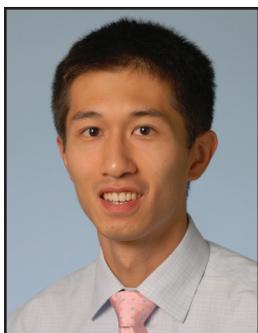


Seymour Katz, M.D., Series Editor

Fecal Microbiota Transplantation in the Elderly: A Need for Early Consideration in Select Cases of *Clostridium difficile* Infection



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Fecal microbiota transplantation (FMT) is recommended treatment for recurrent *Clostridium difficile* infection (CDI). There is also increasing evidence that FMT is effective in severe and severe-complicated CDI and in averting CDI-related complications such as colectomy and mortality. The elderly population (age ≥ 65) is disproportionately affected by CDI and has worse outcomes compared to their younger counterparts. In this article, we explore the role of FMT in elderly patients with CDI and other gastrointestinal diseases. It may be reasonable to offer FMT earlier in the CDI disease course in older individuals, possibly after just the second recurrence and/or for the first episode of severe CDI to halt disease progression and prevent development of associated complications.

INTRODUCTION

Elderly patients (age ≥ 65 years) are considered a unique treatment population due to decreased physiological, immunologic, and cognitive reserve, while also shouldering a greater number of comorbidities and medications compared to their younger counterparts.^{1,2} These factors make elderly patients not only more susceptible to disease, but also less tolerant to aggressive therapies. Additional considerations such as age-related impairments in hepatic metabolism and renal clearance of medications,³ the Beers Criteria of medication contraindications in nursing home residents,⁴ and the heterogenous spectrum

of elderly health status ranging from fit to frail,⁵ introduce multiple levels of complexity when treating disease in this unique population.

Over the past decade, the gut microbiome has risen to prominence after researchers realized its role in pathogen resistance, immunomodulation, epithelial cell propagation and nutrient metabolism.⁶ In parallel, researchers have pursued the allure of manipulating the gut microbiome via fecal microbiota transplantation (FMT), a procedure in which healthy fecal material is transferred into the diseased gut. The intent of FMT is to restore healthy microbial communities, thereby alleviating disease that may have resulted from a dysbiotic gut microbiota.

The purpose of this article is to explore current literature supporting the use of FMT for treatment of various diseases with a particular emphasis on its role in elderly patients.

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***Clostridium difficile* Infection**

Clostridium difficile infection (CDI) disproportionately affects the elderly population, causing greater incidence of first-time and recurrent CDI compared to their younger counterparts^{7,8} as well as an elevated risk of progression to severe and/or complicated CDI.⁹ The combination of these factors culminates in particularly poor outcomes for elderly patients, who represented 93% of CDI-associated deaths in 2008,¹⁰ 92% of CDI-related US hospital admissions in 2009,¹¹ and higher odds of CDI-related colectomy (OR 1.9)¹² compared to patients <65 years of age.

There are likely multiple components contributing to elderly morbidity and mortality when afflicted with CDI. They may be more prone to *Clostridium difficile* colonization due to greater fluctuation in gut microbiome composition due to immunosenescence and alterations in gut transit time.^{13,14} Furthermore, elderly patients have higher rates of exposure to CDI risk factors such as antibiotics, healthcare facilities, chronic kidney disease, and multiple co-morbidities.¹⁵ Risk of healthcare-associated CDI increases by 2% for each year of age.¹⁶

Recurrent CDI

The use of FMT is best described as treatment for *Clostridium difficile* infection. Healthy colonies of bacteria such as bacteroides and firmicutes are transferred via FMT into the diseased gut and re-establish the microbiome diversity, thereby suppressing colonization by *Clostridium difficile*.^{17,18} A single FMT is effective at treating recurrent CDI (RCDI) at a rate approaching 90%,¹⁹ and is currently recommended by the American College of Gastroenterology (ACG).²⁰ More importantly, FMT is superior to traditional antimicrobials at inducing durable cure. Subsequent CDI recurrence after treatment with FMT is lower (5-15%)^{21,22} compared to the traditional antimicrobials vancomycin (35-65%)²³ and fidaxomicin (25%).²⁴

In studies focusing solely on elderly patients, rates of successful RCDI treatment with FMT have been quite comparable to those conducted in the general population. One review article found an 89.6% cure rate among 115 cases of RCDI treated with FMT in the elderly.²⁵ In another systematic review, patients ≥65 were compared to patients <65 years of age and found to have inferior response rates to FMT;²⁶ primary cure for RCDI was 87% versus 99.4%, while CDI recurrence within 90 days was 4.9% vs 0.1%, respectively. The

results suggest that the post-FMT clinical course of elderly patients should be followed closely for signs of recurrence. A significant fraction of patients may require repeat FMT or subsequent medical therapy for adequate treatment.

