HHS Public Access

Author manuscript

Am J Med Sci. Author manuscript; available in PMC 2019 November 01.

Published in final edited form as:

Am J Med Sci. 2018 November ; 356(5): 433–440. doi:10.1016/j.amjms.2018.08.015.

The use of microbiome restoration therapeutics to eliminate intestinal colonization with multi-drug resistant organisms

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Abstract

Antibiotic resistance (AR) has been identified by the World Health Organization as an "increasingly serious threat to global public health." Many mechanisms of AR have become widespread due to global selective pressures as widespread antibiotic use and/or chemotherapy. The intestine has become the primary reservoir for many resulting multidrug resistant organisms (MDROs), leading to the intestinal microbiome being dubbed the "resistome." Intestinal decolonization has been explored as a strategy to eradicate MDROs with selective digestive tract decontamination and probiotics being notable examples with mixed results. This review focuses on fecal microbiota transplantation (FMT) and the early evidence suggesting its efficacy in decolonizing MDROs and potential mechanisms of action to reduce AR genes. Current evidence suggests FMT may have promise in restoring healthy microbial diversity and reducing AR, and clinical trials are underway to better characterize its safety and efficacy.

Keywords

fecal microbiota transplantation; Intestinal microbiota; multidrug resistant organisms; sequencing

Introduction

Bacterial Antimicrobial Resistance

The World Health Organization describes antimicrobial resistance (AR) as an "increasingly serious threat to global public health."[1] Multidrug-resistant organisms (MDROs) have been growing in prevalence[2] and global distribution, accompanied by a related rise in costs,

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Conflict of Interest: All authors report no conflicts of interest relevant to this article.

disability, and mortality.[3–5] These MDROs have emerged from a variety of phyla with new species continually being identified.

Methicillin-resistant *Staphylococcus aureus* (MRSA) was one of the first recognized MDROs, identified in the United Kingdom in 1961.[6] Since that time, MRSA has been associated with increased inpatient mortality, higher hospital costs, worse quality of life, and greater financial costs post-discharge.[7,8] The impact of MRSA extends beyond the hospital setting with community-acquired MRSA (CA-MRSA) emerging as common pathogen in the United States in the early-2000s.[9–11]

Similarly, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae have become a significant source of infection in both nosocomial and community settings, especially with recognition of community-acquired ESBL urinary tract infections (UTIs)[12] that can be complicated by bacteremia requiring inpatient management.[13–15] Further, according to surveillance by the Centers for Disease Control and Prevention (CDC), a rising number of carbapenem-resistant Enterobacteriaceae have been identified since 2001,[16] most prominently in southern Europe and Asia.[17] Infections with carbapenem-resistant Enterobacteriaceae (CRE), including *Klebsiella pneumoniae* carbapenemase-(KPC) producing organisms, have a mortality rate of up to 71.9%, in solid organ transplant recipients.[18,19]

Another notable MDRO to emerge is vancomycin-resistant enterococcus (VRE), which includes *Enterococcus faecium* and *faecalis*. In one meta-analysis, patients with VRE bacteremia were approximately 2.5 times more likely to die than those with *Enterococcus* bacteremia susceptible to vancomycin.[20] VRE bacteremia has also been associated with increased hospital costs[21,22] and length of stay.[23,24] There are several patient groups at risk for VRE, including the critically ill requiring intensive care unit (ICU) stay, those living in a long-term care facility, and the immunosuppressed.[25] In one study of adult patients undergoing allogeneic hematopoietic cell transplantation, 10% developed VRE bacteremia with an associated mortality of 88% within 1.1 months.[26]

