Clinical Infectious Diseases

SUPPLEMENT ARTICLE

The Relationship Between the Microbiome and Antimicrobial Resistance

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Antibiotics have benefitted human health since their introduction nearly a century ago. However, the rise of antibiotic resistance may portend the dawn of the "post-antibiotic age." With the narrow pipeline for novel antimicrobials, we need new approaches to deal with the rise of multidrug resistant organisms. In the last 2 decades, the role of the intestinal microbiota in human health has been acknowledged and studied widely. Of the various activities carried out by the gut microbiota, colonization resistance is a key function that helps maintain homeostasis. Therefore, re-establishing a healthy microbiota is a novel strategy for treating drug resistance organisms. Preliminary studies suggest that this is a viable approach. However, the extent of their success still needs to be examined. Herein, we will review work in this area and suggest where future studies can further investigate this method for dealing with the threat of antibiotic resistance.

Keywords. microbiome; microbiome therapeutics; antimicrobial resistance; multidrug resistant organsisms; *Clostridioides difficile*; microbiota.

ANTIMICROBIAL RESISTANCE ON THE RISE

History of Antibiotics and the Development of Antimicrobial Resistance

Antibiotics have been one of the greatest discoveries in human history. Unlike pre-antibiotic era treatments, antibiotics are a weapon that can effectively and rapidly target specific pathogens. After its discovery in 1928, penicillin became the first mass-produced antibiotic starting in the early 1940s. Subsequently, multiple antibiotics were developed and changed the course of medicine tremendously. Most antibiotics nowadays were introduced during the golden era of antibiotics, which happened in the mid-twentieth century [1, 2]. With the arrival of novel antibiotics, innumerable lives have been saved each year. The introduction of antibiotics has paralleled an increase in life expectancy, which in the United States is currently 79 years [3].

Despite the tremendous benefits of antibiotics, we are currently at risk of losing these drugs as part of our medical armamentarium. As soon as the first antibiotics were introduced, antimicrobial resistance (AMR) was identified in clinically important bacteria. The first case of penicillin resistance was identified before its mass production in 1940 [1]. Today, AMR has become an urgent threat to human health. AMR was the direct cause for at least 1.27 million deaths worldwide and contributed to nearly 5 million deaths in 2019 [4]. Multidrug-resistant organisms (MDROs) such as penicillin-resistant *Streptococcus pneumonia* (PRSP), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE) and multiple-drug-resistant gram-negative bacilli (MDRGNB) have increased substantially over the years, especially as a nosocomial infection (Centers for Disease Control and Prevention [CDC], "Management of Multidrug-Resistant Organisms in Healthcare Settings," 2006). It was recorded that VRE caused approximately 54 500 infections in hospitalized patients in 2017 [4].

Although antibiotic resistance has been on the rise, the development of novel antibiotics has lagged. The development of novel antibiotics has declined over the past decades, in part due to numerous economic and regulatory hurdles faced by pharmaceutical companies that could develop new agents. With the emergence of organisms with increasing resistance to existing agent, we are in danger of entering a "post-antimicrobial era" where we no longer have drugs to treat important infections [5]. As such, novel approaches have been proposed to deal with AMR that do not rely on the development of new antimicrobials. With an increasing understanding of the role of the indigenous microbiota in maintaining health, manipulation of the microbiome has been investigated as one of these novel approaches for mitigating AMR.

The past 20 years has witnessed an explosion in our understanding of the role of the indigenous microbiota in maintaining the health of their host. One of the beneficial functions that

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Clinical Infectious Diseases® 2023;77(S6):S479–86

https://doi.org/10.1093/cid/ciad641

are mediated by the microbiota is colonization resistance, which refers to the ability of a given microbiota to prevent invasion and overgrowth by additional microbes [6, 7]. Although the term initially referred to invasion by any microbe, it has become clear that antibiotic resistant microbes may have a specific advantage in that colonization resistance can be disrupted through the therapeutic use of antibiotics and "collateral damage" to the indigenous microbiota at other sites [8]. With regards to this, the intestinal microbiota has been a particular source of attention as the gut is home to the most abundant community of microbes and is also the reservoir for many antibiotic-resistant pathogens.

