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Meagan E. Stephenson April 29, 2020

Beneficial and Attributable Outcomes of Fecal Microbiota Transplantation in Recurrent *Clostridioides difficile* Patients

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Bachelor of Arts
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2017

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ABSTRACT

Beneficial and Attributable Outcomes of Fecal Microbiota Transplantation in Recurrent *Clostridioides difficile* Patients

By Meagan E. Stephenson

Current literature supports the use of fecal microbiota transplantation (FMT) as a successful treatment for recurrent *Clostridioides difficile* infection (CDI). A retrospective cohort study was performed to analyze clinical outcomes, including reinfection and death, associated with FMT treatment of recurrent *C.difficile* episodes. Data from the Georgia Emerging Infections Program (GAEIP) *C.difficile* population-based surveillance project was utilized to identify FMT-eligible incident episodes for analysis. Eligibility was defined as the second or more episode with no prior infection within the previous 8 weeks. Two cohorts were identified: an unexposed cohort of 1,118 non-FMT-treated eligible episodes, and an exposed cohort of 90 FMT-treated eligible episodes. Accounting for age at specimen collection as a confounder and for episode number and race as interaction terms, FMT was indicated to have a protective effect against re-infection. The relative risk of infection among FMT-treated episodes was 25% less than those non treated with FMT (RR=0.25, 95CI: 0.13, 0.48; p<0.0001). The episode 3 group experienced reduction of risk of the highest magnitude (RR=0.18, 95CI: 0.04, 0.74; p=0.0176). Stratified on race, it was determined that the most significantly protective effect of FMT was within the black category (RR=0.36, 95CI: 0.17, 0.78; p=0.0099). The 46-70 and 71-90+ age groups experienced lower risk of reinfection among FMT episodes (RR=0.15, 95CI: 0.07, 0.29; p<0.0001 and RR=0.17, 95CI: 0.07, 0.39; p<0.0001, respectively). Relative risk of death was found to be highly protective among episodes treated with FMT (RR=0.05, 95CI: 0.02, 0.10; p<0.0001). Risk of death among all three episode groups was significantly reduced among FMT-treated episodes. Relative risk of death among 18-45 year-olds treated with FMT was 0.03 times that of those not treated with FMT (95CI: 0.01, 0.11; p<0.0001). Survival analysis using the logrank statistic indicated a 10% (p=0.0305) difference between the cohorts. Those episodes treated with FMT were more likely to survive over the 7-year study period than those not treated with FMT. This analysis corroborates previous studies and suggests beneficial clinical outcomes associated with FMT as treatment for recurrent CDI.

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TABLE OF CONTENTS

*Disclaimer: The primary dataset used in this project was collected by the Georgia Emerging Infections Program (GAEIP). The GAEIP was not involved in the analyses presented in this thesis.

INTRODUCTION

Clostridioides difficile is one of the most common healthcare associated infection (HAI) with a global incidence of 50.42 cases per 100,000 person-years, and accounting for 4.21 out 1,000 hospital admissions worldwide(1). The epidemiologic history of *C.difficile* began recently, with the first prospective case-control studies beginning in 1986(2). Those first studies found that 87% of cases were hospital-associated. In addition, they provided evidence for asymptomatic colonization of *C.difficile* occurring in hospitalized patients. In the past decade, the average onset rate for infection in US hospitals is 7.4 per 10,000 patient-days. Many patients had multiple healthcare setting exposures such as nursing homes and long-term care facilities (LTCF). In nursing homes, residents are at highest risk within 1 month of admission to the home, ranging from about 50-70% of residents diagnosed within that time(2). *C.difficile* can also be community-associated, with many cases potentially resulting from exposure to household members with active infection and infants who exhibit high rates of colonization. Recent population-based surveillance shows 30-50% of *C.difficile* cases are community-acquired(2).