Severe and Severe-Complicated CDI

Beyond RCDI, there remains a need to introduce new and effective modalities for the treatment of severe and/or complicated CDI (SCCDI). Colectomy is currently standard therapy, particularly for refractory cases of SCCDI. However, post-surgical mortality has remained close to 50% over the last decade despite new surgical techniques and prediction models for poor surgical outcomes.²⁷⁻³⁰ There have been several convincing studies suggesting that FMT may adequately treat SCCDI³¹⁻³⁴ and also decrease rates of colectomy.³⁵

Only one study, published by Agrawal and colleagues, has focused on elderly patients.³¹ In their cohort of 146 patients, 30.8% had severe CDI, 8.2% had severe CDI, and the remainder had RCDI. Overall primary cure rate was 82.9% (91% severe and 66% severe-complicated CDI), which improved to 95.9% after subsequent vancomycin or repeat FMT infusion. Only six patients in the study reported a serious adverse event, which consisted almost exclusively of recurrent diarrhea requiring repeat intervention or hospitalization. Notably, 69.2% of patients reported an improvement in their functional status after FMT.

Since 2013, our center has utilized a sequential FMT protocol with selective use of vancomycin.³³ Compared to the 66% cure rate after a single FMT,³¹ our sequential FMT protocol has a cure rate of 87% for the treatment of severe-complicated CDI.³⁴ Furthermore, since inception of our inpatient sequential FMT program, our center has seen a decrease in CDI-related mortality from 10.2% to 4.5% ($p=0.021$) among patients with SCCDI, and from 43.2% to 12.1% ($p<0.001$) in a subgroup of SCCDI patients who did not respond to 5 days of optimal medical therapy (medically refractory). CDI-related colectomy has also decreased from 6.8% to 2.7% ($P=0.042$) in SCCDI and 31.8% to 7.6% ($P=0.001$) in the medically refractory subgroup [unpublished data].

FMT has an emerging role in the treatment of SCCDI. Its acceptance as a therapeutic modality in elderly patients is particularly important because it can avert the need for colectomy. Furthermore, it can serve as an alternative for patients that are regarded as non-surgical candidates due to age-related frailty and/or

co-morbidities. In instances where FMT is only partially effective, it can also serve as adjunct medical therapy to stabilize patients before surgery, which has been shown to be associated with better surgical outcomes.²⁹

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is similar to CDI in that both diseases are characterized by a dysbiotic microbiome.³⁶ However, it is unclear whether dysbiosis is the result of an inappropriate host immune response to normal gut flora or a proper response to an abnormal microbiome. Almost 15% of inflammatory bowel disease (IBD) cases arise in patients ≥ 65 years of age, coinciding with the secondary peak of IBD incidence in the general population.³⁷ Cases of ulcerative colitis (UC) tend to be more severe at time of diagnosis for elderly patients.^{38,39} However, for both UC and Crohn's disease (CD), the clinical course in elderly patients tends to be less aggressive compared to younger patients,⁴⁰⁻⁴³ with fewer relapses and hospitalizations particularly in UC.^{40,44} Though the overall disease course of IBD may be favorable in elderly patients, outcomes during IBD-related hospitalizations are not. Higher rates of gastrointestinal bleed, anemia, hypovolemia, electrolyte disturbance, and malnutrition among the elderly lead to greater in-hospital mortality (OR 3.91) and post-colectomy length of stay (1.73 days) compared to patients < 65 years.⁴⁵

Poor outcomes among elderly patients with IBD may partially be explained by practical differences in therapy used for IBD suppression. Underutilization of biologic therapy and immunomodulators is well-described, likely driven by the perception that elderly patients are at higher risk of infection, malignancy,⁴⁶ as well as drug interactions from polypharmacy.^{47,48}

The role of FMT as a "natural" means of restoring the normal balance of gut microbiota in patients with IBD has thus piqued the interest of researchers, particularly with elderly patients in mind. Unfortunately, cohort studies of FMT for CD treatment have conflicting results,^{49,50} while several randomized controlled trials (RCT) involving UC patients of all ages have not been convincing. In two RCTs, UC patients who underwent FMT with stool sourced from a healthy donor responded better than those that received placebo, with 25-27% achieving remission.^{51,52} A third RCT did not generate significance between groups of UC patients receiving FMT with healthy versus autologous stool.⁵³

The role of FMT in the treatment of IBD is unclear

at this time. Additionally, the rigorous treatment regimens utilized by the aforementioned studies (daily self-administered FMT enemas for multiple weeks) would not be feasible for many of our elderly patients.