MECHANISMS BY WHICH THE GUT MICROBIOTA MEDIATE COLONIZATION RESISTANCE

Although the term colonization resistance implies that this is a single function, it is clear that multiple characteristics of the gut microbiota act in concert to mediate resistance to exogenous microbes. Some mechanisms are through direct microbe-microbe interaction, whereas some are mediated through the host. The therapeutic manipulation to revise colonization resistance for treating enteric pathogen infection are developed taking advantage of these mechanisms. Below we will discuss each mechanism and introduce how these can be leveraged with therapeutic intent. In the following sections, a more detailed discussion of such strategies will be presented.

Nutrient Competition

One way in which colonization resistance can be generated by the indigenous microbiota is though nutrient competition. The microbiota forms a dense and intertwined metabolic network. Within the gut, members of the microbiota fill up most niches depending on their physiology and nutrient availability. Thus, the growth of exogenous microbes such as enteric pathogens is restricted by members of the indigenous microbiota which have similar need in nutrients such as diet carbohydrate, host mucin, microbial metabolites, or trace metals. This concept of competition for nutrients has been long studied as a mechanism of colonization resistance [9, 10]. Recent work has continued to investigate how this mechanism can affect various bacterial pathogens. For example, the presence of indigenous bacteria has been shown to limit the amount of sialic acid and succinate available to *Clostridium difficile* [11, 12]. The use of antibiotics alters the community structure of the indigenous microbiota, resulting in the release these carbon sources to *C. difficile*. Another example is the use of specific *Escherichia coli* biotypes to prevent the colonization by EHEC based on competition for common carbon sources [13]. The consumption of fructose by a consortium of 5 intestinal microbes can reduce VRE colonization [14]. Conversely, inflammation, unhealthy diet, and antibiotic use can result in a disruption of the gut microbiota, facilitating the expansion of unwanted microbes. Previous studies showed that the microbiota can recover spontaneously, but it is a slow process and may give rise to AMR [15].

Colonization resistance via nutrient competition provides the mechanistic basis for several proposed microbiome-based therapeutic strategies. The use of other microbes, either in the form of fecal microbiota transplantation (FMT), classic probiotics, or defined microbial consortia has been investigated as a way to bolster colonization resistance. In a similar vein, the use of prebiotics, generally complex carbohydrate that are not digestible by the host but can foster the growth of members of the indigenous microbiota, has received considerable attention.

Antimicrobial Peptides and Microbe-microbe Inhibition

Some members of the microbiota can produce peptides with antagonistic effect on other microorganisms. This can also contribute to colonization resistance. An example is nisin-A produced by *Lactobacillus lactis* and *Streptococcus* [16, 17]. Nisin-A has been long used as food preservative due to its activity against gram-positive bacteria. Other substrates with inhibitory effect against VRE include a lantibiotic by *Blautia producta* [18] and bacteriocin by *Enterococcus faecalis* [19].

To take advantage of this mechanism of colonization resistance, early work is investigating if the administration of bacteria producing antimicrobial peptides or the delivering the peptides themselves can improve colonization resistance. In addition to these secreted antimicrobial products, some bacteria have systems, including type VI secretion systems that can directly kill competitors via direct injection of antimicrobial effectors [20].

Modulating the Host Immune System

The gut microbiota plays an important role in educating and stimulating host immunity. It has been observed that the gut microbiota is involved in the maturation of both the cellular and humoral immune compartments [21, 22]. Many aspects of the development of mucosal immunity have been shown to be regulated by the indigenous gut microbiota [23, 24].

Additionally, the microbiota contributes to the health of the intestinal epithelial cells, for example, promoting the regeneration of epithelial cells. Microbial metabolites such as butyrate promote the tight junction protein expression. Other members of the microbiota such as *B. thetaiotaomicron* and *Faecalibacterium prausnitzii* promote the production of the mucous layer, which helps better separate the host from invasive pathogens [25]. The perturbation of the indigenous microbiota by diet change or antibiotics can alter the immune response and reduce the protection role of the barrier [26, 27]. Thus, to improve the immune function for treating

pathogens, one can leverage the interplay between microbiota and the immune system. Microbiota-based therapeutics such as probiotics, microbial consortium transfer, or fecal microbial transplant are being studied as ways to boost colonization resistance and immune homeostasis in the gut.

