

Fecal transplant policy and legislation

Dinesh Vyas, Apoorva Aekka, Arpita Vyas

Dinesh Vyas, Apoorva Aekka, Arpita Vyas, College of Human Medicine, Michigan State University, East Lansing, MI 48912, United States

Arpita Vyas, Department of Pediatrics, Heart Failure Research Lab, East Lansing, MI 48912, United States

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Correspondence to: Dinesh Vyas, MD, MS, FICS, FACS, College of Human Medicine, Michigan State University, 1200 East Michigan Avenue, Suite 655, East Lansing, MI 48912, United States. dines.vyas@hc.msu.edu

Telephone: +1-517-2672491

Fax: +1-517-2672488

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Abstract

Fecal microbiota transplantation (FMT) has garnered significant attention in recent years in the face of a reemerging *Clostridium difficile* (*C. difficile*) epidemic. Positive results from the first randomized control trial evaluating FMT have encouraged the medical community to explore the process further and expand its application beyond *C. difficile* infections and even the gastrointestinal domain. However promising and numerous the prospects of FMT appear, the method remains limited in scope today due to several important barriers, most notably a poorly defined federal regulatory policy. The Food and Drug Administration

has found it difficult to standardize and regulate the administration of inherently variable, metabolically active, and ubiquitously available fecal material. The current cumbersome policy, which classifies human feces as a drug, has prevented physicians from providing FMT and deserving patients from accessing FMT in a timely fashion, and subsequent modifications seem only to be temporary. The argument for reclassifying fecal material as human tissue is well supported. Essentially, this would allow for a regulatory framework that is sufficiently flexible to expand access to care and facilitate research, but also appropriately restrictive and centralized to ensure patient safety. Such an approach can facilitate the advancement of FMT to a more refined, controlled, and aesthetic process, perhaps in the form of a customized and well-characterized stool substitute therapy.

Key words: Stool therapy; *Clostridium difficile*; Fecal microbiota transplantation; Toxin

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Core tip: This article highlights the status of legislation with stool therapy and discusses the potential flaws in the system going forward with ways to fixing it. In this article, we are taking discussion further from a recently published article in *Nature*.

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COMMENTARY ON HOT TOPICS

Recent evidence in support of fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is rapidly

emerging as a viable treatment option for certain recurrent bacterial infections, particularly those caused by *Clostridium difficile* (*C. difficile*). The first randomized control trial evaluating FMT, published in 2013, was terminated prematurely as the procedure proved to be considerably more effective in treating persistent *C. difficile* infections than antibiotics alone. 94% of patients who underwent FMT were cured - 81% just after one infusion. This is much higher than the 31% who recovered after receiving vancomycin alone or the 23% of those who recovered after receiving vancomycin with bowel lavage. Further, those who were successfully cured with FMT demonstrated increased microflora diversity^[1]. Such encouraging results have generated substantial interest in enhancing the method.

***C. difficile* epidemic of today**

The results of this randomized control trial are crucial as the study comes at a time when *C. difficile* infection (CDI) has become the leading cause for antibiotic-associated nosocomial diarrhea and colitis across the industrialized world^[2,3]. *C. difficile* is a gram positive anaerobic and spore-forming bacterial species that thrives in the gut when normal gut flora has been eliminated or significantly altered through the use of broad-spectrum antibiotics. Thus, CDI is usually contracted upon ingestion of environmental spores that germinate following treatment with antibiotics^[4,5].

The main virulence factors of *C. difficile* are Toxin A (TcdA) and Toxin B (TcdB). These are glucosyltransferases that target and inactivate Rho proteins in enterocytes to produce detrimental effects such as cell cycle arrest, cytoskeletal deterioration, increased fluid and electrolyte secretion, and decreased permeability of intestinal mucosa^[6-8]. Ultimately, this damage to the intestinal epithelium generates an inflammatory response that perpetuates tissue injury^[6,8,9]. Patients present with a variety of clinical findings ranging from an asymptomatic carrier state to the development of mild to moderate non-bloody diarrhea that can progress to pseudomembranous colitis and toxic megacolon^[6]. Typically, individuals experience abdominal pain, malaise, nausea, vomiting, dehydration, and fever. Characteristic laboratory tests reveal leukocytosis^[6,10].