The Resistome

There are numerous mechanisms by which bacteria such as the aforementioned MDROs may become resistant to antibiotics. These include variations in antimicrobial targets of activity through changes in gene expression levels or target modification, physical barriers against antibiotics, phenotypic or behavioral changes such as expression or activation of efflux pumps, and inactivation of antimicrobial molecules. Determinants of these mechanisms are often coded by genes that reside on chromosomes or plasmids, the latter being more amenable to horizontal transmission.[27] Novel mechanisms can develop as a result of spontaneous mutations and lateral gene transfer, resulting in the creation and spread of AR genes,[28] which has been noted in varied niches from the soil[27] to the human intestine. The human intestinal microbiota is largely comprised of bacteria, which accounts for its potential for accumulation and transmission of AR genes. Strains of AR bacteria passing through the intestine after ingestion can introduce additional AR genes[29–31] with the gut serving as a reservoir for these drug-resistant opportunistic pathogens. This composite sum of AR genes in a microbial community has been dubbed the “resistome.”[32,33]

For the MDROs in the resistome to become pathogenic, changes in microbiome composition may account for the transition from asymptomatic colonization to development of infectious disease.[33,34] Heathy intestinal microbiota is primarily comprised of a variety of anaerobic species including *Lactobacillus*, *Faecalibacterium*, and *Bacteroides* that demonstrate a mutualistic relationship with the body. Pathogenic species such as *Escherichia* spp. and *Enterococcus* spp. often become more abundant when there is reduced intestinal microbiome density and diversity, particularly with reduced presence of the commensal anaerobes.[35,36]

A well-described cause of intestinal dysbiosis is antibiotic use. Extensive research using mouse models has demonstrated effects of antibiotics on the microbiome with studies dating back to the 1970s.[37,38] In a more recent study, antibiotic treatment was demonstrated to increase resistant bacteria that were then noted to translocate from the intestine to the rest of the body across the epithelial barrier.[39] Ubeda, et al. showed that antibiotic administration promoted *Enterococcus*, including VRE, *Enterobacteriaceae*, and *Clostridium* spp. colonization of the small and large intestines.[40] In another murine study, antibiotics that suppress anaerobes such as piperacillin-tazobactam and clindamycin promoted KPC colonization.[41] Caballero et al. demonstrated that the intestinal colonization of one MDRO, namely VRE, did not impede that of another, in this case KPC. The researchers suggested that while these MDROs may be present in the same intestinal lumen, they grow independently through distinct mechanisms within their niches in the microbiome.[42] In humans, the resistome and AR potential have been shown to vary across countries and have been suspected to be related to historically different antibiotic usage patterns in each place.[32] Furthermore, patients who received anti-anaerobic antibiotic therapy have been found to have significantly more MDRO colonization, such as with VRE, than those who had received minimal anti-anaerobic treatment.[43]

There are additional causes of dysbiosis that increase the risk of MDRO infection in certain patient populations. In patients preparing for hematopoietic stem cell transplantation (HSCT), chemotherapy was associated with significantly increased concentration of Proteobacteria, Firmicutes, and Actinobacteria.[44] The HSCT itself, in combination with antibiotics that may have been started for empiric or prophylactic therapy, reduces microbiome diversity, leading to dominance of certain bacteria. *Enterococcus* found to be the most common genus at 40.4% of patients in one study; of these patients, 92% had *vanA* gene expression consistent with VRE.[45] A mouse model suggests that burn injury may also lead to dysbiosis as it was found to decrease aerobic and anaerobic species in a manner similar to antibiotic therapy.[46]

Decolonization as Treatment

Given the importance of the intestinal microbiome as a reservoir for AR, decolonization of the intestine has been studied as a treatment option to eradicate MDROs. Studies of the natural history of MDRO colonization suggest that spontaneous clearance of these organisms is hard to predict and frequently incomplete. In two studies of VRE colonization in oncology patients, at least 60% of patients had either intermittent or persistent presence of VRE on surveillance after at least two weeks.[47,48] Similarly, in a study of renal and liver transplant recipients, only 35% of the patients were deemed to have VRE clearance, defined