Catabolism

Members of the indigenous microbiota can metabolize complex indigestible carbohydrate and mucin to short chain fatty acids (SCFAs), such as acetate, propionate, butyrate, valerate, and isovalerate. These SCFAs not only promote the growth of intestinal cell barrier [28] but also maintain the acidic pH in the gut. Butyrate has been examined as a critical SCFA. In addition to serving as the preferred energy source for colonic enterocytes [29, 30], it can contribute colonization resistance against pathogen such as *C. difficile* [31].

In addition, bile acids comprise another set of metabolites regulating the resistance against pathogens. It was previously reported that taurocholate and cholate are potent germinants for *C. difficile* spore in the gut [32, 33]. The degradation of these primary bile acids by bacteria such as *C. scindens* can inhibit *C. difficile* growth [34, 35] and *V. cholerae* virulence [36]. Thus, the presence of indigenous microbiota and their metabolites creates a non-favorable environment for pathogens. Both microbes themselves and their metabolites are being investigated as potential therapies.

STRATEGIES FOR INCREASING COLONIZATION RESISTANCE TO TREAT ENTERIC PATHOGENS

Given the fact that the microbiota plays a central role in mediating colonization resistance against enteric pathogens, including MDROs, it is reasonable to entertain the idea that modulating the microbiota can restore or augment colonization resistance. As noted above in the discussion on the mechanisms of colonization resistance, there are several strategies that are being investigated as a way to modulate the microbiota to either prevent colonization by bacterial pathogens, including MDROs, or to eliminate/reduce these pathogens in patients who are already colonized.

At the outset of this discussion, it should be noted that much of this work in recent years has focused on the treatment of *C. difficile* infection (CDI). *C. difficile* does not necessarily fit within the rubric of a classic MDRO. Although it does flourish in the setting of therapeutic antibiotic use, in general its ability to colonize and cause disease in antibiotic-treated patients reflects the intrinsic resistance of the organism to antibiotics and not due to acquisition of additional antibiotic resistance determinants. Despite this, it is instructive to briefly review the literature on the use of microbiome-based therapies for CDI [37] as an introduction to microbiome therapeutics for more typical MDROs.

Diet

As the composition of the microbiota is dependent on the host consumption, a change in diet can shift microbiota composition and thus alter colonization resistance. Appropriate diet manipulation could promote the growth of beneficial taxa and encourage nutrient competition and production of metabolites that could boost colonization resistance against pathogens. Research found a strong link between a high-fiber diet and colonization resistance restoration. In vitro and ex vivo studies demonstrated that a diet high in soluble fiber was associated with inhibition of *C. difficile* growth and toxin production [38]. Among the mechanisms proposed for this effect was the transformation of fiber to butyrate [31]. With these benefits, fiber can be used as a supplement to support the growth of beneficial taxa and reinstate CR.

Probiotics

Probiotics are classically defined as "Live microorganisms which when administered in adequate amounts confer a health benefit on the host" [39]. Unfortunately, this definition is not always adhered to and this has generated confusion in the scientific literature [40]. For the purposes of this discussion (and provide clarity and distinction between different strategies that use "live microorganisms") we will discuss probiotics as single, cultivated strains of microbes (generally microbiota and some yeast) or defined combinations of such strains. In the past, many probiotics have been organisms isolated from fermented foods, with the bulk of these being members of the lactic acid producing bacteria. In practice, these organisms have been administered as cultured microbes or can be given in the form of the fermented food itself, which contains these microbes.

For CDI, there has been conflicting evidence on the use of probiotics for the treatment of disease, especially recurrent disease or for the prevention of CDI in patients receiving antibiotics. At this time, there appears to be enough promising data to warrant additional study, with careful selection of agents and clear clinical endpoints [41, 42].

