COMMENTARY

Fecal Microbiota Therapy: Ready for Prime Time?

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(See the article by Lofgren et al, on pages 18–27.)

Clostridium difficile infection (CDI) has emerged as the most frequently encountered cause of nosocomial diarrhea worldwide.[1] The human intestinal microbiota is a diverse ecosystem with at least 1,000 species of bacteria,[2] a fact that informs the widely accepted pathogenesis of CDI: broad-spectrum antibiotics alter the microbiota into a less-diverse, susceptible state; *C. difficile* spores are introduced; and spores germinate, grow vegetatively, produce toxin, and damage the intestinal epithelium. After infection, the gut microbiota can remain susceptible, and recurrent CDI can occur, either as a relapse or as reinfection from a different strain.[3] This can lead to numerous recurrent episodes of CDI that are refractory to traditional methods of therapy.

Pharmacologic strategies for treatment of recurrent CDI include prolonged courses of vancomycin in a pulsed or tapered regimen[4] and use of rifaximin[5] or fidaxomicin[6] as a "cap" following vancomycin therapy, although many patients have disease refractory to these treatments. Fecal microbiota transplantation (FMT) transfers stool from a healthy donor into a patient and restores their microbiota to a state that resists colonization with *C. difficile*. FMT has been demonstrated by numerous case reports[7] and a randomized, controlled trial[8] to be a promising solution to this recalcitrant problem. The safety and efficacy of FMT seen in this research has spurred interest in expanded use of FMT for primary disease, with the hope of preventing recurrence and transmission.

In this issue of *Infection Control and Hospital Epidemiology*, Lofgren et al[9] present the results of an interesting, novel study that uses a mathematical model to examine the impact of FMT for prophylaxis and treatment of primary CDI on the transmission of CDI and recurrent disease in a 12-bed intensive care unit (ICU). Their model used separate compartments for healthcare personnel (uncontaminated or contaminated with *C. difficile* spores) and patient health and treatment states (risk of CDI with or without colonization with *C. difficile*, development of CDI, and receipt of FMT). The transmission pathways modeled used colonized patients as the source for *C. difficile* spores and contaminated healthcare workers as the vector. Flow between patient compartments was intuitively modeled from uncolonized to colonized states followed by CDI. Outcomes from hospitalization included discharge from the hospital in good health, development of recurrent CDI, and death. Parameters (inputs) for the model used data from surveillance and billing, a prospective cohort, and published literature. Potential differences among the various routes of FMT, such as cost and success rate, were not included in this analysis. One-year simulations were run to track 2 primary outcomes: the number of incident infections and the number of infections that develop into recurrent cases.

The study's major finding was a decreased median incidence of recurrent CDI in patients with primary CDI who were treated with FMT. The magnitude of this effect increased as a greater percentage of patients were treated with FMT. Incidence of primary CDI was not affected by the use of FMT for primary CDI. Use of FMT for prophylaxis did not reduce recurrent CDI but did decrease the number of incident cases, although the authors question the clinical usefulness of this finding because of the small effect size. The investigators concluded that routine use of FMT "represents a promising tool to prevent complicated, recurring episodes of CDI."[9(p24)] The ability of the model to output incidence curves that are convincing analogs of the real world, including outbreaks of CDI interspersed with periods of low incidence, is an impressive accomplishment.

The study is not without limitations, and the investigators appropriately and explicitly acknowledge several simplifying assumptions inherent in the model. One such assumption was that medication-induced disruption of fecal microbiota was permanent and that patients would not lose their "high-risk for CDI" status unless an active intervention was made to recolonize their intestinal tract. The validity of this assumption is far from certain. Patients who recover from pri-

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mary CDI without recurrence have been shown to have a more diverse microbiota than those who develop recurrent disease,[10] and spontaneous reversal of antibiotic-induced changes in the microbiota after cessation of antibiotics has also been shown,[11] which suggests that some recovery from perturbations in fecal microbiota can occur without intervention. Also, several factors known to influence the epidemiology of CDI were not modeled; these include infection with epidemic strains, such as ribotype 027,[12] the higher incidence of CDI seen in surgical versus medical ICUs, advanced age, functional status,[13] and greater burden of comorbid disease.[14,15]

Because most of the data regarding the performance of FMT comes from uncontrolled studies, with only a single randomized, controlled trial, it is subject to various biases, including publication bias. Unlike the model's setting, most patients treated with FMT in the literature, including the randomized, controlled trial upon which the model was based,[8] were not hospitalized in an ICU or critically ill. Also, the model uses a single specific protocol for FMT,[8] and the literature suggests there may be differences related to stool preparation, type of donor, and route of infusion.[7] As a result, it is difficult to know the true success rate of FMT in this population, and the study's use of a 93.8% figure may not reflect all scenarios. The omission of the above modifying factors warrants caution regarding the applicability and generalizability of these results.

Furthermore, although a paucity of adverse events associated with FMT are reported in the literature, the short- and long-term risks of FMT have not been fully characterized. Transmission of pathogens is possible, and proper screening of donors is mandatory. FMT is largely untested in patients with severe CDI, and a study of a single-agent probiotic in critically ill patients with acute pancreatitis found an increase in mortality.[16] The route of FMT administration may have its own inherent complication rate, such as intestinal perforation during colonoscopy or nasal mucosal damage during nasojejunal intubation. With more widespread use of FMT, the costs associated with donor screening, stool preparation and infusion, and management of adverse events need to be weighed against the potential benefit, and this has not yet been assessed in a rigorous manner.

Several broader concerns stem from an incomplete understanding of the complex interactions between the host and intestinal microbiota and whether FMT can lead to unintended consequences. A flare of inflammatory bowel disease, previously quiescent for 20 years, has been described after FMT,[17] and mouse models have been able to show the induction of colitis through transfer of microbiota.[18,19] Data on potential long-term consequences of FMT are also lacking, although the intestinal microbiota has been associated with colon cancer, diabetes, obesity, atopy, and asthma.[18] These concerns reinforce the need for caution in routine use of FMT for primary CDI and underscore the importance of long-term follow-up as use of FMT becomes more widespread.

Although Lofgren et al[9] describe a new mathematical model that can be deployed to help understand the transmission of CDI and prevent recurrent disease, several queries should be made regarding applicability of the model to clinical practice, including (i) how their model would perform with the inclusion of additional known risk factors, such as advanced age; (ii) whether widespread use of FMT in hospitalized patients, especially those with severe disease, is cost-effective and safe; (iii) what potential unintended long-term consequences exist; and (iv) how specific characteristics of the intestinal microbiome interact with the host to affect these parameters. Although FMT may prove to be a useful treatment for hospitalized or critically ill patients with CDI, these issues should be addressed before routine use of FMT for prophylaxis or treatment of primary CDI can be recommended.

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