as negative rectal cultures on three consecutive occasions at least one week apart, with a subsequent 11% relapse rate, which prompted the authors to conclude that VRE colonization often persists for months to years in this population.[49] In an ICU population, approximately 50% of patients were decolonized after two months with a median time for clearance of all MDROs of 4.8 months.[50] In patients at a long-term acute care hospital, KPC colonization was lost in only 17% of patients within four weeks with more than half of the patients still colonized on readmission over nine months later.[51] In another study of patients with history of positive CRE culture, mean time to CRE negativity was calculated to be 387 days with 39% of patients still with positive cultures at one year.[52] A systematic review calculated via pooled analysis the median clearance time of MRSA to be 88 weeks and that of VRE to be 26 weeks.[53]

Selective digestive tract decontamination—Proactive MDRO decolonization has also been pursued with selective digestive tract decontamination (SDD), which involves prophylactic parenteral and systemic antibiotic therapy in the ICU setting. In one randomized control trial (RCT), SDD consisting of intravenous cefotaxime and topical application of tobramycin, colistin, and amphotericin B in the oropharynx and stomach reduced the ICU mortality rate by ~3.5% at day 28.[54] Another RCT similarly showed a significantly lower ICU mortality of 15% in the SDD group versus 23% in the control as well as a significantly lower hospital mortality of 24% compared to 31% in the control.[55] Oostdijk, et al. demonstrated that SDD led to decolonization in 60–80% of cases, depending on the MDRO.[56] However, in a more specific look at the resistome, SDD was shown to have a high patient-specific variance on the eradication of aminoglycoside resistance genes with SDD in some patients actually increasing the copy number of resistance genes, as determined by quantitative polymerase chain reaction.[57] In another study from Oostdijk, et al., gram-negative bacteria resistance to either ceftazidime, tobramycin, or ciprofloxacin increased from 5, 7, and 7%, respectively, to 15, 13, and 13% after SDD. There was a brief period during SDD where resistance levels decreased, but ceftazidime resistance in particular significantly increased during SDD itself with all resistance levels peaking months after the intervention, which was in part theorized to be a rebound effect.[58] Similarly, another study revealed significantly increased colistin and tobramycin resistance as well as more frequent bacteremia among patients with ESBL-*Klebsiella pneumoniae* isolates treated with SDD.[59] Such concerns have raised doubt over SDD and whether it may be counterproductive in the long-term.[60]

Probiotics—Probiotics have become a more mainstream method of altering the gut microbiome. The principle with probiotics is that the introduction of commensal bacteria, often including *Lactobacillus* and *Bifidobacterium*, would promote health[61] through various mechanisms including enhanced immunity[62] and infection prevention.[63] In terms of MDRO decolonization, research regarding the role of probiotics has produced mixed results.

In vitro and murine studies have demonstrated *Lactobacillus* species being effective in limiting growth of MRSA isolates[64] and decolonization of MDR *E. coli*.[65] Early isolated case reports demonstrated a lactic acid bacteria preparation removing MRSA from a decubitus ulcer[66] as well as a treatment regimen involving oral vancomycin and oral

administration of *Saccharomyces boulardii*, a yeast species, contributing to resolution of antibiotic-associated diarrhea from MRSA.[67] In another report, Roos, et. al presented a case series involving seven patients among whom five had resolution of throat and nasal carriage of MRSA with a *Lactobacillus* probiotic.[68]

There have since been several clinical trials further exploring the efficacy of probiotics for MDRO decolonization. In an open prospective trial, a probiotic drink containing two species of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus thermophilus* reduced the nasal carriage of several organisms, including *S. aureus*, *Streptococcus pneumoniae*, β-hemolytic streptococci, and *Haemophilus influenzae*, by 19% though they were not necessarily drug-resistant strains.[69] Conversely, in a randomized controlled trial (RCT) involving ICU patients, there was no significant difference in acquisition or loss of colonization of MDROs, including ESBL/CRE, VRE, and *Pseudomonas aeruginosa*, between patients who received a *Lactobacillus rhamnosus* probiotic versus standard of care.[70] Similarly, upon evaluating a probiotic strain of *E. coli*, Tannock et. al concluded that the probiotic did not effectively compete against MDR *E. coli* for gut colonization in a group of patients from a long-term care facility.[71] Likewise, a RCT in Brazil found that a *Lactobacillus* probiotic was not effective in decolonizing hospitalized patients with MDR gram-negative bacilli.[72]