The Use of Fecal Microbial Transplantation for Treatment of CDI

The use of FMT to restore colonization resistance against *C. difficile* represents the most well-studied case for a microbiome therapeutic. The use of this strategy for the treatment of antibiotic-associated colitis predates the fulfillment of Koch's postulates for *C. difficile* as the causative agent of this condition [43]. The "modern age" of FMT for the treatment of recurrent CDI (rCDI) was ushered in with the 2013 report of a placebo-controlled trial that demonstrated that FMT was associated with a 90% successful rate, surpassing standard of care vancomycin [44]. This work confirmed the data from many case reports and case series of the success of FMT for rCDI [45]. In addition to the treatment of rCDI, FMT is a highly efficient method for treating first time CDI [46].

More recently, there have been attempts to refine FMT to provide a more standardized material for treatment and to decrease the risk of transmitting pathogens while maintaining the efficacy seen with the use of freshly voided feces. Two of these products were recently approved by the Food and Drug Administration (FDA) for the treatment of rCDI, representing the first time that microbiome therapeutics have been approved for specific indications [47, 48].

Defined Microbial Consortia

Given the success of FMT for rCDI, there has been a desire to further refine the technique by developing defined mixtures of microbes, derived from the feces of healthy subjects, that can be used to restore the structure and function of the microbiota.

These consortia consist of taxa having strong association with colonization resistance against CDI. In small clinical trials, consortiums of 13 and 33 bacteria successfully eradicated *C. difficile* [49–51]. A more well-studied consortium consists of 8 strains of bacteria belonging to the *Clostridia*. A phase 1 trial in healthy volunteers demonstrated that this consortium could colonize volunteers following pretreatment with vancomycin [52]. In a follow-up, phase 2, dose-ranging study, a high dose of this consortium (8×10^9 colony-forming units) prevented recurrent CDI when compared to placebo [53].

LESSONS FROM CDI AS APPLIED TO MICROBIOME THERAPEUTICS FOR ANTIBIOTIC RESISTANT ORGANISMS

Animal studies have been conducted to investigate the use of therapy with microbes for the eradication of colonization with MDROs. For example, it has been reported that in mice colonized with VRE or carbapenem-resistant Enterobacteriaceae (CRE), the transfer of feces from healthy mice could eliminate colonization [54]. Subsequently, this group demonstrated that defined consortium of bacteria including *Clostridium* cluster XIVa species, *Blautia producta* and *Clostridium bolteae* was shown as effective as fecal transplantation in eliminating VRE colonization [55].

During the treatment of recurrent of human patients with rCDI using FMT, it was noted that this treatment could have a secondary effect of reducing recurrent urinary tract infections (UTIs) [56, 57]. A recent retrospective chart review extended these case reports and small case series demonstrating that among 25 patients with a history of recurrent UTI who underwent FMT for rCDI, there was a significant reduction in the rate of subsequent UTI when compared to patients with rCDI and recurrent UTI who were treated with antibiotics [56]. These observations has led to trials of using FMT to directly treat UTIs. In a case report, FMT administered in the form of lyophilized feces in capsules successfully treated a patient with recurrent UTIs caused by *K. pneumoniae* that produced an extended spectrum beta-lactamase [58].

There have been several case-series and small trials that studied the use of FMT for treating eliminating colonization with MDROs (Table 1). In a study of 8 patients colonized with VRE, FMT resulted in decolonization in 7 of 8 [59]. In the setting of colonization of with CRE, another study observed that FMT successfully decolonized 10 of 13 patients [60]. Similar efficacy has been observed in other uncontrolled, cohort studies [61–63]. Another small study demonstrated that 3 of 3 patients with CRE treated with FMT were successfully decolonized [64]. The main goal of this study was to examine how the FMT treatment altered the community structure of the microbiota, including both bacteria and viruses in their examination. This study suggested that bacteriophage specific for the CRE might play a mechanistic role in the efficacy of FMT for decolonization [64].