Management of CDI has become more difficult over the past two decades given the considerable epidemiological changes the disease has undergone. The appearance of new hypervirulent strains; greater worldwide spread; the rise in community-acquired rates as opposed to hospital-acquired rates; and higher prevalence among historically immune groups such as children under the age of two, peripartum women, and young adults without previous antibiotic exposure, are all facets of the current experience of CDI^[2,11-14]. The rising severity and frequency of the disease, and the corresponding economic impacts, compel the medical community to take swift action in developing an effective treatment.

Vancomycin and metronidazole are currently the

most commonly used antibiotics for CDI^[6]. However, with recurrence rates reported between 15% and 35% among patients with one previous episode of CDI and as high as 33% to 65% among patients with more than two previous episodes, there is need for more potent treatment approaches^[15]. Few federally authorized alternatives to the conventional broad-spectrum antibiotic therapy exist today. In 2011, the Food and Drug Administration (FDA) approved the use of the narrow-spectrum antibiotic fidoxamicin or Dificid, which was the first drug sanctioned for treating CDI in 25 years^[2]. Considerable research is now being focused upon identifying novel targets in the development of prophylactic and therapeutic vaccines. Advancements in passive immunotherapy are also underway, for instance in the formulation of antibodies specific for TcdA and TcdB^[4,16,17]. Probiotics are proving to be a potential treatment avenue as well - *Lactobacillus rhamnos* GG and *Saccharomyces boulardii* have been identified as useful in altering the gut microflora to prevent CDI in healthy individuals^[4,18].

Fecal microbiota transplantation: A promising method

Fecal microbiota transplantation has come to the forefront as one of the most promising treatments for CDI, especially in light of the encouraging results from the randomized control trial conducted recently. FMT is the process by which commensal bacteria, derived from stool samples of healthy individuals, are introduced in patients with gut bacterial infections through colonoscopy, nasoduodenal tubes, or enemas. These new microbes improve health by colonizing the gut and outcompeting pathogenic bacteria for a limited nutrient supply^[19,20]. Successfully treated patients demonstrate a more diverse microflora population. The innate immune response and secondary bile salts generated by certain transplanted bacterial species might also play a role in suppressing pathogenic bacterial growth^[20,21]. Essentially, FMT appears to be a multidimensional therapy that creates an intestinal environment uncondusive for the growth of pathogenic *C. difficile* strains. It is a unique approach that seeks to utilize microbes, rather than antimicrobials, to address bacterial infections^[22]. Thus, there is immense potential for the use of FMT in treating certain infections that are refractory to conventional antibiotics.

With the recent transition in viewing gut microflora as a virtual organ, FMT is increasingly being understood as much more than a fecal infusion. It is now widely considered a body organ transplant, and therefore, a process that must be subject to rigorous screening standards similar to other organ transplant procedures^[23,24]. As of now, stool samples are screened mainly for human immunodeficiency virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, syphilis, and cultured for enteric pathogens. Medical histories of donors are also collected for information regarding history of high risk sexual behaviors, known exposure to infectious diseases, presence

of autoimmune diseases, history of inflammatory bowel disease, and travel to areas where diarrheal diseases are prevalent^[24,25].

Limitations of FMT

Although FMT has substantial therapeutic potential, it is limited in several aspects. Firstly, though there is ample evidence of the effectiveness of FMT from case series and case reports, the lack of sufficient randomized control trial data still hinders it from becoming a federally approved or broadly accepted procedure. In fact, even the positive results from the single randomized control trial should be taken cautiously given the small and unrepresentative sample size, the lack of blinding in data collection, and the fact that there was crossing over among subjects. Nonetheless, as one of the first studies of its kind, it should serve as a starting point for similar research initiatives. Other important limitations of the process include the lack of standardization or consensus regarding the optimal protocol, the risk of transmitting infectious diseases, and the unaesthetic nature of transplanting bacteria^[22].

Additional barriers in the delivery of FMT exist as well. For instance, the current screening process is inefficient and slow. It can take several days to weeks to receive donor profiles before physicians are able to implement FMT. The further time delay between screening and stool collection runs the risk of missing donors who might have acquired a pathogen between screening and collection but are asymptomatic. Laboratory costs associated with screening can be an additional disincentive for frequent use^[26]. Another problematic point is that fecal material is not conducive to being handled by pharmaceuticals precisely because it is complex, variable, and abundant, and the consequential difficulty in collaboration with pharmaceutical companies might impede the technological development of FMT in the future^[27].