In another study of patients receiving either a *L. rhamnosus* probiotic versus placebo for four weeks, gastrointestinal (GI) carriage of MRSA decreased by only 3% compared to 12% in the placebo group. However, three patients with VRE colonization tested negative after the four weeks of probiotics.[73] In a more recent clinical trial, a *L. rhamnosus* probiotic reduced the odds of methicillin-sensitive *S. aureus* (MSSA) carriage in the gastrointestinal tract by 73% and all *S. aureus* presence by 83% compared to placebo; however, there was no data regarding efficacy with MRSA decolonization.[74]

In addition to the mixed data on the efficacy of probiotics, concerns have been raised regarding its potential dangers. This includes various gastrointestinal side effects ranging from minor ones such as abdominal cramping and nausea[75] to bowel ischemia.[76] More notably, Doron and Snydman found numerous reports of systemic infection; they cited 33 cases of fungemia as well as at least eight cases of *Lactobacillus* bacteremia and nine cases of sepsis. The Food and Drug Administration (FDA) has highlighted the particular risk in the immunosuppressed population, many of whom may be risk of intestinal dysbiosis due to chemotherapy exposure.[75] Thus, despite extensive research into several microbiome restoration techniques, including SDD and probiotics, definitive solutions have yet to be found.

Fecal Microbiota Transplantation

Mechanism—Considering the limitations and risks of the aforementioned modalities, fecal microbiota transplantation (FMT) has begun to emerge as a promising approach to eradicating MDROs from the intestine. The safety and efficacy of FMT has been evaluated extensively, primarily through studies involving its role in treating recurrent *Clostridium difficile* infection, and appears to be related to a variety of factors. Firstly, it has been shown to increase microbial diversity. After successful FMT, the microbiome composition of a recipient becomes similar to that of the donor with a demonstrated decrease in pathogenic

Enterobacteriaceae and increase in commensal bacteria, including *Bacteroides* and *Firmicutes*.[77,78] Also observed after FMT via deep gene sequencing are increases in *Streptococcaceae* and *Enterococcaceae*[79] as well as an overall increase in phylogenetic diversity.[80] While the microbiome may diverge from that of the donor in the long-term, it appears to do so in a manner similar to the natural dynamic change seen in healthy patients[77] rather than through a rebound of opportunistic pathogens as described with SDD.

Genetic studies have also revealed another mechanism by which FMT may be effective – decreasing AR genes. Millan, et al. demonstrated FMT decreasing the number of AR genes from a mean of 34.5 (± 6.7) to 12.2 (± 7.0) and decreasing the diversity of genes. This was posited to be clinically significant as the patients whose CDI did not initially respond to FMT also did not have a significant decrease in the number of AR genes; when they underwent a second round of FMT that was successful, a significant decrease in AR genes was noted as well.[81] In response to this study, Jouhten et al. presented similar findings with a reduction in the number and diversity of AR genes in 20 patients post-FMT.[82] Another study showed a 2.4-fold decrease in the abundance of AR genes in a patient post-FMT that persisted after one year; the resistome was also noted to have a profile similar to that of the donor.[83] Metagenomic sequencing data in a more recent study demonstrated the depletion of 95 AR genes, including clinically relevant loss of quinolone, β-lactamase, ESBL, and vancomycin resistance genes in the FMT recipients. There was also acquisition of 37 AR genes from the donors though only a few of these were clinically relevant; this was thought to be expected since there are some AR genes endogenous to the commensal bacteria.[84]