Larger controlled trials for the use of FMT in eliminating colonization with MDROs have had variable results (Table 1). One randomized, multicenter trial studying patients colonized with multidrug-resistant Enterobacteriaceae compared control patients (N = 17) to patients (N = 22) who were treated for 5 days with non-absorbable antibiotics followed by FMT [65]. The efficacy of FMT was 40.9%, which was not significantly different from the control group (29%). However, this trial did not enroll the targeted number of patients based on a power analysis (N = 64) before it was prematurely terminated due to logistical reasons. In a subsequent report, this group reported the changes that the antibiotic pretreatment and the FMT had on the microbiota, including changes in antibiotic-resistant determinants [66]. Another case-control study reported an 80% efficacy (8 of 10 patients) compared to controls (2 of 20) for decolonization of CRE [67]. The high success rate of this study may have resulted from the treatment that FMT recipients received before the procedure. Prior to FMT, these patients had 2 bowel wash procedures, treatment with non-absorbable antibiotics, and stomach acid neutralization with a proton-pump inhibitor. In addition, a second FMT was administered for those who failed the first FMT. As we discuss below, the specifics of FMT likely have a great influence on the efficacy of the procedure.

In addition to decolonization, there are preliminary data that suggest that treatment of patients colonized with MDROs using FMT could have other beneficial, clinical endpoints. In a non-randomized, non-controlled study of 20 patients colonized with MDROs who were treated with FMT, there was a significant decrease in the days of antibiotic treatment, incidence of bacteremia and length of stay [68]. The comparison was made comparing with the patients in the 6 months following FMT compared to the 6 month prior to treatment and also with a comparator group of patients colonized with MDROs who did not get treated with FMT. Interestingly, in this study, the efficacy of decolonization was only 41% suggesting that decolonization was not required to see the beneficial clinical effects of FMT.

Table 1. Human Studies of Microbiome Modulation to Treat or Prevent MDRO Infection and Colonization

Reference	Number of Patients	Study Type	Intervention	Outcomes/notes
Bier et al [58]	1	Case report	FMT (lyophilized capsules) administered orally	Decolonization of ESBL-producing *K. pneumoniae* in patient with an ileal conduit and urostomy
Davido et al [59]	8	Case series	FMT with frozen, stored feces from healthy volunteers administrered via nasoduodenal tube	Decolonization of 7/9 patients with vancomycin-resistant enterococci (VRE) during outbreak setting
Silva et al [60]	13	Case series	FMT with fresh stool administered via esophagogastroduodenoscopy (EGD)	Decoloniztion of 10/13 patients with carbapenamase-producing Enterobacteriaceae (CPE). Eight of the patients also had refractory or recurrent CDI in addition to CPE colonization.
Bar-Yoseph et al [61]	15	Prospective cohort	FMT with oral capsules	Decolonization of 9/15 patients colonized with CPE.
Lee et al [62]	10	Prospective cohort	FMT via several modalities including colonoscopy (with EGD as backup for failed colonoscopy) and in 1 patient, encapsulated feces. Patients received between 1 and 3 FMT	Non-standardized administration of FMT in patients with CPE. Overall, 4/10 decolonized at 1 m, 5/10 at 3 m and 5 of 10 at 5 m.
Seong et al [63]	35	Prospective cohort	FMT with multiple modalities including colonoscopy, duodenoscopy, percutaneous jejunostomy tube and capsules	35 patients: 4 with CPE, 19 with VRE and 12 with both CPE/VRE colonization. Overall, 24 of 35 were decolonized.
Liu et al [64]	3	Case series	Frozen stool administrered via EGD × 2	All the patients were decolonized for CRE. Not a trial, main focus was on characterizing the longitudinal changes in the bacterial and viral microbiota after FMT using shotgun metagenomic sequencing.
Huttner et al [65]	22 treated, 17 controls	Randomized controlled trial (multicenter)	antibiotic therapy (colistin/neomycin × 5 d) followed by FMT given either by nasogastric tube of capsules.	All subjects colonized with extended spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E) or CRE. 9/22 (41%) treated patients and 7/17 (29%). Difference did not reach statistical significance. Did not reach the calculated sample size of 64 participants. A followup paper did report the changes FMT had on the microbiota [66].
Saidani et al [67]	10 treated, 20 controls	Retrospective case-control	FMT via NG tube or gastric tube if present. Extensive pretreatment with chlorhexidine, bowel lavage, and non-absorbable antibiotics	8/10 treated patients and 2/20 controls were decolonized CRE or CR-Acinetobacter. The authors state that the pretreatment regimen was potentially responsible for the high success rate, but it is not clear if the controls had the same regimen but no FMT as the study design was retrospective.

