episode number impacts the likelihood of both subsequent recurrence as well whether a patient is offered FMT.

Univariable and multivariable logistic regression analysis was conducted on the propensity matched cohort. The multivariable analysis evaluated recurrence at one year as an outcome with covariates of FMT received, hospitalization following CDI episode, antibiotics following CDI episode and propensity score.

Results

Overview of Patients with CDI in this study period

A total of 13,852 adults were identified as having at least one CDI diagnosis during this study period. Of these patients, 10,814 (78%) had only a single episode. 2,055 (15%) had a maximum of two episodes in one year during this study period. 983 (7%) patients had two or more recurrences. Incidence of rCDI decreased yearly in our study period (Figure 2).

Overall, more females were found to have CDI than men. CDI was slightly more common among white patients than black patients. Patients between ages 45 to 79 years of age, were the largest age group diagnosed with CDI. Recurrence among age groups was similar (Table 2).

When incidence is calculated by age group, older patients (>65 years of age) were found to be more likely to be diagnosed with rCDI compared to the younger age groups. This trend was stable in all four years of the study period (Figure 3).

The time between episodes one and two was associated with recurrence (Table 2). Time between the first two episodes was longer in the patients who had a maximum of two episodes in one year, conversely this time was shorter in patients who went on to have a third or greater total episodes in one year (mean 82 days vs 65 days; $p < 0.01$).

Most of the diagnosis was completed with nucleic acid amplification testing (NAAT) only. NAAT testing alone, combination enzyme immunoassay (EIA) and glutamate dehydrogenase

(GDH) testing (listed as EIA, GDH) and combination GDH and NAAT (listed as GDH, NAAT) testing became less common. By 2019, rates of combination EIA and NAAT testing increased (Figure 4).

Overview of FMT recipients

A total of 250 were linked from the FMT database to the EIP database, with 109 (43%) from Emory Healthcare and 141 (56%) from the Hospital System 2. The number of FMTs provided per year varied between 76-49 FMTs (Table 3). FMT recipients were more likely to be female and white (Table 4). Younger patients were more likely receive FMT than older patients.

Of the 250 patients who received FMT, 25 patients (10%) had two FMTs, eight patients (3%) had three FMTs and one patient had four FMTs during this study period. Of the 34 patients who had multiple FMTs, 11 patients (33%) had at least two FMTs within eight weeks and 3 patients had three FMTs within eight weeks (Figure 5).

We anticipated most patients would have received an FMT after two recurrences. We found that 127 (52%) of patients were provided an FMT prior to the second recurrence (Table 5). A larger proportion of patients with multiple recurrent episodes received an FMT as they sequentially progressed in episode number (ie only 0.4% of patients with a single episode or more received an FMT after episode 1, but 10% of patients with ≥6 episodes received an FMT on or after episode 6).

Among patients who received FMT prior to episode two in the Emory Healthcare system, 32% received an FMT for refractory disease. 24% received the FMT earlier than episode three, usually due to anticipated immunosuppression or a presently immunosuppressed state. For example, some patients were planned for chemotherapy or organ transplantation, and FMT was provided prior to planned therapy. 16% of patients actually were found to have a total of three episodes, but one or more of these three episodes were not captured in EIP, typically due to

travel or recent move into the catchment area. In 27% of cases the reason for FMT was not clearly stated in the chart.

Predictors of recurrent CDI at the episode level

A total of 2495 individuals were linked to the discharge database. These individuals represented 4052 distinct episodes of rCDI (Table 6).

At the episode level, demographic differences were evaluated between episodes followed by recurrence vs episodes not followed by recurrence (Table 7). Gender and race were similar between episodes with recurrence and episodes without recurrence. This difference also only reached statistical significance in the 80+ group compared to the 18-44 years of age group.

On univariate analysis, chronic pulmonary disease, congestive heart failure, mild liver disease, diabetes with complications, renal disease and dialysis were found to be higher in patients with episodes with subsequent recurrence (Table 7).

At the episode level, admission after CDI, but not hospital onset CDI or admission or antibiotics before CDI, was associated with subsequent recurrence. In unadjusted analysis, FMT receipt was not associated with recurrence (Table 7).

Predictors of FMT receipt at the episode level

FMT recipients were more likely to be white, female and under the age of 45 (Table 8) compared to non-recipients. Patients with cerebrovascular disease, congestive heart failure, diabetes with complications and renal disease were less likely to have received FMT than those without those conditions (Table 8). Episodes sequentially higher in number of recurrences were usually more likely to be affiliated with an FMT (Table 8).

Estimating benefits attributed to FMT among Propensity Matched Cohort

The propensity matched cohort included 150 cases and 150 controls. Propensity scores were well matched between cases and controls (Figure 7). Characteristics were well balanced between cases and controls (Table 9).

In univariable analysis, FMT receipt in the propensity matched cohort was found to be protective against recurrence (Table 10). Readmission following CDI was associated with higher recurrence, but antibiotics following CDI were not found to be a statistically significant risk factor. In multivariate analysis, only FMT receipt was significantly associated with lower rCDI (aOR 0.6, p-value 0.03).

Discussion

This is the first study evaluating the real-world application of FMT in the Atlanta Metropolitan area inclusive of multiple institutions. Of all patients diagnosed with CDI in this study population, 22% had at least one recurrence, which is in keeping with national trends[20]. The vast majority of cases were diagnosed using NAAT testing alone, which was the most common methodology during this study period. It is important to note that NAAT testing may not reflect true symptomatic disease, but rather colonization [34] and more recent protocols recommend multi-step testing for diagnosis [3].

