The Dawning of Microbiome Remediation for Addressing Antibiotic Resistance

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The Centers for Disease Control and Prevention estimates that over two million infections in the United States each year are caused by antibiotic-resistant pathogens described as urgent, serious, and concerning threats, leading to 23,000 deaths and billions of dollars in excess medical costs [1]. Nearly half of these 18 antibiotic resistant threats are health care-associated pathogens and at least five frequently colonize the lower intestinal microbiota of patients. Among the many host and environmental factors that influence the composition of our microbiota, the most significant is the receipt of antibiotics [2–4]. Treatment with antibiotics eliminates not only pathogenic but also beneficial bacteria, resulting in severe disruption of the intestinal microbiota for an extended period of time (>6 months) [2]. This loss of diversity in the intestinal microbial composition places individuals at increased risk for poor outcomes, including colonization by pathogens, such as *C. difficile* and other multidrug-resistant organisms (MDROs), which can give way to their expansion, dominance, and infection and bacteremia [5–8].

Among the almost 500,000 cases of *Clostridium difficile* infection (CDI) that occur each year, there are an estimated 83,000 recurrences of infection annually [9]. In recent years, the use of fecal microbiota transplantation (FMT) has garnered attention as a method for treating recurrent CDI by restoring the intestinal microbiota to a healthy state, preventing further recurrences [10]. The FDA has determined that FMTs are a biological product and a drug, and an investigational new drug (IND) application is required to use FMT for clinical indications, except for recurrent CDI for which an application is encouraged, but not required (http://www.regulations.gov/#!documentDetail;D=FDA-2013-D-0811-0002). This leaves a window open to use FMT for eradication of other MDROs, provided an IND application is submitted. Efforts to treat recurrent CDI have found concomitant eradication of other MDROs [11] and other groups have demonstrated clearance of ongoing colonization or recurrent infection by MDROs through FMT [12, 13].

In this issue of *Clinical Infectious Diseases*, Millan et al. report on a small study (N=20) of patients who underwent FMT via colonoscopy for recurrent CDI. The investigators demonstrated, using a combination of deep sequencing metagenomics and resistance gene microarray, a reduction in the diversity and number of resistance genes in patients' microbiota (i.e., resistome) following FMT. Although this was a small, uncontrolled study,

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there was additional indirect evidence for a causal role for FMT in shrinking the resistome found in the 9 of 20 patients who failed their initial FMT, requiring a second FMT. This clinical failure correlated with a failure to reduce the resistome, along with a failure to increase bacterial diversity (i.e., resistance gene diversity varied inversely with bacterial diversity) and a persistent dominance by Proteobacteria, especially *Escherichia coli* and *Klebsiella pneumoniae*. In addition, the investigators demonstrated that the microbiomes of the 3 FMT donors were similar in diversity to a healthy cohort (age 18–40 years) from the Human Microbiome Project.

Nonetheless, the study lacks a recurrent CDI control group that did not receive FMT, and therefore one cannot assess how much FMT contributes to shrinkage of the resistome over and above simply avoiding subsequent antibiotic exposure. In addition, current metagenomics methods are unable to link an antibiotic resistance gene to a particular species member of the microbiome and thereby identify potentially pathogenic MDROs present. Finally, the load of antibiotic resistance genes present in these patients and correlation of the load with risk of developing a subsequent MDRO infection or transmitting MDROs or determinants to other patients are unknown.

We can anticipate various routes to the future use of microbiome remediation as a means to address antibiotic resistance. While FMT using screened, healthy donors is currently widely practiced in the treatment of recurrent CDI, one can foresee a possible day when a patient's own microbiome is electively harvested, frozen or otherwise 'banked', and later used for autologous re-transplant following a microbiome-disrupting therapy or intervention [14]. Examples of this might include intense periods of antibiotic and other microbiome disruptive exposures as encountered during organ transplantation, hematopoietic stem cell transplantation, or chemotherapy. This of course presupposes that the episode of microbiome disruption can be planned for ahead of time and that the patient has a baseline microbiome that is rich and diverse with a relatively contracted resistome. While donor FMT remains an option for patients whose microbiome is already disrupted, another hope for the future is the development of defined, advanced probiotics. The recent report of successful treatment of multiply recurrent CDI using a processed preparation (SER-109) of approximately 50 anaerobic spores derived from human donors is one step along the path toward development of such advanced probiotics that are defined and sourced in vitro [15].

To explore how understanding the status of the microbiome can be used to tailor antibiotic stewardship and infection control decisions, as well as prepare for future FDA-approved methods for microbiome remediation, CDC is working to develop Microbiome Disruption Indices (MDIs). The goal is to develop standardized criteria that characterize the major human microbiomes (beginning with the large intestine) with regard to their vulnerability to MDRO colonization and, once colonized, to MDRO dominance that increases the risk for infection or transmission of the MDRO to other patients. In addition, such indices can communicate the disruptive potential of various drugs, including antibiotics. Potential MDIs include compositional indices of diversity, species richness, the presence or absence of protective species and, as demonstrated here by Millan et al., measurement of the resistome. In addition, MDIs may include indices of the functional status of the microbiome based upon either an inferred metagenomics approach (i.e. predicting major metabolic pathways

present) or a more direct metabolomics approach (i.e. direct measurement of metabolites). With these indices in use, a patient's status of disruption could be ascertained, and, as a patient reaches a threshold suggesting extreme vulnerability to colonization, special reverse isolation precautions could be instituted to prevent the acquisition of new resistance traits and MDROs while pre-emptive microbiome restoration is considered to achieve improved indices. Once colonization has occurred with an MDRO, specific antibiotics that predictably drive such patients to a state of MDRO dominance could be avoided. And finally, if microbiome dominance by a specific MDRO becomes detected and the patient is at increased risk for transmitting the MDRO to another patient, special isolation precautions can be undertaken, along with steps to reduce the dominant strain and restore the microbiome to a state of increased diversity and lower antibiotic resistance gene burden. The current priority in the development of such MDIs is for natural history studies to understand the dynamics of microbiome status throughout and between hospitalizations. Given the tremendous burden of diseases like CDI, the growing problem of resistance, and the lack of effective therapies for many MDROs, there should be a sense of urgency across all the major sectors of academia, industry, and government to further develop and establish the role for microbiome remediation in the future of medical care and public health.

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