A cumbersome regulatory policy

The greatest hurdle in the advancement of FMT, however, is the poorly defined policy regulating the use of human feces for medical purposes. In 2012, the FDA's initial classification of human feces as a drug met with dissatisfaction from patients and physician-investigators alike. Highly variable and widely available, human feces is quite unlike drugs, which are meticulously formulated through reproducible methods under controlled conditions. Moreover, fecal samples are composed of various strains of live microbiota that are metabolically active and dynamic^[28]. For these reasons, human feces cannot be subject to the same stringent restrictions applied to drugs^[29]. A secondary matter that has spawned discontent is that drug classification would place fecal material under the jurisdiction of hospital pharmacies, requiring feces to be stored within the pharmacies themselves^[30].

As FMT has not been approved by any agency for

any clinical purpose, the FDA requires physicians to file an investigational new drug (IND) application prior to implementing the procedure. This complicated and lengthy approval process has discouraged physicians from exploring FMT and has prevented patients from taking advantage of it. In response to these issues, the FDA eventually relaxed the IND requirement for the use of FMT in treating CDI specifically, however, it mandates IND applications for use with other clinical conditions^[29]. There are three types of IND applications that investigators can file. The first is an emergency IND, which can be used in the case of acutely ill patients, if patients do not meet the criteria for a study protocol, or if a protocol does not exist. There is an expanded access IND, which should be submitted for experimental therapies that appear hopeful for serious cases. Finally, an investigator IND should be filed if data for patients enrolled in the protocol will be used in subsequent studies or if FMT will be used to address a condition other than CDI^[30]. Although there is much resistance to the IND requirement, there is considerable support for it as well. Those in favor stress that because the lasting effects of FMT are still unknown, IND applications will allow for a certain level of control over the process, ensuring patient safety. Further, the data collected through IND applications can aid in the assessment of risks and benefits associated with FMT.

The FDA's arbitrary "enforcement discretion" guideline with regard to the IND requirement suggests that the current policy is only temporary - there is no guarantee that this discretion will remain in place indefinitely^[30,31]. Hence, efforts must be made to create an enduring regulatory framework that is flexible enough to ensure patient access to care and facilitate broader research opportunities, but also appropriately restrictive to ensure patient safety.

Formulating an effective regulatory framework

Classifying human feces as a body tissue or placing it within a category of its own might support the development of this type of optimal policy. Such a classification would not only ease limits to promote research and expand access to care, but it would also mandate the thorough screening of samples to which all human tissues are subject. This would reduce long-term risks associated with FMT, including the spread of infectious diseases or increased susceptibility to particular chronic conditions. Considering feces as a human tissue would have multiple benefits for both patients and physician-investigators^[29].

This regulatory approach might involve the eventual establishment of stool banks that monitor the collection, processing, storage, and dissemination of stool samples and national registries that track donors, patients, and adverse effects of FMT. Registries could also collect information regarding family relationships, health status, and diet^[31]. Another suggestion is to develop fecal transplant material manufacturing facilities that are subject to good

manufacturing practice guidelines (GMP). Introducing GMP guidelines would ensure that manufacturing processes are consistent, controlled, specific, recorded, and ultimately enforceable by administrative agencies^[28]. Essentially, these centralized supervisory mechanisms can help to achieve the standardization required to protect patients, provide sufficient but controlled access to care, and reduce costs^[29].

In addition to determining the logistics of fecal processing, maintenance, and delivery systems, the FDA also faces the challenge of dealing with commercialization of stool products. Currently, several private research companies are conducting phase one and two trials testing the efficacy of well-characterized fecal samples^[30].

Thus, the FDA remains in the complicated process of determining the most suitable way to regulate FMT and recommends that until a comprehensive set of guidelines has been established, physicians and investigators who plan to utilize the procedure should submit an IND application even though it is not required in cases of CDI^[30].

Lessons to learn

C. difficile infection is an international issue, and hence there is much to learn from the approaches other countries have taken toward FMT regulation. Health Canada, the Canadian federal health department, regulates stool in a category of its own, as a “new biologic drug”, under the biologic and genetics therapies directorate. New biologic drug trials require a clinical trial application (CTA), which includes a risk benefit analysis. The CTA also involves on-site evaluation to assess and verify that production techniques and facilities correspond to what is presented in the application and that consistency is maintained in terms of potency, purity, and safety of products. Upon CTA approval, Health Canada provides a no objection letter that permits investigators to proceed with the trial^[26].

Health Canada is also committed to developing an efficient, standardized FMT protocol that minimizes associated risks and costs. Sample screening and administration are two of the main processes in need of standardization. Some suggestions to achieve this include stability testing to determine whether freezing samples preserves efficacy and using prescreened samples from select donors to facilitate more rapid, cost-effective administration. Details should be determined in collaboration with the United States FDA and other federal-level health and medical centers^[26].