Clostridium difficile infection in IBD patients

CDI in patients with underlying IBD (CDI-IBD) is another noteworthy group that could benefit from treatment with FMT. Among all age groups, the likelihood of IBD patients contracting CDI is 2.5 to 8-fold higher than the general population.⁵⁴⁻⁵⁶ Moreover, mortality and colectomy rates are much higher for hospitalized CDI-IBD patients compared to patients with solely IBD or CDI.⁵⁷⁻⁵⁹

Successful treatment of CDI with FMT in IBD patients is close to 90%, similar to that of non-IBD patients.⁶⁰⁻⁶² However, there is concern that patients can have an unpredictable IBD clinical course post-FMT. Fischer and colleagues found that 17.9% of patients had worsening IBD activity after treatment of CDI. 12% of this study group also experienced a serious adverse event, though not directly related to the FMT itself.⁶²

The literature is currently devoid of studies on this topic, but it would not be unreasonable to expect worse outcomes among elderly patients with CDI-IBD. Previous comparisons to younger patients demonstrated worse rates of colectomy and mortality when elderly patients are hospitalized with IBD or CDI alone. Early intervention with FMT could attenuate progression to severe-complicated CDI thereby improving outcomes. However, a possible IBD flare after FMT could itself lead to colectomy and/or mortality. In elderly patients with CDI-IBD, aggressive anti-CDI medical therapy should be balanced with selective use of FMT after a thorough discussion with the patient about risks and benefits.

FMT Applications on the Horizon

The impact of the gut microbiome on host metabolism, immunogenicity, and neuro-hormonal responses has opened multiple avenues of research for the application of FMT.^{63,64} Larger case series have identified a potential for FMT in the treatment of pouchitis⁶⁵⁻⁶⁷ and irritable bowel syndrome.^{68,69} Further targets of treatment via FMT have only progressed to the level of case reports: hepatic encephalopathy,⁷⁰ acute graft-versus-host disease,⁷¹ multiple sclerosis,⁷² and chronic fatigue syndrome.⁷³

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As it pertains to the elderly population, researchers have theorized that the gut microbiome may have a role in the development of Alzheimer's disease. Disturbances to the elderly microbiome caused by immunosenescence or external factors such as antibiotics allows for colonization of fungi and bacteria capable of secreting amyloids and lipopolysaccharides into their environment,⁷⁴⁻⁷⁶ which induces host inflammation and gut permeability.^{77,78} Researchers hypothesize that the leaky gut could allow amyloids to reach the level of the brain where they could polymerize into the beta-pleated sheets characteristic of Alzheimer's disease.⁷⁴ Alternatively, proinflammatory bacterial colonizers may also induce cytokines and reactive oxygen species contributing to neurodegeneration.⁷⁸⁻⁸⁰ Further studies are needed to validate these theories.

Safety and Delivery of FMT

FMT is delivered in various methods including nasoduodenal/jejunal tube, esophagogastroduodenoscopy, pill, and enema, though colonoscopy is the most widely practiced. There are multiple benefits of colonoscopy including targeted delivery of fecal material, direct visualization of the colonic mucosa, and ability to rule out alternate etiologies such as IBD, ischemia, microscopic colitis, or malignancy.⁸¹ Importantly, there is strong evidence that treatment of CDI is superior when FMT is delivered via lower rather than upper GI modalities. In a cohort of over 2000 patients who received FMT for recurrent, severe, and/or refractory CDI, cure was 85.8% via colonoscopy versus 74.1% with an upper GI route ($p < 0.01$).⁸²

Previous studies have found increased risk of perforation in elderly patients after diagnostic colonoscopies. In one study, the incidence of perforation increased by age group: 0.026% for age 50-64, 0.087% for 65-79, and 0.317% for ≥ 80 years.⁸³ Another study placed the odds of perforation at 1.33 when patients > 65 were compared to those < 65 years.⁸⁴

Endoscopic injury and sedation-related aspiration events appear to be negligible after FMT, though no direct comparison to diagnostic colonoscopies or among age groups has been published. One review found that among 1,555 FMTs only 4 resulted in a direct procedural complication (mucosal tear or perforation) and 3 were associated with death that could not be directly attributed to the FMT itself.⁸⁵ Another review

comprised of 1,089 FMTs described adverse events in 17.7% of lower GI versus 43.6% upper GI FMTs. Severe adverse events, or procedural complications leading to death or hospitalization was found in 6.1% of lower GI versus 2.0% upper GI FMTs.⁸⁶ In most cases, side effects from FMT were described as mild, self-limited, and confined to the gastrointestinal tract. In a study comprised exclusively of 146 elderly patients, the treatment of recurrent, severe, and/or complicated CDI with FMT resulted in only 6 serious adverse events, most of which were severe, recurrent diarrhea requiring hospital admission.³¹ The authors suggest that elderly age may be a relative contraindication to upper GI delivery of FMT due to risk of aspiration and small intestinal bacterial overgrowth.

CONCLUSION

The adage of "start low and go slow" for initiation of therapeutics in the elderly may not apply to FMT for the treatment of CDI, where rates of cure and CDI relapse are superior compared to traditional antimicrobials. Elderly patients may also appreciate the benefits of avoiding colectomy or having alternative therapy when they are non-surgical candidates due to age or comorbidities. It may be reasonable to offer FMT earlier in the CDI disease course, possibly after just the second recurrence and/or the first episode of severe CDI to decrease progression of CDI severity and development of associated complications.

There is insufficient evidence to suggest that FMT for the sole purpose of treating IBD is beneficial. However, when elderly patients have CDI-IBD, clinicians will need to balance the benefit of FMT for treating CDI and its potential to induce an IBD flare. ■

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