By far, the strongest risk indicator for *C.difficile* is antibiotic usage(3). According to CDC's 2019 Threat Report, fluoroquinolones, alongside other antibiotic classes, are highly associated with *C.difficile* infections (CDI). The risk of antibiotic usage has been documented globally(1). Several European countries have reported national decrease in *C.difficile* incidence in conjunction with national decrease in antibiotic prescription. North American and Western Asian countries use three-fold the amount of antibiotics as

Central American countries, yet they experience about four times the incidence of infection. Additionally, high-income countries exhibit higher incidence of *C.difficile* than low-income countries, likely due to better access to antibiotics. Antibiotic stewardship and decline in prescriptions have been shown to significantly reduce incidence in LTCFs.

4th-century Chinese physician Ge Hong first documented fecal transplants, or "yellow soup", as treatment for gastrointestinal issues(4). Since then, fecal microbiota transplantation (FMT) has emerged as a promising restorative treatment for CDI, progressing in 2013 from being an experimental intervention to becoming a recognized treatment of choice among physicians(5). Many randomized clinical trials comparing FMT to standard-of-care treatments indicate high efficacy and safety of the procedure, leading to a significant increase of procedures in the US in the past two decades. Current literature suggests the procedure to have an 80-90% efficacy rate, which is higher than standard prescription treatments of fidaxomicin and vancomycin. Since the introduction of FMT as a standard treatment, the frequency of severe disease requiring surgical treatments, such as colectomy, have declined.

Donor stool can be delivered via endoscopy or in encapsulated form depending on the clinical indication, with consideration of the advantages and disadvantages of each method. It has been shown that, due to the replenishment of bacterial diversity, the gut appears to reflect a healthy microbiome as soon as one day following endoscopic FMT. Encapsulated FMT appears to have a more gradual effect, returning to a healthy microbiome in about one month(6). In both scenarios, patients present normal levels of beneficial bacterial families following treatment, which are critical to maintaining a gut flora that keeps the digestive tract healthy(5-7).

FMT has been documented to have positive clinical outcomes related to both *C.difficile* and other conditions. For standard *C.difficile* therapy, recurrent infection occurs in 20-30% of patients following first treatment with FMT(5). Recent literature suggests that FMT has a 70-100% success rate in preventing recurrence of CDI(8). A recent cohort study found a rate of recurrent infection among FMT recipients to be 4.5% compared to 16.7% among non-recipients(9). In addition, mortality rates following FMT are significantly less than standard antibiotic treatments. Assessment three months post-diagnosis indicates a 12% mortality rate among patients who received FMTs, yet a 42% mortality rate among those who did not. Most of these deaths occur in elderly populations ranging from 81-90 years old(8). Severe negative prognosis is seen without FMT applied as treatment. When compared to surgical interventions FMT has a good safety profile and is seen as more favorable to patients who receive it, with 95% of patients willing to repeat the procedure and 70% indicating FMT as the preferred method of treatment over antibiotics(10).

More investigation is needed to expand literature on efficacy of FMT for treatment for CDI. The intention of this analysis is to further study outcomes associated with FMT as treatment for CDI. A retrospective cohort study was conducted using data from the Georgia Emerging Infections Program's (GAEIP) ongoing *C.difficile* surveillance project. The incidence of reinfection and death were measured and compared among *C.difficile* patients who did and did not receive FMT as treatment from 2012-2018.