Females were more likely to have an incident case of CDI, but not appreciably more likely to have a recurrent episode. This gender difference has been reported in multiple studies, though the mechanism has yet to be elucidated [35, 36]. It is well established that gender differences in the gut microbiome are influenced by hormones, which may influence propensity for colonization and subsequent infection [37]. In our study, the absolute number of patients in older age groups was similar to the number of patients in younger age groups, however when the incidence of CDI and rCDI was calculated among age groups, elderly patients had a much higher

incidence of CDI. Older age is typically considered a risk factor for rCDI [21, 24, 38]. Time between the prior two episodes appears to be a major risk factor for second recurrence. This is likely reflective of a level of dysbiosis which allows for a more susceptible microbiome and has been found in other studies as well.

Several comorbid conditions were found to be risk factors for recurrence including chronic pulmonary disease, congestive heart failure, liver disease, diabetes with complications, renal disease and use of dialysis. All of these conditions commonly require hospitalization or frequent visits to healthcare facilities which could increase risk of exposure to CDI and possibly antibiotics as well. While malignancy and inflammatory bowel disease are both often cited as risk factors for CDI or rCDI, this was not found in our study. In the case of inflammatory bowel disease, there were few patients with this condition represented in our cohort. Finally, gastric acid suppression is often cited as a risk factor for rCDI [21, 23, 24]. This could not be directly measured using these datasets, however peptic ulcer disease, a condition for which gastric acid suppression is a mainstay of therapy, also was not associated with increased risk of rCDI.

Admission following CDI was found to be a significant risk factor for recurrence, which is consistent with prior studies. However, antibiotic use following CDI as well as hospital onset infection were not found to be risk factors in the univariate analysis though these are often cited as risk factors for CDI [23, 24]. Antibiotic use was extrapolated from ICD-10 codes, which may have allowed for some misclassification error of patients who did or did not actually receive antibiotics, though our numbers are in keeping with prior data that approximately 50-55% of patients will receive at least one antibiotic during hospitalization [39, 40]. Additionally, in this study, the number of antibiotic days was not measured, which would also influence the degree of dysbiosis [41].

Of all patients with recurrent CDI, only 6% of received an FMT. Many patients who received FMT received this prior to having three episodes of CDI. Among patients with three or more episodes of CDI, 12% received an FMT after episode three. This low rate of administration likely reflects a combination of several barriers to FMT administration including provider familiarity with the procedure and understanding of where to refer patients to receive this, difficulty of insurance coverage, concerns about subjecting patients to an invasive procedure and possibly patient perceptions of the procedure. While many of the studies evaluating provider and patient attitudes towards FMT predate our study, in a systematic review providers cited some concerns about infection transmission in more chronically ill patients, concern about patient acceptability and difficulty accessing this therapy as a reason they would not refer patients to receive an FMT [42]. For example, FMT was not offered at the large safety net hospital in Atlanta but was offered at academic and private centers during this study period.

The reason for increased FMT administration among females is not clear. However, it does appear that there was a preference to administer FMT to younger patients and patients without several serious comorbid conditions such as cerebrovascular disease, congestive heart failure, renal disease, diabetes and liver disease. Given that all FMTs administered in this study were administered through colonoscopy, physicians may have been reluctant to consider this therapy in older patients or patients with comorbid conditions which may make FMT a higher risk procedure.

Among the propensity matched cohort, FMT receipt was found to be protective against recurrence (aOR 0.6). Among patients who received an FMT, 34% had a recurrence (sustained non-recurrence at 365 days was 66%). This is higher than the recurrence rates cited in many studies. The vast majority of the patients in this cohort (87%) received a single infusion of FMT. Among patients in the literature with a single infusion, rates of resolution varied from 49%-95%

[43]. This heterogeneity likely reflects both different definitions of recurrence/resolution (in this study, we were unable to determine symptomatic cure), and the heterogeneity of the product itself given each dose is derived from different donors with different microbiota.

One of the most important findings in this study is that older patients and patients with liver disease, diabetes and renal disease were both more likely to experience rCDI and less likely to receive a therapy which has an up to superior sustained cure rate for CDI. We hypothesize the lower rates of FMT in these that this is due to the invasive nature of this therapy. While FMT has generally been shown to be safe in patients with significant co-morbid conditions such as organ transplantation and cirrhosis [44, 45], there have been reports of infection transmission through FMT [46]. These results demonstrate that an alternative therapy may increase uptake. Newer therapeutics include an oral product which utilizes bacterial spores derived from donor stool, but purified from additional microbiomes, and an enema with a known consortia of donor microbiota [8, 9, 47]. Both of these products may be a preferred option for patients with multiple co-morbid conditions as they do not require anesthesia or invasive procedures.

This work is an important addition to the literature evaluating real world use of FMT including variations in practices from guidelines and demographic and clinical differences in patients who were and were not offered FMT. Given that many studies evaluating FMT outcomes are often restricted to single institutions, this study allowed for capturing data on a community-level basis, allowing for the evaluation of practice patterns across multiple institutions.

