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Environmental Management in the Gut: Fecal Transplantation to Restore the Intestinal Ecosystem

Vincent B. Young, MD/PhD[1] and **Mary K. Hayden, MD**[2]

[1]Department of Internal Medicine/Infectious Diseases Division, University of Michigan Medical School, Ann Arbor, MI

[2]Department of Medicine/Infectious Diseases Division, Rush University Medical Center, Chicago, IL

Restoring essential ecosystem services is a key goal of environmental managers following a disaster such as a forest fire. The recent attention being paid to the indigenous human microbiota, the collection of microbes that live in and on the human body, has driven a desire to understand the role that this microbial community can play in human health and disease [1, 2]. Changes in this human/microbial ecosystem are associated with various diseases and thus there is a desire to restore a "beneficial" community in order to restore health.

One of the key ecosystem services provided by the indigenous microbiota is that of providing colonization resistance [3]. Defined as the ability of an established community of microbes to prevent the establishment of additional potentially pathogenic microbes, colonization resistance is thought to be an essential defense mechanism against a variety of infectious diseases. Perhaps the best example of the loss of colonization resistance is the development of *C. difficile* infection (CDI) in patients whose indigenous gut microbiota is disrupted via the administration of antibiotics [4]. While the majority of patients with CDI respond to antibiotic therapy directed against the pathogen, recurrent disease whereby patients experience a recrudescence of symptoms after discontinuing anti-*C. difficile* therapy can be a major problem. In patients who remain unresponsive to additional rounds of treatment, restoration of the intestinal microbiota through the administration of feces obtained from a normal donor is a successful and viable alternative treatment [5].

Although there has been considerable recent attention paid to the use of fecal microbiota transplantation (FMT) for *C. difficile* it should be noted that the use of fecal transplantation to treat antibiotic-associated pseudomembranous colitis predates the recognition that this clinical entity was often due to CDI. A case series of four patients who were successfully treated by healthy donor feces administered via enema was published in 1958 by Eiseman and colleagues [6]. A more recent development has been the attempted use of FMT to eliminate colonization or treat infections with multiply drug-resistant organisms (MDROs) such as vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and Enterobacteriaceae that harbor carbapenamases or extended-spectrum beta-lactamases (ESBLs). In this issue of *Infectious Diseases* [7], Manges and colleagues review eight recent case reports/case series where fecal transplantation was used to decolonize patients with an enteric MDRO. In the published reports that they review, the

authors note that there was considerable success although they acknowledge that there could be a bias against reporting negative results.

Given the fact that the review [7] focuses on the available published literature on the use of FMT for eliminating MDRO colonization and that this evidence consists solely of small case series and case reports, some of which were not peer-reviewed, it could be asked if it is far too early to review this area. However, the authors take the opportunity to identify and discuss several key questions regarding the practical use of FMT to eliminate MDRO colonization and also point to future needs and directions for research. We will spend some time here reviewing these future directions and presenting some of our own ideas regarding further developments in this area.

Manges and colleagues identify three practical considerations regarding FMT administration: 1) the route of administration, 2) donor selection and 3) the need for bowel preparation in the recipient. They rightfully point out that the experience using FMT for treatment of recurrent CDI may not necessarily apply to decolonizing patients with MRDOs due to potential differences in the mechanisms by which the indigenous microbiota mediates colonization resistance against various organisms. For recurrent CDI, variability in approaches to the three practical concerns raised above does not appear to have a significant effect on the efficacy of FMT. Even given potential publication bias in favor of positive results, the eight case reports reviewed by Manges et al have a remarkable success rate, on par with the early case reports and case series of the use of FMT for recurrent CDI, and suggesting that FMT for elimination of MDRO carriage may yield similarly robust results. We agree that larger clinical trials of FMT for MDRO decolonization are needed and it is important to note that the authors identified five trials that are currently enrolling patients for such studies. Hopefully these studies will provide better quality results on the efficacy of FMT for eradication of MDROs in a manner analogous to the first large, controlled trial for FMT in recurrent CDI [8]. An additional line of human study involves a more detailed examination of the specific changes in the gut microbiota that are associated with susceptibility to MDRO colonization, and of exposures such as antibiotic treatment that may be risk factors for these changes. McDonald and colleagues recently published a report that suggested that the establishment of a “microbiome disruption index” might be able to improve prevention of infection with MDROs by identifying patients at greatest risk for colonization based on the status of the community structure of the gut microbiota [9]. Such patients could be targeted for interventions such as antibiotic stewardship, probiotic administration, or even FMT with the goal of restoring a colonization-resistant microbial community. Only additional studies can determine whether this will turn out to be a viable strategy.