Murine models also suggest a beneficial immune response associated with FMT. In one study, dysbiosis was established through administration of ceftriaxone, resulting in intestinal membrane compromise and increased expression of inflammatory cytokines. After FMT, the intestinal barrier was noted to recover with cytokine levels returning to normal levels after three weeks.[85] Similarly, in another study, mice were subjected to eight weeks of broad-spectrum antibiotics. This resulted in a decreased presence of B and T lymphocytes as well as less active dendritic cells, particularly in the intestinal lamina propria. FMT was associated with a reversal of these findings with restoration of the lymphocytes and dendritic cell activity to that seen in mice that were not administered antibiotics.[86]

Specific human cases of MDRO elimination with FMT—Given FMT's more established role in the treatment of CDI, there have been cases incidentally hinting at FMT's possible effect on other infections in patients who were being treated for CDI. For example, in a study of patients treated with FMT for recurrent CDI, the frequency of recurrent urinary tract infections (UTIs) was found to decrease from a median of four episodes per year to one episode in the year after FMT. Furthermore, the UTIs that did occur post-FMT rarely involved bacterial isolates with any significant resistance.[87] Another patient with recurrent CDI was also found to have intestinal colonization with KPC; FMT not only successfully treated the CDI but also resulted in follow-up stool cultures being negative for KPC up to 100 days post-FMT.[88] In another case involving KPC colonization, an elderly patient with recurrent CDI was found to have eradication of VIM-1 producing *Klebsiella oxytoca*.[89]

Similarly, in an organ transplant recipient treated with FMT for recurrent CDI who had also had multiple episodes of VRE infections, FMT decreased *Enterococcus* abundance from 84% to 24% after three months and 0.2% after seven months with increased microbiota diversity.[90] In another case report, a patient with quadriplegia resulting from a spinal epidural abscess who had CDI treated with FMT had a marked reduction in colonization of several MDROs, including CRE, MRSA, and MDR *Acinetobacter baumannii*. In total, the MDROs found on cultures decreased from 12 to 4 by 15 weeks after FMT, and while he had recurrent infections and episodes of sepsis prior to FMT, he only had one UTI in the post-FMT period from a newly acquired pathogen not previously isolated in the patient and required a 5-day course with a single antibiotic. Furthermore, despite ongoing care in the ICU post-FMT for his other conditions, the number of MDROs remained low, and he did not re-colonize with CRE, CR *Pseudomonas* species, or VRE. Over the following two years, he only became recolonized with MRSA in the urine and had one episode of sepsis secondary to *Streptococcus pyogenes* bacteremia that was treated with cefazolin.[91]

Mouse models have more directly explored the effect of FMT on MDROs. A study found that reintroducing a diverse intestinal microbiome through FMT to mice densely colonized with VRE resulted in clearance of VRE. They particularly noted a negative correlation between recolonization of *Barnesiella*, a member of the *Bacteroidetes* phylum, and VRE colonization.[92] In another study, mice were infected with *Citrobacter rodentium*, which was used as a model for human enteropathogenic and enterohaemorrhagic *E. coli*. FMT resulted in improved innate defense, particularly with increased IL-22 gene expression, and delayed *C. rodentium* recolonization as well as reduced mortality with these effects persisting at least four weeks post-FMT.[93] Mahieu, et al. inoculated mice with VRE and a strain of *Escherichia coli* producing a New Delhi metallo-β-lactamase-1 (NDM-1) and then performed FMT. After FMT, the MDRO colonization significantly decreased, particularly with VRE though in this case, the bacteria were not definitively eradicated.[94] Murine studies have even looked into the role of FMT in treating tuberculosis (TB). FMT reconstituted the intestinal microbiota and reduced *Mycobacterium tuberculosis* (MTB) load in the lungs and spleen. Mice treated with FMT also had fewer and smaller granulomas with lesser infiltration of lymphocytes and were thus noted to have less severe cases of TB.[95]