There were several limitations to this work. Given that this study used surveillance data and we were unable to capture information about diarrheal symptoms, it is likely that some positive tests included in the study did not correspond with clinical disease; this is a limitation of all CDI studies completed through the Emerging Infections Program. Because one of the area

institutions did not keep a record of FMTs, there was some risk of misclassification bias as some patients classified as non-recipients may have had an FMT. However, given conversations with that group, they reported that their institute completed a total number of FMTs which would have constituted <10% of FMTs provided in this time period. There were 3,902 possible control episodes, 150 (4%) of which were used in the final propensity score analysis, so the chances of misclassification in the propensity matched model is relatively low. Additionally, information about comorbid conditions were restricted to ICD-10 codes entered by inpatient physicians which may not be reflective of all comorbid conditions of a patient. Finally, we were unable to capture outpatient antibiotics in this study which is also a risk factor for CDI.

This study launched several additional questions. We are presently working on a study evaluating the social vulnerability index (SVI) of patients with CDI with plans to compare whether there was difference in the SVI of patients who did and did not receive an FMT. A formal study evaluating attitudes towards both FMT and other microbiome products would be an natural extension of this work in order to better understand the reasons for the demographic and clinical differences observed in FMT recipients and non-recipients. Finally, we plan to model earlier use of FMT in the progression of CDI to evaluate possible differences in outcomes in different high-risk cohorts to evaluate which patients may benefit most from these therapies in the future.

Conclusions

This study improves understanding how microbiome products can benefit patients in a real-world setting. We describe factors that may represent barriers to receiving FMT including concerns about invasive procedures in patients with significant comorbidities. In this cohort of patients with at least one episode of rCDI and hospitalization in a large metropolitan area, FMT

receipt did appear to be reduce likelihood of further recurrence by roughly 50% adjusting for propensity to receive an FMT

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Figures and tables

Figure 1: Flow Diagram of CDI patients and Linkage to External Datasets

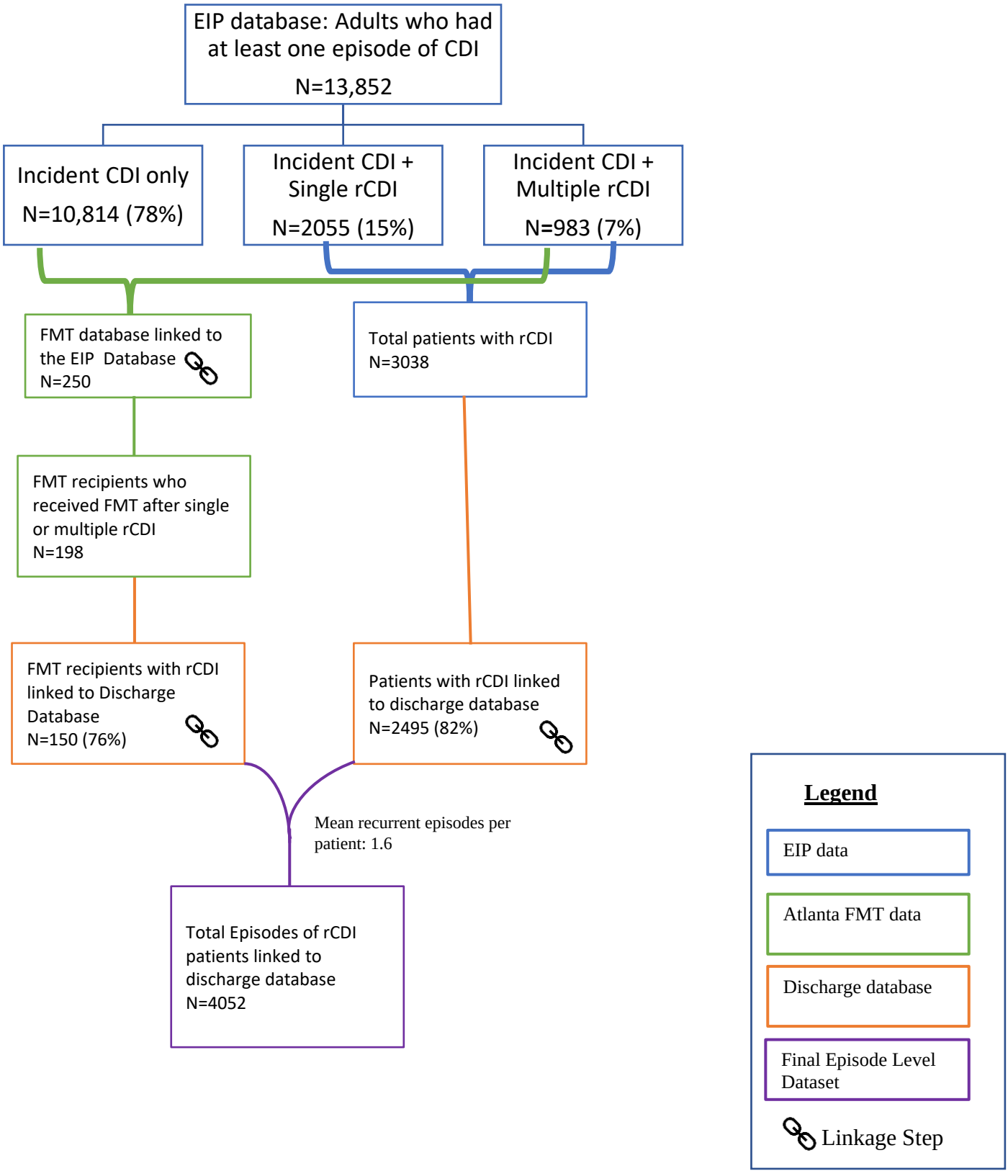


Figure 2: Crude Annual Incidence of Recurrent CDI per 100,000 population in the Atlanta Metropolitan Area, 2016-2019