METHODS

Study Design

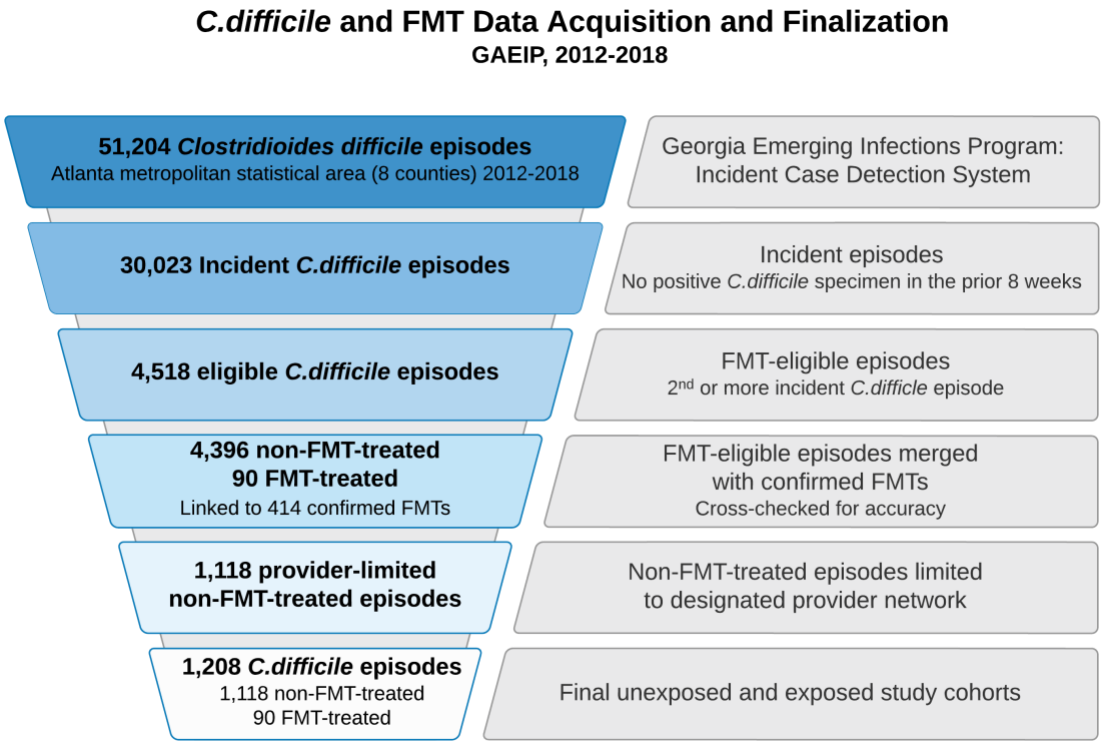
A retrospective cohort study was conducted among patients diagnosed with recurrent CDI between 2012 and 2018. The research protocol was reviewed and approved by the Institutional Review Board at Emory University. The primary dataset used in this project was collected by GAEIP. GAEIP was not involved in the analyses presented in this thesis. GAEIP facilitated the surveillance data collection in conjunction with the Georgia Department of Public Health and the Centers for Disease Control and Prevention. Data abstraction was done through laboratory-confirmed case audits as well as population-based surveillance within the 8-county Georgia Health District-3: Fulton, Cobb, Dekalb, Gwinnett, Clayton, Rockdale, Newton, and Douglas counties. All positive episodes are reviewed to ensure they adhere to case definition. Reinfection was assessed through 2018 and death was assessed through March 2019.

Study Population

Stepwise process detailed in Figure 1. The cohorts were narrowed down from a large dataset of approximately 50,000 *C.difficile* episodes between 2012 and 2018. First, incident cases were defined as non-newborns with an initial *C.difficile* episode without any positive tests in the previous 8 weeks. FMT eligibility was determined at the second incident FMT episode. The exposed cohort, eligible episodes treated with FMT, was ascertained from a line list of confirmed FMT procedures in Georgia Health District-3. The unexposed cohort, eligible episodes not treated with FMT, was limited to a set of

providers where lack of FMT procedure could be confirmed. The final FMT-eligible cohorts yielded 90 exposed and 1,118 unexposed *C.difficile* episodes.

Figure 1. Data flow for finalization of exposed and unexposed study cohorts



Study Outcomes

Clinical outcomes of interest primarily included reinfection with *C.difficile* and death. Reinfection was determined based on subsequent laboratory-confirmed case audits and chart reviews and limited to incident episodes. The unexposed cohort was deemed reinfected with an incident episode following the specimen collection for the eligible episode. For the exposed cohort, reinfection was defined as an incident episode following FMT. Death data was ascertained through vital record deathmatching, conducted in Link

Plus. Time until death was calculated in months since specimen collection for survival analysis.

