Fecal microbial transplantation as a therapeutic option in patients colonized with antibiotic resistant organisms

Michael Laffin, Braden Millan, and Karen L. Madsen

Department of Medicine, CEGIR: Center of Excellence for Gastrointestinal Inflammation and Immunity Research, University of Alberta, Edmonton, Alberta; Cumming School of Medicine, University of Calgary, Calgary, Alberta

ABSTRACT
Despite increasing interest in fecal microbiota transplantation (FMT), its full therapeutic potential has yet to be determined. Since its increase in popularity, FMT has been shown to be highly effective in the treatment of both Clostridium difficile infection (CDI) and its recurrent form. Interest in FMT now expands well beyond the treatment of CDI to other processes with known associations to the microbiota such as antibiotic resistant infections, inflammatory bowel disease (IBD), hepatic encephalopathy, neuropsychiatric disorders, and metabolic disease. The rampant use and misuse of antibiotics in both medicine and agriculture has resulted in an increase in antibiotic resistant organisms which pose a significant risk to human health. The purpose of this commentary is to address the general issue of antibiotic resistance in the human microbiota and the restorative potential of FMT in this area.

ARTICLE HISTORY
Received 17 October 2016
Revised 15 December 2016
Accepted 28 December 2016

KEYWORDS
Intestinal microbiome; antibiotics; antibiotic resistance; resistome; Fecal Microbiota Transplantation; Clostridium difficile

Introduction
Selective pressures created by the clinical and agricultural use and misuse of antibiotics have resulted in the development of multidrug resistant (MDR) bacteria. The development of antimicrobial resistance has become a major threat to human health due to a lack of effective treatments of MDR bacterial infections. Patients infected with MDR bacteria stay in hospital longer and experience higher rates of morbidity and mortality. Both methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE) infections have been shown to be associated with worse clinical outcomes. Indeed, infections with MDR bacteria are associated with an increased risk of septic shock, acute kidney injury, and death. MDR bacteria are believed to colonize the gastrointestinal tract, contributing to the reservoir of antibiotic resistant (ABR) genes within the gut, and subsequently infecting their host. Patients that become colonized with MDR bacteria often require prolonged hospitalization, which increases the risk of acquiring further MDR bacteria. Unfortunately, persistent reservoirs of MDR can occur in hospital settings, leading to a spread of MDR throughout the patient population.

The Centers for Disease Control and Prevention recommend contact precautions (i.e. patient isolation procedures) to prevent this spread; however, despite these precautions, these reservoirs lead to an increased incidence of adverse events, increased symptoms of depression and anxiety, and decreased patient satisfaction with care. Previous strategies aimed at intestinal decolonization through disinfectant, bowel preparations, and antibiotic treatment have been met with limited success. Antibiotic resistance is not a modern phenomenon and predates the use of antibiotics. The genes responsible for ABR can be acquired by bacteria through conjugation, transformation, transduction and mutation. However, the inappropriate over prescription of antibiotics was identified in North America as early as the 1970s. In addition, the indiscriminant use of antibiotics in agriculture to promote growth and act as prophylactic agents was also recognized as a concerning threat to human health. The concept of the ‘resistome’ was first introduced in 2006 by Wright and colleagues to describe the ABR gene profile of the microbiota, taking into account both genes contained in relevant human pathogens and non-pathogenic
bacteria. Our improved understanding of the antibiotic resistome and the clinical reality of increasing ABR infections suggest the need for new and different approaches to their treatment.