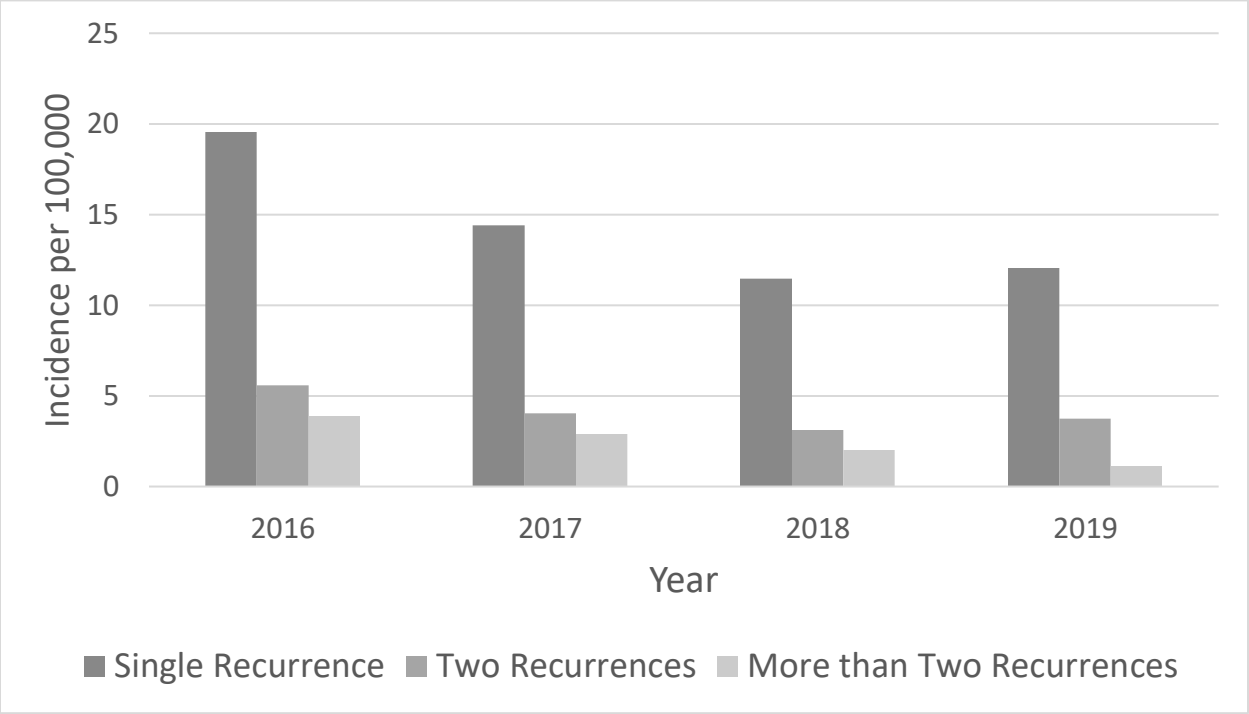


Figure 3: Annual Incidence of Recurrent CDI per 100,000 population in the Atlanta Metropolitan Area between 2016-2019 by Age Group