Statistical Analysis

Data analysis was conducted using SAS. A p-value of 0.05 was used as the statistical significance threshold. Due to small sample size, Fisher's exact test was used to assess episode and outcome distribution. Log-binomial regression was used to fit the models and attain relative risk of reinfection and death among the cohorts. The covariates used in the regression included race, age at specimen collection, sex, ethnicity, and episode number. Interaction assessment was conducted for both reinfection and death models, followed by confounding assessment. Regarding reinfection, interaction with both race and episode number were identified via backwards elimination. Age was also included in the model as a confounder of the association between FMT status and reinfection. The Likelihood ratio test was used to assess significance of interaction terms for reinfection. No interaction was found to be present with death as the outcome, and age and episode number were included as confounders. Stratified analysis was performed to examine relationships within strata of race, episode number, and age for reinfection, and within strata of episode number and age for death. A Kaplan-Meier survival plot examining death between cohorts was generated with 95% equal precision bands, assessed with the logrank test for significance.

RESULTS

Cohort Demographics

In total, 1,208 individual *C.difficile* episodes were analyzed, with 90 episodes exposed to FMT and 1,118 episodes not exposed. Table 1 contains demographic data for both cohorts. The mean age for the entire study population was 60.3 years (SD: 18.2). The unexposed cohort reflects this closely with 60.2 years being the mean, and the unexposed cohort being slightly higher at 61.5 years. There was a higher proportion of females in the study, however the exposed cohort showed a larger sex difference, where females accounted for 69% of the *C.difficile* episodes. The most common races across the cohorts were white and black/African American. Interestingly, more FMT-treated episodes were white than black (59% and 29%, respectively); however, the opposite was true for the episodes not treated with FMT (40% and 49%, respectively). The majority of the study population was non-Hispanic or Latino. 87% of the unexposed cohort were diagnosed in an outpatient setting, in comparison with 63% of the exposed cohort. Most FMT-treated episodes were treated following the second episode. Over half of the FMT treatments occurred within 8 weeks of specimen collection, 24% between 9 and 16 weeks. Frequencies of outcomes among cohorts are displayed in Table 2. The exposed cohorts demonstrated lower risk of death compared to the unexposed cohort, however risk of reinfection was higher among the exposed compare to the unexposed. This is likely due to large number of episodes concentrated within the “episode 2” strata.

Table 1. Demographics of FMT-eligible episodes by FMT status; GAEIP, 2012-2018

	Not FMT-treated (n=1,118)	FMT-Treated (n=90)	Total (N=1,208)
Age (mean, SD)*	60.2 (18.1)	61.5 (19.5)	60.3 (18.2)
Sex (n, %)			
Male	455 (41)	28 (31)	483 (40)
Female	663 (59)	62 (69)	725 (60)
Race (n, %)			
Black/Af. Am.	553 (49)	26 (29)	579 (48)
White	443 (40)	53 (59)	496 (41)
Unknown	32 (3)	<5 (3)	35 (3)
Multiple	58 (5)	7 (8)	65 (5)
Other	32 (3)	<5 (1)	33 (3)
Ethnicity (n, %)			
Hispanic or Latino	12 (1)	1 (1)	13 (1)
Not Hispanic or Latino	1,005 (90)	80 (89)	1,085 (90)
Unknown	101 (9)	9 (10)	110 (9)
Provider type (n, %)**			
Hospital-based	977 (87)	57 (63)	1,034 (86)
Outpatient-based	141 (13)	33 (37)	174 (14)
No. episodes (n, %)			
2	784 (70)	51 (57)	835 (69)
3	225 (20)	25 (28)	250 (21)
4+	109 (10)	14 (15)	123 (10)
Time to FMT (n, %)			
0-8 weeks	--	51 (57)	--
9-16 weeks	--	22 (24)	--
17-24 weeks	--	9 (10)	--
25+ weeks	--	8 (9)	--

*Age at specimen collection

**specimen collection; limited to specified provider network for unexposed

Outcomes

Frequencies of outcomes among cohorts are displayed in Table 2. The exposed cohorts demonstrated lower risk of death compared to the unexposed cohort, however risk of reinfection was higher among the exposed compared to the

unexposed. This is likely due to large number of episodes concentrated within the "episode 2" strata. While 22 percent of non-FMT-treated episodes resulted in death, compared to 12 percent of FMT-treated episodes.