Long-term observational studies are also needed to evaluate whether FMT eradicates MDRO carriage or merely suppresses it below the limit of detection, with recrudescence possible after subsequent re-exposure to antibiotics or other stressors. As discussed by Manges and colleagues [7], even temporary suppression of MDRO colonization would have the potential benefit of protecting patients from invasive infection during vulnerable clinical periods, such as prolonged neutropenia after myeloablative cancer chemotherapy, and of reducing the risk

that a colonized patient would act as a source of MDRO cross-transmission during hospital stays requiring substantial hands-on care, such as during critical illness.

In addition to human clinical trials and natural history studies, we think that more mechanistic studies of the role of the microbiota in establishing colonization resistance against MDROs are also needed. Using the case of CDI once again, the use of small animal models (generally hamster and mouse models of CDI) has provided important information of the mechanisms by which the indigenous gut microbiota can prevent colonization by *C. difficile* [10]. Manges et al. suggest that in the future "a clearly defined and regulated complex mixture of functional microbiota organisms" could be developed for elimination of MDRO colonization. In order to better define the important functions that are needed to eliminate MDROs, animal models are likely to have great utility. Returning to CDI, the role of bile acids in mediating colonization resistance against *C. difficile* has been defined in rodent models of disease [11]. Also the role of the microbiota modulating protective intestinal immune responses has been shown in a murine model [12]. A recent publication has demonstrated that administration of vancomycin to alter the gut microbiota can render mice susceptible to colonization with VRE and carbapenam-resistant *Klebsiella* [13]. Thus there is every reason to think that a greater understanding of the molecular mechanisms desirable to be possessed by a "designer microbiome-based therapy" could come from the use of animal models.

A final point raised by Manges et al. is that the legal, regulatory and safety issues associated with FMT (and any microbiota-targeting therapy for that matter) are underappreciated. We agree that this is an important consideration. In particular, the regulatory aspects of FMT have the potential to block widespread implementation of this promising therapeutic alternative for the treatment and prevention of important nosocomial infections [14]. Additionally this would have repercussions for the use of microbiome-targeting therapy for a variety of non-infectious conditions. It should be recognized that ethical concerns related to FMT for treatment of asymptomatic MDRO decolonization may be different from those related to treatment of severe, recurrent CDI. Only about 20% of intensive care unit (ICU) patients who are colonized with an MDRO develop an infection with the same MDRO during their ICU stay [15, 16]; the risk of infection may be lower among patients in long term care facilities [17, 18], which have been identified as important reservoirs for MDROs in several studies [19]. While FMT holds promise as a groundbreaking strategy for control of MDROs in these settings, its therapeutic index must be proven to be very high before treatment of asymptomatic patients who may be at low risk of infection can be justified.

We would like to join with Manges and colleagues in calling for active discussion between investigators, clinicians and regulatory bodies including the US Food and Drug Administration to be proactive in considering the ethical, legal and social issues surrounding the use of FMT and other therapies that may alter the microbiota. These are exciting times for reconsidering mechanisms of disease pathogenesis and developing novel preventative and therapeutic approaches that are based on an understanding of the intricacies of the interaction between humans and their indigenous microbial partners.

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