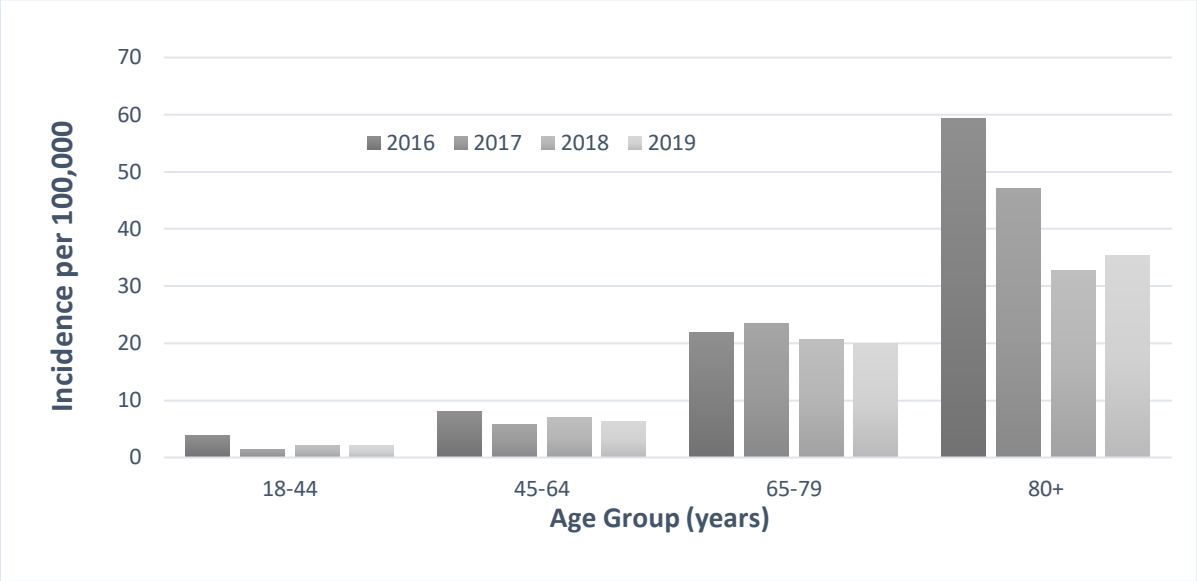


Figure 4: Clostridioides difficile Diagnostic Methodology by Year

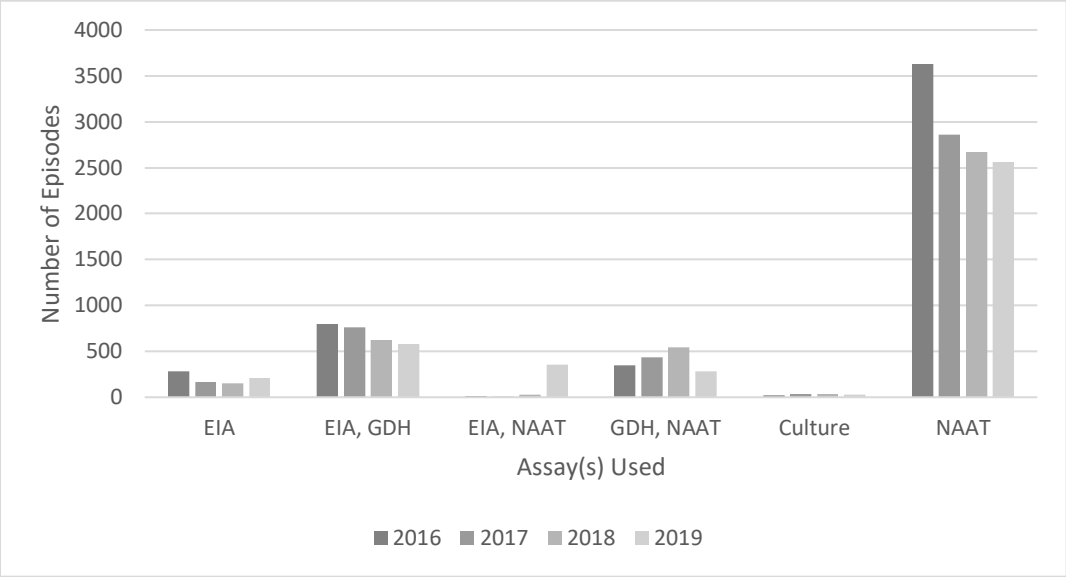


Figure 5: Days between Sequential Fecal microbiota transplant (FMT) Administration in Patients with Multiple FMTs, 2016-2019, by Sequence