Table 2. Outcomes by FMT status; GAEIP, 2012-2018

	Not FMT-treated (n=1,118)	FMT-Treated (n=90)	Total (N=1,208)	p-value
Re-infection (n, %)				0.0012
Yes	255 (23)	35 (39)	290 (24)	--
No	863 (77)	55 (61)	918 (76)	--
Death (n, %)				0.0421
Yes	241 (22)	11 (12)	252 (21)	--
No	877 (78)	79 (88)	956 (79)	--

Tables 3a-c demonstrate strata of age at specimen collection, episode number, and race. The 71-90+ age group had the highest overall death rate (32 percent) and the highest death rate among non-FMT-treated episodes (34 percent). However, it had the lowest overall rate of reinfection (20 percent). Th highest overall rate of reinfection was seen in the 18-45 age group (26 percent).

The episode number distribution was heavily skewed towards 2 episodes, with 69 percent of all episodes falling into the 2nd episode category. The 2nd episodes that were FMT-treated showed much higher percentages of reinfection when compared to the 3rd and 4th+ episode groups. The 2nd episode group also had a higher percentage of death overall.

Race showed large differences between strata, with whites having almost double the number of FMT-treated episodes when compared to blacks. Blacks exhibited the highest proportion of reinfections (25 percent) and deaths (23 percent).

Table 3a. Primary Outcomes by Age Group (years)* and FMT Status; GAEIP, 2012-2018

	18-45			46-70			71-90+		
	Not FMT-Treated (n=233)	**FMT-Treated (n=21)**	**Total (N=254)**	**Not FMT-Treated (n=555)**	**FMT-Treated (n=40)**	**Total (N=595)**	**Not FMT-Treated (n=330)**	**FMT-Treated (n=29)**	**Total (N=359)**
Re-infection (n,%)									
Yes	73 (31)	13 (62)	83 (34)	176 (32)	31 (78)	207 (35)	85 (26)	13 (45)	98 (27)
No	160 (69)	8 (38)	164 (66)	379 (68)	9 (23)	388 (65)	245 (74)	16 (55)	261 (73)
Death (n, %)									
Yes	32 (14)	2 (10)	34 (13)	98 (18)	4 (10)	102 (17)	111 (34)	5 (17)	116 (32)
No	201 (86)	19 (90)	220 (87)	457 (82)	36 (90)	493 (83)	219 (66)	24 (83)	243 (68)

*At specimen collection

Table 3b. Primary Outcomes by Episode No. and FMT Status; GAEIP, 2012-2018

	Episode 2			Episode 3			Episode 4+		
	Not FMT-Treated (n=784)	**FMT-Treated (n=51)**	**Total (N=835)**	**Not FMT-Treated (n=225)**	**FMT-Treated (n=25)**	**Total (N=250)**	**Not FMT-Treated (n=109)**	**FMT-Treated (n=14)**	**Total (N=123)**
Re-infection (n, %)									
Yes	167 (21)	27 (53)	194 (23)	53 (24)	4 (16)	57 (23)	35 (32)	4 (29)	39 (32)
No	617 (79)	24 (47)	641 (77)	172 (76)	21 (84)	193 (77)	74 (68)	10 (71)	84 (68)
Death (n, %)									
Yes	179 (23)	9 (18)	188 (23)	42 (19)	1 (4)	43 (17)	20 (18)	1 (7)	21 (17)
No	605 (77)	42 (82)	647 (77)	183 (81)	24 (96)	207 (83)	89 (82)	13 (93)	102 (83)