Use of FMT to promote colonization resistance

Colonization resistance refers to the ability of a healthy gut microbiota to prevent pathogen colonization. Mechanisms underlying colonization resistance include competition for nutrients, the production of antimicrobial factors, alterations in pH, and prevention of access to adherence sites or niches associated with the mucosa, and production of microbial metabolites that directly antagonize other species. Using fecal microbial transplantation as a method to replenish a healthy gut microbial environment and restore colonization resistance has showed astonishing effectiveness in the treatment of recurring infection with Clostridium difficile with cure rates ranging from 80–95% following a single infusion. In our single center study of 20 patients who underwent FMT for recurrent CDI, we showed using a combination of metagenomics and DNA microarray that the number of antibiotic-resistant genes in the resistome of patients was significantly reduced following the procedure. These results were further corroborated by Jouhten et al. in 8 patients undergoing FMT for recurrent CDI using a quantitative PCR array containing 85 ABR genes. In both studies, FMT proved to be a safe and effective therapeutic option for recurrent CDI. FMT was also effective in reducing the number of ABR genes in the patients’ resistome. Manges and colleagues recently published a review summarizing 8 different case reports on the success of FMT in the eradication of MDR organisms, further supporting the concept of using FMT for this purpose. In these studies, the MDR organisms included extended spectrum β-lactamase producing Escherichia coli, carbapenemase-producing Klebsiella pneumoniae, methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, highly drug-resistant A. baumannii, carbapenemase-producing P. aeruginosa, and vancomycin-resistant Enterococcus faecalis. There were no reports of adverse events in any of the case reports. Although no larger randomized controlled trials have been performed to study the efficacy and safety of FMTs for MDR organisms, preliminary evidence is promising and suggests that a non-antibiotic therapy for ABR infections may be in the future of health care.

The future of FMT in the health care system

Since their discovery, antibiotics have drastically changed the clinical approach to the treatment of bacterial infections. However, the emergence of MDR organisms as a result of widespread antibiotic usage has left the world on the cusp of a ‘post-antibiotic’ era. An approach to address these MDR organisms is required in the healthcare setting to prevent the resurgence of previously preventable infection-related adverse outcomes. A role for FMT as a decolonization therapy may be fast approaching. The principle behind decolonization therapy is to identify, isolate, and treat carriers, with the goal of eradicating the pathogen from health care facilities. In the case of MRSA, targeted decolonization of carriers may reduce the spread of the resistant organism. FMT may prove useful in the decolonization of intestinal MDR organisms. Currently, those colonized by MDR organisms are managed with contact isolation precautions, without any established protocols for decolonization. The use of FMT as a decolonization agent may prove effective in preventing disease outbreaks, and in minimizing the length of time colonized patients spend under costly and dangerous contact isolation precautions. At this point, FMT has only demonstrated efficacy in reducing MDR organisms within the bowel, and may need to be used in combination with other decolonization strategies to ensure MDR-eradication of all contaminated sites.

Decolonization of enteric MDR organisms may prove especially useful in the subset of immunocompromised patients who are susceptible to infection from endogenous bacteria through the gastrointestinal tract, such as those undergoing haematopoietic stem cell transplantation. MDR infections are rampant in this patient population, and are associated with significant mortality. FMT, which is safe in immunocompromised patients, may not prevent bacterial translocation and subsequent bacteremia in these patients, but it may select for infections that are more easily treated.

FMT offers substantial benefits over antibiotics as a decolonization therapy. The side effect profile of FMT is modest, with no direct serious adverse effects noted. Most importantly, selective decontamination antibiotic treatment is associated with an increase in the overall incidence of ABR genes in intestinal microbes. As such, there is a reluctance to institute
widespread selective decontamination antibiotic treatment despite its apparent beneficial effect on adverse outcomes. FMT may act as an alternative therapy to decontamination, without perpetuating the problem of MDR organisms.

**Conclusion**

A joint statement released by the World Health Organization, World Organization for Animal Health, and the United Nations in September 2016 identified AMR as “a fundamental threat to human health, development, and security.” The ability of FMT to dramatically reduce the number of ABR genes in a patient’s resistome offers a potentially important therapeutic option. Further study regarding the efficacy of FMT in specific clinical situations is warranted.

**Abbreviations**

- ABR: Antibiotic Resistance
- CDI: *Clostridium difficile* infection
- FMT: Fecal Microbiota Transplantation
- IBD: Inflammatory Bowel Disease
- MDR: Multi-drug Resistance

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

**Funding**

This work was supported by Alberta Health Services, Alberta Innovates, and CIHR.