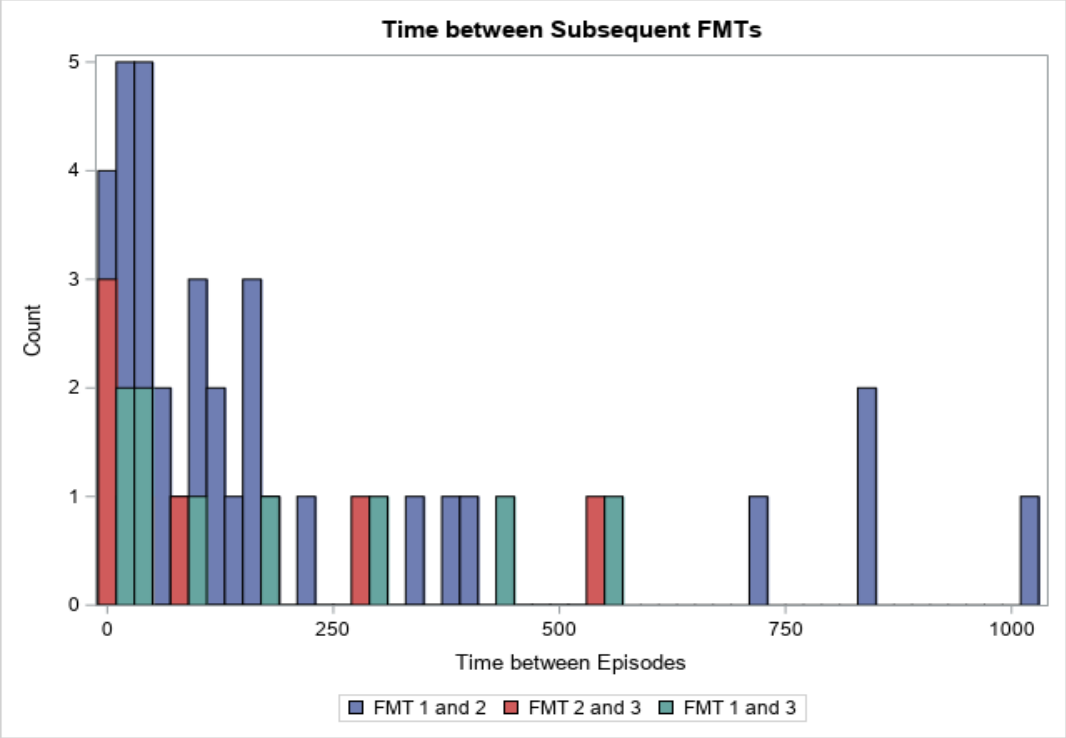
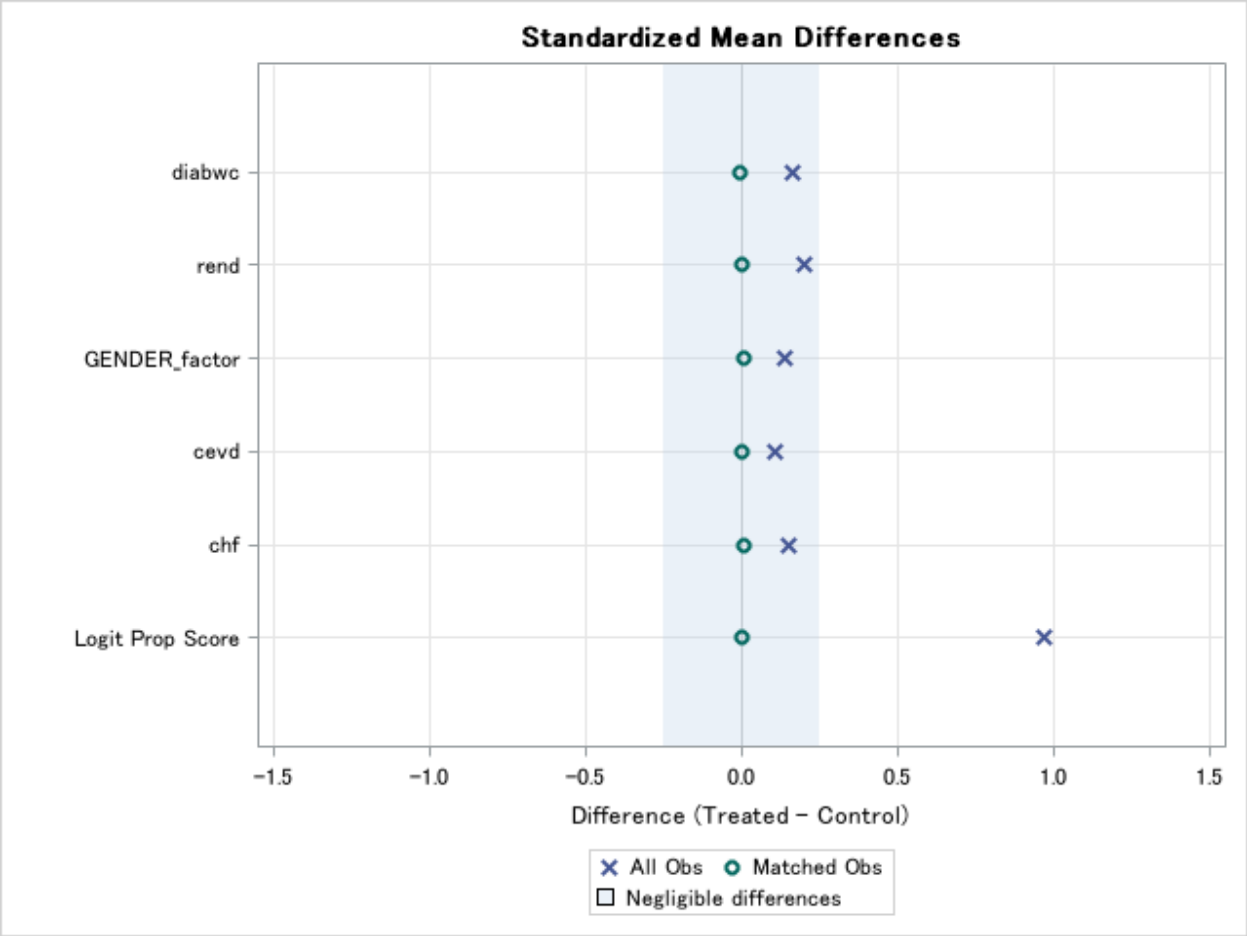


Figure 6: Standardize mean differences between cases in controls in the Propensity Matched Cohort compared to all observations



diabwc: diabetes with complications
rend: renal disease
GENDER_factor: gender
cevd: cerebrovascular disease
chf: congestive heart failure

Table 1: Definitions and datasets of origin

Term	Definition	Data set of origin
Incident Case of CDI	First laboratory assay positive for CDI within 365 days for a patient (resident in the GA EIP catchment area)	EIP
Recurrent CDI	One or more positive laboratory assay positive for CDI within 14-365 days of an Incident Case	EIP
Single Recurrent CDI	Recurrent CDI with two positive tests between 14-365 days	EIP
Multiple recurrent CDI	Recurrent CDI with more than two positive tests between 14-365 days	EIP
Antibiotics prior to CDI	Inpatient IV antibiotic use associated with an admission prior to CDI as noted by predefined per ICD-10 codes	Discharge Database
Admission following CDI	Overnight admission to an acute care hospital within 90 days of episode, but prior to next episode if applicable	Discharge Database
Antibiotics following CDI	Inpatient IV antibiotic use associated with an admission following CDI	Discharge Database
Hospital onset infection	CDI episode diagnosed 3 or more days after admission date	Discharge Database
FMT after Episode	Assigned to the last episode of CDI prior to FMT	Discharge database

EIP= Emerging infections program
Discharge database=Georgia Hospital Discharge Database

Table 2: Demographic and Baseline Characteristics of CDI patients, by recurrence category: Patient level Data

	No Recurrence	**Single recurrence**	**Two or more recurrence**	p-value*
	N=10814	N=2055	N=983	
Patient Characteristic	N (%)	N (%)	N (%)	
Sex				
Female	6436 (60%)	1233 (60%)	604 (61%)	0.28
Male	4378 (40%)	822 (40%)	379 (39%)	
Age Category (years)				
18-44	2338 (21%)	329 (16%)	163 (17%)	<0.01
45-64	3546 (32%)	665 (32%)	314 (32%)	
65-79	3202 (30%)	682 (33%)	332 (33%)	
80+	1728 (16%)	379 (18%)	174 (18%)	
Race				<0.01
White	4236 (39%)	825 (40%)	464 (47%)	
Black	3445 (32%)	705(34%)	324 (33%)	
Other	238 (2%)	41 (2%)	14(1%)	
Days between Episode 1 and 2, mean (SD)	N/A	89 (114)	65 (59)	<0.001