Table 3c. Primary Outcomes by Race and FMT Status; GAEIP, 2012-2018

	White			Black			Multiple			Other		
	Not FMT-Treated (n=443)	**FMT-Treated (n=53)**	**Total (N=496)**	**Not FMT-Treated (n=553)**	**FMT-Treated (n=26)**	**Total (N=579)**	**Not FMT-Treated (n=58)**	**FMT-Treated (n=7)**	**Total (N=65)**	**Not FMT-Treated (n=64)**	**FMT-Treated (n=4)**	**Total (N=68)**
Reinfection (n, %)												
Yes	89 (20)	26 (49)	115 (23)	140 (25)	7 (27)	147 (25)	15 (26)	0 (0)	15 (23)	11 (17)	2 (50)	13 (19)
No	354 (80)	27 (51)	381 (67)	413 (75)	19 (63)	432 (75)	43 (74)	7 (100)	50 (77)	53 (83)	2 (50)	55 (81)
Death (n, %)												
Yes	85 (19)	6 (11)	91 (18)	129 (23)	4 (15)	133 (23)	13 (22)	0 (0)	13 (20)	14 (22)	1 (25)	15 (22)
No	358 (81)	47 (89)	405 (82)	424 (77)	22 (85)	446 (77)	45 (78)	7 (100)	52 (80)	50 (78)	3 (75)	53 (78)

Tables 4a-b demonstrate the relative risk and statistical significance of the associations between FMT status and reinfection (Table 4a), and FMT status and death (Table 4b). Regarding reinfection, the overall risk among FMT-treated episodes was 0.2527 times that of non-FMT-treated episodes, indicating a protective effect of FMT on reinfection when controlling for age as a confounder, and episode number and race as covariates demonstrating interaction. A decreased risk was also seen for episode numbers 2 and 3. Blacks and whites both showed decreased risk for reinfection, with blacks exhibiting a slightly stronger protective effect. The decreased risks indicated for multiple races (RR=0.64; 95CI: 0.01, 32.72) and other races (RR=0.10, 95CI: 0.01, 1.14) were not statistically significant ($p > 0.05$). The 18-45 age group did not show a significant risk reduction, however both the 46-70 (RR=0.15, 95CI: 0.07, 0.29; $p<0.0001$) and 71-90+ (RR=0.17, 95CI: 0.07, 0.39; $p<0.0001$) age groups showed a very low risk among FMT-treated episodes compared to non-FMT-treated episodes.

Regarding death, FMT showed a highly protective effect (RR=0.05, 95CI: 0.02, 0.10; $p<.0001$) against death overall when controlling for age and episode number as confounders. Relative risk was low among all three episode groups [2:(RR=0.3, 95CI: 0.02, 0.07; $p<0.0001$); 3:(RR=0.03, 95CI: 0.01, 0.48; $p=0.0001$); 4:(RR=0.06, 95CI: 0.01, 0.47; $p=0.0082$)]. The most protective effect for age was among the 18-45 age group, which demonstrated 0.03 (95CI: 0.01, 0.11; $p<0.0001$) times the risk of death among FMT-treated episodes than among non-FMT-treated episodes. All relative risks for death were statistically significant.

Table 4a. Relative Risk of reinfection in FMT-eligible episodes by FMT status; GAEIP, 2012-2018

	Not FMT-Treated (n=1,118)	FMT-Treated (n=90)	RR (95% CI)	p-value
Crude	1,118	90	0.25 (0.13, 0.48)	<.0001
Episode no.				
2	784	51	0.40 (0.20, 0.80)	0.0099
3	225	25	0.18 (0.04, 0.74)	0.0176
4+	109	14	0.31 (0.06, 1.68)	0.1755
Race				
White	443	53	0.39 (0.16, 0.95)	0.0389
Black	553	26	0.36 (0.17, 0.78)	0.0099
Multiple	58	7	0.64 (0.01, 32.73)	0.8219
Other	64	4	0.10 (0.01, 1.14)	0.0634
Age*				
18-45	233	21	0.39 (0.14, 1.08)	0.0702
46-70	555	40	0.15 (0.07, 0.29)	<.0001
71-90+	330	29	0.17 (0.07, 0.39)	<.0001