**References**

[1] Lye DC, Earnest A, Ling ML, Lee TE, Yong HC, Fisher DA, Krishnan P, Hsu LY. The impact of multidrug resistance in healthcare-associated and nosocomial Gram-negative bacteraemia on mortality and length of stay: cohort study. Clin Microbiol Infect 2012; 18:502-508; PMID: 21851482; http://dx.doi.org/10.1111/j.1469-0691.2011.03606.x

[2] Picot-Gueraud R, Batailler P, Caspar Y, Hennebique A, & Mallaret M.R. Bacteremia caused by multidrug-resistant bacteria in a French university hospital center: 3 years of collection. Am J Infect Control 2015; 43:960-64; PMID: 26082260; http://dx.doi.org/10.1016/j.ajic.2015.05.004

[3] Schmidt-Hieber M, Blau IW, Schwartz S, Uharek L, Weist K, Eckmanns T, Jonas D, Rüden H, Thiel E, Brandt C. Intensified strategies to control vancomycin-resistant enterococci in immunocompromised patients. Int J Hematol 2007; 86:158-162; PMID: 17875531; http://dx.doi.org/10.1532/IJH97.E0632

[4] Ubeda C, Taur Y, Jenq RR, Equinda MJ, Son T, Samstein M, Viale A, Socci ND, van den Brink MR, Kamboj M, et al. Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. J Clin Invest 2010; 120:4332-41; PMID: 21099116; http://dx.doi.org/10.1172/JCI43918

[5] Morgan DJ, Diekema DJ, Sepkowitz K & Perencevich EN. Adverse outcomes associated with contact precautions: a review of the literature. Am J Infect Control 2009; 37:85-93; PMID: 19249637; http://dx.doi.org/10.1016/j.ajic.2008.04.257

[6] Siegel JD, Rhinehart E, Jackson M & Chiarello L. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control 2007; 35:S65-S164; http://dx.doi.org/10.1016/j.ajic.2007.10.007

[7] Arnow PM, Carandang GC, Zahn R & Irwin ME. Randomized controlled trial of selective bowel decontamination for prevention of infections following liver transplantation. Clin Infect Dis 1996; 22:997-1003; PMID: 8783700; http://dx.doi.org/10.1093/clinids/22.6.997

[8] Bion JF, Badger I, Crosby HA, Hutchings P, Kong KL, Baker J, Hutton P, McMaster P, Buckels JA, Elliott TS. Selective decontamination of the digestive tract reduces gram-negative pulmonary colonization but not systemic endotoxaemia in patients undergoing elective liver transplantation. Crit Care Med 1994; 22:40-49; PMID: 8124972; http://dx.doi.org/10.1097/00003246-199401000-00011

[9] Katchman E, Marquez M, Bazerbachi F, Grant D, Cattral M, Low CY, Renner E, Humar A, Selzner M, Ghanekar A, et al. A comparative study of the use of selective digestive decontamination prophylaxis in living-donor liver transplant recipients. Transpl Infect Dis 2014; 16:339-47; PMID: 24862338; http://dx.doi.org/10.1111/tid.12235

[10] Ananthakrishnan AN, Cheng SC, Cai T, Gagan A, Gainer VS, Szolovits P, Shaw SY, Churchill S, Karlson EW, Murphy SN, et al. Serum inflammatory markers and risk of colorectal cancer in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2014; 12:1342-48; PMID: 24407106; http://dx.doi.org/10.1016/j.cgh.2013.12.030

[11] Kunin CM, Topuşi T & Craig WA. Use of antibiotics. A brief exposition of the problem and some tentative solutions. Ann Intern Med 1973;79:555-60.

[12] Khachatourians GG. Agricultural use of antibiotics and the evolution and transfer of antibiotic-resistant bacteria. CMAJ 1998; 159:1129-36; PMID: 9835883

[13] D’Costa VM, McGrann KM, Hughes DW & Wright GD. Sampling the antibiotic resistome. Science 2006; 313:374-7; PMID: 16424339; http://dx.doi.org/10.1126/science.1120800

[14] Kamada N, Chen GY, Inohara N & Nunez G. Control of pathogens and pathobionts by the gut microbiota. Nat Immunol 2013; 14:685-90; PMID: 23778796; http://dx.doi.org/10.1038/ni.2608
van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijsen JG, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med; 2013; 368:407-15; PMID: 23323867; http://dx.doi.org/10.1056/NEJMoA1205037