*Chi square test across all groups

Table 3: Location and date of FMTs administered in HD3: Patient Level dataset

FMT Treatment Location	
Emory Healthcare	109 (43%)
Hospital System 2	141 (56%)
Year of FMT	
2016	54 (20%)
2017	71 (28%)
2018	76 (30%)
2019	49 (20%)

Table 4: Demographic characteristics of Patients with CDI, by FMT receipt status: Patient level evaluation

	FMT not received	**FMT received**	**P-value***
	N=13602	N=250	
Patient Characteristic	N (%)	N (%)	
Sex			
Female	8085 (59%)	188 (75%)	<0.001
Male	5517 (41%)	62 (25%)	REF
Age group (y)			
18-44	2769 (20%)	61 (24%)	REF
45-64	4443 (33%)	82 (33%)	0.30
65-79	4153 (31%)	63 (25%)	0.04
80+	2237 (16%)	44 (17.6%)	0.57
Race			
White	4236 (39%)	825 (40%)	REF
Black	3445 (32%)	705(34%)	0.05
Other	238 (2%)	41 (2%)	0.66

*univariate analysis

Table 5: Patient's Sequential CDI Episode Number Immediately Prior to FMT Administration among CDI Patients with at least one Recurrent CDI and at least one Hospitalization: Episode Level Dataset

Episode	Patients, n	Patients receiving FMT, n (%)
1	13852	52 (0.4%)
2	3038	75 (2.5%)
3	983	68 (7%)
4	441	35 (8%)
5	196	6 (3%)
≥6	92	10 (10%)

Table 6: Frequency of Episodes at Each Recurrence of CDI (Recurrence Number) among CDI Patients with at least one Recurrent CDI and at least one Hospitalization: Episode level dataset.

Recurrence	Frequency
1	2495
2	861
3	356
4	161
5	72
6	41
7	22
8	14
9	10
10	9
11	5
12	4
13	2
Total	**4052**

Table 7: Demographic and Clinical Characteristics Associated with Episodes of CDI that had recurrence within 365 days: Episode Level dataset

	Episode has recurrence within 365 days				
	No (N = 2,429)	**Yes (**N = 1,623)	Odds Ratio	95% CI	P-value
Characteristic					
Race					
White	1057 (44%)	770 (47%)	REF		
Black	872 (36%)	606 (37%)	0.7	(0.49, 1.02)	0.06
Other	34 (1.4%)	21 (1.3%)	0.93	(0.23,3.73)	0.92
Unknown	466 (19%)	226 (14%)	0.41	(0.25, 0.66)	<0.01
Gender					
Female	1446 (60%)	955 (59%)	REF		
Male	983 (40%)	668 (41%)	0.95	(0.82, 1.10)	0.52
Age Category					
18-44	344 (14%)	334 (21%)	REF		
45-64	794 (33%)	524 (32%)	0.6	(0.36, 1.02)	0.06
65-79	821 (34%)	488 (30%)	0.6	(0.36, 1.01)	0.06
80+	470 (19%)	277 (17%)	0.52	(0.3, 0.933)	0.03
Comorbidities					
Peripheral Vascular Disease	298 (12%)	203 (13%)	1.15	(0.93, 1.41)	0.19
Cerebrovascular Disease	449 (18%)	255 (16%)	0.97	(0.81, 1.17)	0.80
Dementia	337 (14%)	206 (13%)	0.97	(0.78, 1..19)	0.74
Chronic pulmonary Disease	**630 (26%)**	**517 (32%)**	**1.28**	**(1.09, 1.5)**	**0.0028**

Congestive Heart Failure	**1003 (41%)**	**780 (48%)**	**1.34**	**(1.16, 1.55)**	**<0.0001**
Rheumatoid disease	134 (6%)	96 (6%)	1.05	(0.77,1.44)	0.74
Peptic Ulcer Disease	187 (8%)	159 (10%)	1.23	(0.96, 1.60)	0.11
Mild Liver Disease	**262 (11%)**	**235 (14%)**	**1.29**	**(1.03, 1.61)**	**0.024**
Diabetes	805 (33%)	592 (36%)	1.12	(0.95, 1.29)	0.16
Diabetes with complications	**687 (28%)**	**565 (35%)**	**1.25**	**(1.06, 1.46)**	**0.006**
Hemiplegia or paraplegia	185 (8%)	104 (6%)	0.97	(0.75, 1.27)	0.83
Renal Disease	**973 (40%)**	**813 (50%)**	**1.45**	**(1.25, 1.67)**	**<0.0001**
Cancer	446 (18%)	273 (17%)	0.91	(0.76, 1.10)	0.35
Moderate to severe liver disease	98 (4%)	68 (4%)	1.04	(0.73, 1.49)	0.81
HIV	89 (4%)	78 (5%)	1.06	(0.72, 1.56)	0.78
Inflammatory Bowel Disease	14 (0.6%)	35 (2.16)	1.37	(0.50, 3.78)	0.54
Dialysis	**145 (6%)**	**179 (11%)**	**1.82**	**(1.4, 2.37)**	**<0.0001**
Exposures prior to or during Episode					
Recent Hospital Admission	1747 (72%)	1114 (69%)	0.92	(0.63, 1.34)	
Recent IV Antibiotics	1108 (46%)	648 (40%)	0.9	(0.64, 1.28)	
Onset during Hospital Admission	256 (11%)	141 (9%)	0.82	(0.46, 1.49)	
Exposures within 90 days after Episode					
Readmission	**831 (34%)**	**818 (50%)**	**1.78**	**(1.36, 2.34)**	
IV Antibiotics	488 (20%)	429 (26%)	1.29	(0.93, 1.77)	
Therapy for Episode					
FMT received	99 (4%)	51 (3%)	0.76	(0.54, 1.08)	