*Age at specimen collection

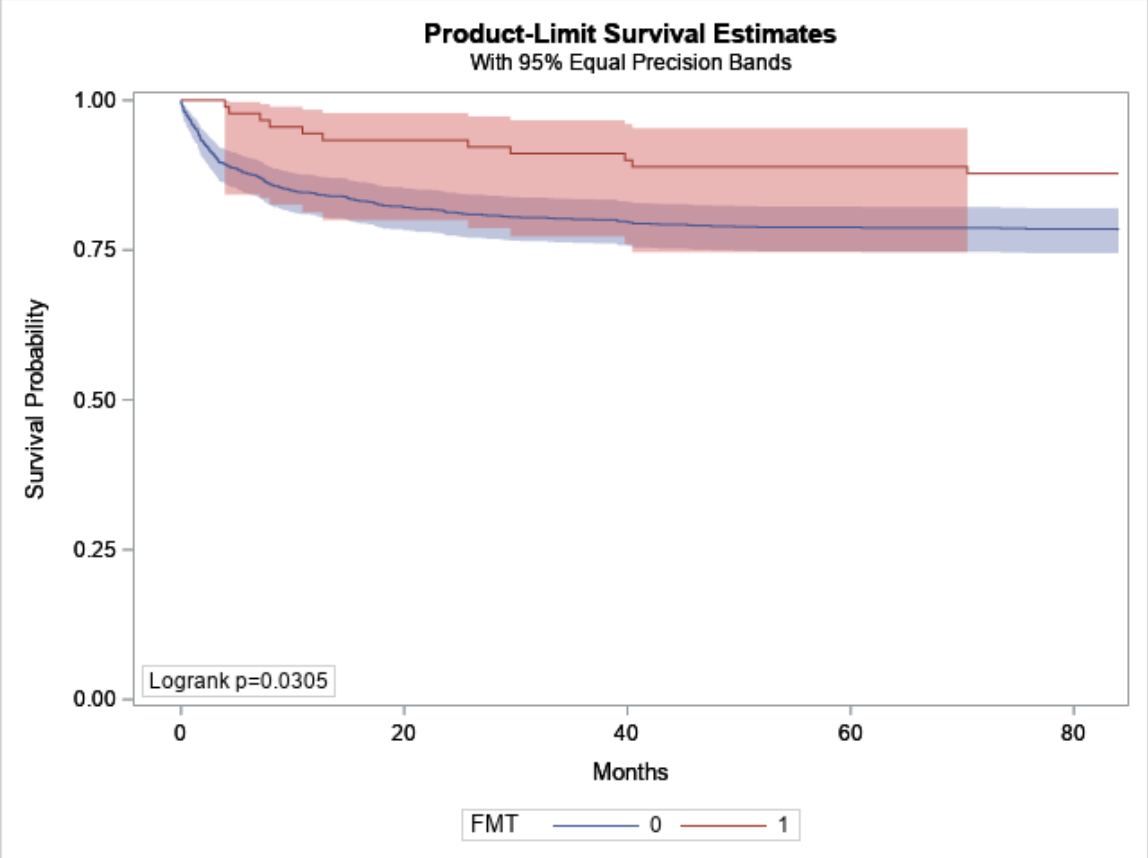
Table 4b. Relative Risk of death in FMT-eligible episodes by FMT status; GAEIP, 2012-2018

	Not FMT-Treated (n=1,118)	FMT-Treated (n=90)	RR (95% CI)	p-value
Crude	1,118	90	0.05 (0.02, 0.10)	<.0001
Episode no.				
2	784	51	0.03 (0.02, 0.07)	<.0001
3	225	25	0.03 (0.01, 0.48)	0.0001
4+	109	14	0.06 (0.01, 0.47)	0.0082
Age*				
18-45	233	21	0.03 (0.01, 0.11)	<.0001
46-70	555	40	0.31 (0.15, 0.67)	0.0028
71-90+	330	29	0.33 (0.16, 0.70)	0.0033