Most notably, there are a growing number of cases of FMT being used solely to manage MDROs in humans. In response to Mahieu's murine study, Leung et al. described VRE clearance in seven out of eight patients three months after FMT.[96] In a more extensive prospective study, 20 patients with hematologic disorders whose intestines were colonized with various MDROs, including NDM-1+ *Klebsiella pneumoniae*, carbapenem-resistant *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, underwent 25 FMTs. Partial MDRO decolonization was achieved in 20/25 (80%) of cases at one month and 13/14 (93%) of cases at six months. When accounting for some of the patients who required multiple rounds of FMT, 15/20 (75%) of the participants had complete decolonization. In particular, the gene encoding carbapenemase was eradicated in 9/17 (53%) of the patients at one month and 8/9 (89%) of those at six months. After one month, 6/10 (60%) cases of NDM-1+ *K. pneumoniae* were eradicated while 100% of ESBL (11 patients) and oxacillinase-48 (OXA-48) (1 patient) *E. coli* were eradicated. Also of note in this high-risk population, there were no significant adverse events noted.[97]

Another report of FMT eradicating OXA-48 has been documented in an 82 year old patient with KPC whose stool cultures were negative 7 and 14 days post-FMT.[98] In another case, here involving an end-stage renal disease (ESRD) patient with recurrent episodes of ESBL *E. coli* induced pyelonephritis, FMT resulted in the eradication of the MDRO at 2-week follow-up that persisted 12 weeks post-FMT. During this period, the patient had no recurrence of infection and was able to be actively listed for renal transplantation.[99] In a 14 year old patient with a hematologic disorder who had recurrent KPC infections, FMT resulted in documented fecal clearance of MDRO 8 months later with no subsequent infections noted for 1.5 years.[100] FMT has also been used in active infection; one such report found five patients with MRSA enteritis that clinically resolved along with eradication of MRSA in the feces using FMT.[101] Thus, there is a growing literature highlighting the potential of FMT and suggesting its long term role in clinical practice to address MDRO colonization and infection.

Limitations and Future Considerations

Despite the cases described above, there are some limitations and concerns raised regarding FMT. There have been some documented reports of MDRO colonization persisting despite FMT or returning shortly after the procedure, both in mouse models[102] and patients.[103,104] One particular report presented a patient with recurrent UTIs from MDR *Pseudomonas aeruginosa* with both *Pseudomonas* and ESBL-*Escherichia coli* colonization; FMT resulted in *Pseudomonas* clearance with no more infections in the next 18 months of follow-up, but the ESBL-*E. coli* persisted.[105] In studies of FMT in CDI, adverse effects have been described,[106] including bacteremia[107–109] and fatal aspiration.[109,110] These appear to be rare with the more common complications being relatively mild in morbidity, such as abdominal cramping, distention, and diarrhea.[106] Nevertheless, there is a limited long term outcomes data so there may be unintended consequences of FMT that are presently unknown.

As described above, the literature involving FMT in MDRO colonization and infection has consisted primarily of isolated case reports, small series of cases and small uncontrolled clinical trials. There is a lack of standardization of products used in FMT, lack of standardization of delivery, lack of characterization of the microbiome in the FMT produces, all confounding the comparability of studies. Just as with FMT to treat CDI,[111] structured, randomized, controlled trials are needed to better characterize the safety and efficacy of FMT for MDRO elimination, many of which are currently underway (www.clinicaltrials.gov). Nevertheless, given the limitations of the current antibiotic development pipeline and infection prevention methods, these early signals of FMT support its investigation and potential application as a therapeutic option for MDRO colonization and infection in the future.

Acknowledgments

Source of funding: C.S.K. has funding through an Emory University Research Committee grant, as well as by the Center for AIDS Research (P30 A1050409). MHW and CSK are supported by supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award number UL1TR000454. MHW is supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number UM1AI104681.

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