Notes: Recent exposures occurred during 90 days prior to CDI episode; IV, intravenous;

Table 8: Predictors for Receipt of FMT among CDI episodes among patients with at least one recurrence and hospitalization: Episode Level Data

	CDI Episode was Treated with FMT		**Odds Ratio**	**95% CI**
	No (N=3,902)	**Yes (N=150)**		
Characteristic				
Race				
White	1737 (45%)	90 (60%)	REF	
Black	**1444 (37%)**	**34 (23%)**	**0.19**	**(0.08, 0.46)**
Other	52 (1.33%)	3 (2%)	1.25	(0.09, 18.6)
Unknown	669 (17%)	23 (15%)	0.424	(0.15, 1.19)
Gender				
Female	2292 (59%)	109 (72%)	REF	
Male	**1610 (41%)**	**41 (27%)**	**0.55**	**(0.39, 0.78)**
Age Category				
18-44	641 (16%)	37 (25%)	REF	
45-64	1258 (33%)	50 (33%)	0.4	(0.16, 1.02)
65-79	**1272 (33%)**	**37 (25%)**	**0.22**	**(0.08, 0.6)**
80+	721 (18%)	26 (17%)	0.352	(0.11, 1.07)
Comorbid Conditions				
Peripheral Vascular Disease	488 (13%)	13 (9%)	0.67	(0.38, 1.17)
Cerebrovascular Disease	703 (18%)	11 (7%)	0.35	(0.19, 0.65)
Dementia	531 (14%)	12 (8%)	0.56	(0.31, 1.00)
Chronic pulmonary Disease	1106 (28%)	41 (27%)	0.98	(0.69, 1.39)
Congestive Heart Failure	1739 (45%)	44 (29%)	0.55	(0.39, 0.77)
Rheumatoid disease	220 (6%)	10 (7%)	1.24	(0.68, 2.26)
Peptic Ulcer Disease	336 (8.6%)	10 (7%)	0.77	(0.41, 1.44)
Mild Liver Disease	487 (12%)	10 (7%)	0.51	(0.27,0.97)
Diabetes	1363 (35%)	34 (23%)	0.54	(0.37, 0.79)
Diabetes with complications	1229 (32%)	23 (15%)	0.41	(0.27, 0.64)
Hemiplegia or paraplegia	283 (7%)	6 (4%)	0.53	(0.23, 1.19)
Renal Disease	1749 (45%)	37 (25%)	0.42	(0.29, 0.6)
Cancer	698 (18%)	21 (14%)	0.78	(0.50, 1.22)
Moderate to severe liver disease	165 (4.2%)	1 (0.7%)	0.14	(0.02, 1.0)
HIV	163 (4%)	4 (3%)	0.75	(0.31, 1.78)
Inflammatory Bowel Disease	48 (1%)	1 (0.01)	0.52	(0.03, 2.5)
Dialysis	318 (4%)	6 (4%)	0.47	(0.18,0.98)
Episode				
2	2442 (63%)	53 (35%)	REF	
3	806 (21%)	55(37%)	13.9	(5.66, 34.14)
4	326 (8%))	30 (20%)	26.7	(9.06, 78.81)
5	156 (4%)	5 (3%)	2.25	(0.24, 20.65)
>5	172 (4%)	7 (5%)	3.32	(0.50, 22)

Table 9: Baseline Characteristics in Propensity Score-Matched Controls and Cases, matched on likelihood for CDI episodes receiving FMT: Propensity Matched Cohort

	No FMT Received after Episode	FMT Received after Episode	
Characteristic	**N = 150**	**N = 150**	P-value
Episode Number			>0.9
2	53	53	
3	55	55	
4	30	30	
5	5	5	
>5	7	7	
Gender			>0.9
Female	109	109	
Age Category			>0.9
18-44	38	37	
45-64	49	50	
65-79	36	37	
80+	27	26	
Race			>0.9
White	93	90	
Black	33	34	
Other	1	3	
Comorbid Conditions			>0.9
Cerebrovascular Disease	11	11	
CHF	45	44	
Renal Disease	37	37	
Diabetes with complications	22	23	

Table 10: Univariate and Multivariate analysis Predicting Recurrence of CDI: Propensity Matched Cohort

	No recurrence (N=180)	Recurrence (N=120)	Odds Ratio	P-value	aOR	P-value
Exposure						
FMT received for treatment	**99 (66%)**	**51 (34%)**	**0.60**	**0.03**	**0.60**	**0.03**
Readmission in 90 days following episode	**49 (27%)**	**47 (39%)**	**1.72**	**0.03**	1.76	0.11
IV Antibiotics in 90 days following episode	29 (16%)	27 (23%)	1.15	0.16	1.04	0.92