Gough E, Shaikh H & Manges A.R. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis 2011; 53:994-1002; PMID: 22002980; http://dx.doi.org/10.1093/cid/cir632

Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. JAMA 2014; 312:1772-78; PMID: 25322359; http://dx.doi.org/10.1001/jama.2014.13875

Millan B, Park H, Hotte N, Mathieu O, Burguiere P, Tompkins TA, Kao D, Madsen KL. Fecal Microbial Transplants Reduce Antibiotic-resistant Genes in Patients With Recurrent Clostridium difficile Infection. Clin Infect Dis 2016; 62, 1479-86; PMID: 27025836; http://dx.doi.org/10.1093/cid/ciw185

Jouhten H, Mattila E, Arkkila P & Satokari R. Reduction of Antibiotic Resistance Genes in Intestinal Microbiota of Patients With Recurrent Clostridium difficile Infection After Fecal Microbiota Transplantation. Clin Infect Dis 2016; 63:710-1; PMID: 27317794; http://dx.doi.org/10.1093/cid/ciw390

Manges AR, Steiner TS & Wright AJ. Fecal microbiota transplantation for the intestinal decolonization of extensively antimicrobial-resistant opportunistic pathogens: a review. Infect Dis (Lond) 2016; 48:587-592; PMID: 27194400; http://dx.doi.org/10.1002/203744235.20161177199

World Health Organization. Antimicrobial resistance global report on surveillance: 2014 summary. 2014.

Muto CA, Jernigan JA, Ostrowsky BE, Richet HM, Jarvis WR, Boyce JM, Farr BM, SHEA. SHEA guideline for preventing nosocomial transmission of multidrug–resistant strains of Staphylococcus aureus and Enterococcus. Infect Control Hosp Epidemiol 2003; 24:362-86; PMID: 12785411; http://dx.doi.org/10.1086/502213

Cho OH, Baek EH, Bak MH, Suh YS, Park KH, Kim S, Bae IG, Lee SH. The effect of targeted decolonization on methicillin-resistant Staphylococcus aureus colonization or infection in a surgical intensive care unit. Am J Infect Control 2016; 44:533-8; PMID: 26847518; http://dx.doi.org/10.1016/j.ajic.2015.12.007

Taur Y & Pamer EG. The intestinal microbiota and susceptibility to infection in immunocompromised patients. Current opinion in infectious diseases 2013;26:332; PMID: 23806896; http://dx.doi.org/10.1097/QCO.0b013e3283630dd3

Mikulska M, Del Bono V & Viscoli C. Bacterial infections in hematopoietic stem cell transplantation recipients. Current opinion in hematology 2014; 21:451-58; PMID: 25295742; http://dx.doi.org/10.1097/MOH.0000000000000088

Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, Aroniadis O, Barto A, Borody T, Giovanelli A, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. Am J Gastroenterol 2014; 109:1065-71; PMID: 24890442; http://dx.doi.org/10.1038/ajg.2014.133

Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, Stollman N, Rohlke F, Surawicz C. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. Am J Gastroenterol 2012; 107:1079-87; PMID: 22450732; http://dx.doi.org/10.1038/ajg.2012.60

Oostdijk EA, de Smet AM, Blok HE, Thieme Groen ES, van Asselt GJ, Benus RF, Bernards SA, Fréinay IH, Jansz AR, et al. Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. Am J Respir Crit Care Med 2010; 181:452-7; PMID: 19965807; http://dx.doi.org/10.1164/rcrm.200908-1210OC

De Smet A, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, van der Hoeven JG, Pickkers P, Pickkers P, Bogaers-Hofman D, et al. Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 2009; 360:20 PMID: 19118302; http://dx.doi.org/10.1056/NEJMoA0800394

van der Meer J & Vandenbroucke-Grauls C. Resistance to selective decontamination: the jury is still out. Lancet Infect Dis 2013; 13, 282; PMID: 23375416; http://dx.doi.org/10.1016/S1473-3099(13)70014-8

OGPA/WHO/FAO/OIE. At UN, global leaders commit to act on antimicrobial resistance. Vol. 2016 (World Health Organization, who.int, 2016).