Abbreviations: CDI, *Clostridioides difficile* infection; CPE, carbapenemase-producing Enterobacteriadeae; CR-Acinetobacter, xxx; CRE, carbapenem-resistant Enterobacteriaceae; EGD, esophagogastroduodenoscopy; FMT, fecal microbial transplantation; *K. pneumoniae*, xxx.

SUMMARY: WHAT DO WE KNOW ABOUT MICROBIOME THERAPEUTICS FOR MDROS AND WHERE DO WE GO FROM HERE

As noted from the discussion above, research on manipulating the indigenous microbiota with therapeutic intent for patients at risk for or with MDROs is still in its early phase. Meta-analyses of the use of FMT for decolonization reinforce this conclusions and suggest that well-designed randomized controlled studies are required to confirm the promising preliminary studies reported in the literature [69, 70]. Answering this call, the protocols for 2 different randomized, controlled studies testing the use of FMT for decolonization of patients with MDROs have been published, but no results have been published in the literature as yet [71, 72].

In addition to FMT, where there are the most data currently, there are reports of testing other microbiome-based therapies for decolonization of patients harboring antibiotic-resistant organisms. In addition to preliminary reports of using a 33 species consortium to treat CDI as noted above [51], this consortium has been tested for its ability to reduce the burden of antibiotic resistant *Pseudomonodata* and antibiotic-resistance genes (ARG) in patients. Administration of this consortium had a significant effect on the relative abundance of *Pseudomonodata* and also reduced the total number of ARG [73]. Secondary analysis of patients who were treated with one of the commercial, processed fecal preparations that recently received FDA approval for the treatment rCDI demonstrated that this treatment also reduced the carriage of antibiotic-resistant *Enterobacteriaceae* and antibiotic resistance genes [74]. Preliminary studies have also demonstrated that probiotic preparations may have a beneficial effect on reducing the abundance of bacterial pathogens including MDROs in the gut [75, 76].

Although the efficiency is still not well defined, FMT appears to be a promising method for treating MDROs, and most data are currently available for this modality. As many authors note, there still needs to be careful study of the use of FMT for

treating MDROs. We will summarize what we feel are some of the important considerations for the design and conduct of these studies.

Given the success of FMT for the treatment of rCDI, it is not surprising that many trials with FMT for MDROs employ similar procedures to those that have been developed for rCDI. However, it should be noted that there are characteristics of *C. difficile* and the techniques for FMT that may not necessarily translate to other pathogens. *C. difficile* is a spore forming gram-positive bacterium and studies have shown that the spore-forming fraction of the gut microbiota alone has the ability to mediate colonization resistance against *C. difficile*. Indeed, the "classic" method for preparing feces for FMT, which involves mixing human feces in a blender under ambient oxygen, will lead to the death of non-spore forming anaerobic bacteria, which in turn compose a significant fraction of the gut bacterial community. If the functions necessary to restore colonization resistance reside within the oxygen-sensitive fraction of the microbiota, these cannot be restored by fecal preparations that are appropriate for treatment of rCDI. Furthermore, although we have referred to "MDROs" as a group, it must be stressed that this includes microbes with widely different physiology. Thus, if rational microbiome therapeutics are to be designed for a given MDRO, then this should be based on the specific biology of the pathogen as it relates to colonization resistance. It has been shown that VRE and CRE appear to occupy distinct metabolic niches within the gut; thus, it is unlikely that the same microbiome therapeutic, if it is highly targeted in terms of mechanism, can work with both. In some ways, the use of FMT (with the caveats above) can obviate the need for specificity, as a wide range of ecosystem functions can be supplied by FMT.