*Age at specimen collection

Using the Kaplan-Meier survival plot (Figure 2) and the logrank test including age and episode number as confounders, a statistically significant (p=0.0305) difference in survival was observed when comparing death among FMT-treated episodes (coded FMT=1) and non-FMT-treated episodes. FMT-treated episodes had a survival probability of 88 percent, compared to 78 percent for non-FMT-treated episodes over a 7-year period. The 95% confidence bands indicate greater precision with the survival data for non-FMT-treated episode death.

Figure 2. Kaplan-Meier survival plot comparing death among episodes treated with FMT and episodes not treated with FMT; GAEIP, 2012-2018



DISCUSSION

Findings

With the growing threat of healthcare-associated infections, this study aimed to add to the body of evidence supporting FMT as a standard and recommended treatment for recurrent CDI. We aimed to analyze relationships between *C.difficile* and clinical outcomes of FMT among a general population, with attention paid to subgroups there within. Valuable insight into the association between these two factors was gained through analysis of the surveillance data in order to provide a better understanding of the effect of FMT on recurrence and mortality.

In this study, we pursued evidence of positive CDI outcomes associated with FMT, including relative risk of reinfection and death. Through epidemiologic modeling and survival analysis, it was concluded that *C.difficile* episodes treated with FMT experienced better outcomes that those not treated with FMT. Systematic reviews of current literature consistently indicate decreased risk of adverse outcomes associated with FMT(11). In some regions, such as Hong Kong, a regulated service for providing FMT for CDI is proposed to fulfill demand for the procedure(12). The results from this study's analysis support the current opinion on FMT as treatment for CDI, by demonstrating positive outcomes. FMT crudely reduced the risk of reinfection and death among *C.difficile* episodes by 75% and 95%, respectively ($p<0.0001$). Risk of reinfection was significantly less in older age groups, as well as in the black racial group. The relative of risk of death was significantly reduced in all age groups. It was found that mortality was

significantly lower (12%) among episodes treated with FMT when compare to those not treated with FMT (22%), indicating a protective effect provided by FMT.

Deeper investigation into the findings indicated a relationship between race, infection, and FMT. Although whites were less likely to experience CDI than blacks, they were more likely to receive FMT as treatment for infection. Blacks were more likely to experience both reinfection and death. Looking specifically at reinfection, risk among blacks was decreased by 64% when treated with FMT, whereas risk among whites was decreased by 61%. This may be an indicator of socioeconomic status and its effect on initial infection, reinfection, and access to medical care.

Limitations

Limitations of this study include the small sample size, which may affect magnitude and statistical significance of associations. In addition, any FMTs received as treatment for CDI not captured by the surveillance system may have been excluded from the study cohort. Finally, time between specimen collection and FMT as well as time between specimen collection and death was not limited to a specific interval. Limiting may have had an impact on data for reinfection and death. The data is likely generalizable as the associations are significant, the population was fairly comprehensive, and the analysis reflects current literature.

Conclusion

Further investigation is needed to supplement evidence for FMT as a standard

treatment for recurrent CDI. Deeper examination into subpopulations and the associations between CDI and FMT may be valuable in understanding in what populations FMT may be more efficacious, and where improvements and expansions can be made. Specifically, research into racial differences in CDI and FMT procedures may yield results crucial to improving healthcare access and clinical outcomes among minority groups.

The results of our study confirm the efficacy and beneficial outcomes of FMT as treatment for recurrent CDI. Both reinfection and death were significantly reduced among FMT-treated *C.difficile* episodes. Further investigation is needed to support the recommendations for use of FMT as standard treatment for recurrent CDI, as well as research into racial and socioeconomic differences in access to healthcare and CDI treatment and prognosis.

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