The choice of donor should be more case-specific because there is no one size fits all. Moreover, the success of FMT is highly associated with the recipient microbiome [63, 77]. Ideally, the microbiota of the donor and recipients should be carefully paired. In addition, some evidence suggests an association between drug-resistant organism and efficacy. Research by Seong and colleagues [63] and Dinh and colleagues [78] found differences in efficacy between FMT for CRE versus VRE.

As noted above, the preparation of feces to treat rCDI often eliminates obligate anaerobes that cannot form spores. Related to this, it was demonstrated that obligate anaerobic bacteria are necessary to clear VRE, whereas oxygen-tolerant bacteria are not able to restore colonization resistance to this pathogen [79]. In another aspect, sample should be prepared fresh or frozen with cryopreservation additives as it would substantially affect the bacterial abundance [80].

In addition to the preparation of the material for FMT, there are multiple considerations regarding the administration of the material. The dose of feces for FMT should be considered. For rCDI, a dose of at least 50 g is advised. In many MDROs trials, the net amount of feces was <50 g, which might account for low efficacy. Trials with higher dose seem to have higher efficiency [67, 81]. Also, because antibiotics have direct effect on the microbiota and potentially on the microbes present in the FMT preparation, the timing of antibiotics in relationship to FMT should be considered. For many studies in the literature, FMT was performed without stopping antibiotics or stopping from one to two days in advance. Of course, in some cases, the use of antibiotics, in particular non-absorbable antibiotics, is an integral part of the FMT strategy itself. In addition, antibiotic use after FMT could affect the decolonization rate [78].

With regards to the route of administration, there have been studies in *C. difficile* that indicate that administration to the upper versus lower GI tract can affects efficacy, presumably because this can affect the survival of transferred bacteria. For regimens where oral route is employed, the acidic condition in the stomach should be taken into consideration. A common approach to neutralizing the stomach acid is via the of a proton pump inhibitor or chemical antacid prior to FMT [67, 81]. For the administration of FMT via the rectal route, there needs to be consideration of whether bowel preparation might increase efficacy. A bowel wash increases the engraftment of a new microbiota [67]. Eunseok Choi et al presented a comprehensive mechanical decolonization of VRE and CRE, including weekly glycerin enemas. The final yield is a 62.5% success rate [82]. Nadia Saïdani et al, who employed 2 bowel wash procedures, observed an even higher FMT efficacy [67].

Repeated FMT might be considered if the first FMT failed. Saidani et al [67] reported an equal 40% eradication rate after the first FMT. The number increased up to 80% after a second FMT, suggesting that repeated FMT might be considered if it does not negatively affect patient health [67].

CONCLUSION

The microbiota has a critical role in preventing the colonization of harmful pathogens. Restoring colonization resistance represents a novel and potentially quite attractive route for the specific control of antibiotic-resistant organisms. The use of microbiome-based therapies is a promising yet under-investigated approach to accomplish. The preliminary results reviewed here provide hope that this approach can be honed in the future, but careful additional research needs to be done to confirm these results and to further tune this approach for specific MDROs.

Notes

Financial support. This work has been funded by AI162787.

Supplement Sponsorship. This article appears as part of the supplement "The Microbiome and Human Health Perspective," sponsored by Ferring Pharmaceuticals Inc., Seres Therapeutics Inc., and Nestlé Health Science.

Potential conflicts of interest. V. Y. reports grant support from the National Institutes of Health (NIH) and National Institute for Allergy and Infectious Diseases (NIAID); collaboration on phase 1 trial of VE303

in patients with hepatic encephalopathy with Vedanta biosciences; consulting fees from Vedanta Biosciences and Debiopharm; honoraria payments from Oklahoma University Health Sciences Center, Illinois Society for Microbiology, and Michigan State University; support for attending the American Society for Microbiology meeting; participation in the VRBPAC meeting regarding the approval application of RBX2660 by Ferring Pharmaceuticals; holds leadership roles with the American Society for Microbiology and the Peggy Lillis Foundation; and is the journal senior editor of mSphere and chair of the council on microbial sciences with the American Society for Microbiology. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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