Although standards are necessary with regard to any procedure, it is important to refrain from establishing excessive and disparate suggestions, which can have harmful consequences for patients. Guidelines are thought to be evidence-based, reliable, and precise - and therefore unbiased - but they are inherently biased in unique ways. Most guidelines are consensus reports, and as such, are influenced by authors' convictions and their connections to external parties, including pharmaceuticals. Further, guideline articles are not

reviewed as rigorously by journals.

Yet, the immense emphasis placed upon guidelines pressures physicians to conduct unwarranted tests to avoid malpractice issues, and this is not only uneconomical, but it subjects patients to increased rates of false-positives^[32]. Guidelines cannot be assumed to guarantee quality in healthcare unless patient safety, standard of care, and efficiency of procedure are all considered. Hence, in developing a standardized approach to FMT, researchers and regulators should remain conservative and selective in the number of guidelines they produce and present to the scientific community.

Broad scope for application

A successful, streamlined regulatory policy can advance the field of FMT far beyond its current applications as gut microflora has been determined to be involved with a variety of physiological processes, including energy metabolism, immune function, carcinogenesis, and neurologic development. These findings suggest that manipulating gut microflora may aid in the treatment of numerous conditions other than recurrent CDI, such as metabolic syndrome and obesity, anorexia nervosa, autoimmune diseases, and food allergies. The potential applications are numerous, extending to non-gastrointestinal conditions as well^[27,28,33].

Substantial connections have also been identified between gastrointestinal health, gut microbiota, and certain neurodegenerative and neurodevelopmental disorders and those involving mood and thought^[34]. The discussion surrounding autism is particularly interesting. A variety of observations linking autism to the gut microflora, such as disease onset often correlating with antimicrobial administration; increased levels of particular *Clostridium* species found in stool samples of autistic individuals; and the alleviation of autistic symptoms following oral vancomycin, have all supported the expansion of the traditional model of the brain-gut axis to a brain-gut-microbiota axis. Such data further allude to the vast therapeutic potential of FMT^[34-36].

FMT appears to be especially helpful in alleviating symptoms of inflammatory bowel disease. Various bacteria have been shown to differentially activate helper T cells, such as pro-inflammatory Th-17 cells or anti-inflammatory regulatory T cells. Some have been found to secrete metabolites that reduce the production of the pro-inflammatory cytokines IL-2 and interferon-gamma and increase levels of anti-inflammatory cytokines such as IL-10^[27,37]. High levels of intestine specific IL-10 are thought to mediate the communication between the systemic immune response and the gut epithelium, resulting in a decrease of pro-inflammatory cytokine release^[38]. Essentially, FMT might be useful for patients suffering from IBD if donor flora can produce a net anti-inflammatory environment^[20].

Future directions

Ultimately, progress in the field of FMT can shed light

upon which microbial populations are optimal for treating different infections, allowing researchers to culture and transplant preformed, well-characterized, and customized mixtures of microbes. These synthetic communities can be more strictly regulated as they would be less variable and less widely accessible than stool samples that are naturally available^[29]. This technique could subsequently address some of the main limitations of FMT, including inability to standardize, pathogen transmission, and patient acceptance. In fact, synthetic stool substitutes have already been shown to be effective against CDI and more so than conventional probiotic treatments because they have demonstrated long-term colonization of the gut^[39]. Administration of such controlled mixtures could, therefore, become the preferred treatment.

However, the trials that have been conducted thus far have been limited in number and in scope, which is why synthetic stool infusion remains a solution of the distant future as of now. One potential complication with this process is that mixtures may not produce the same results among all patients given individual differences in gut flora. Considerations and adjustments must be made in terms of host genotype, diet, environment, and immune system response - determining the relationship between microbiota and these various aspects should be a topic of future study^[20]. Additionally, the precise associations between microbiota and various conditions are not yet completely understood in all cases and the long-term risks of altering microflora have not been determined either^[28]. These areas must also be explored before synthetic stool substitution can be developed and implemented on a broader scale.

Advancements in transplant method are also underway. For instance, we may progress toward oral FMT administration through the use of lyophilized, encapsulated, and enteric-coated capsules. Perhaps there will come a time when oral FMT will be routinely given along with antibiotics in efforts to preserve the gut microflora^[40].

Again, the extent to which FMT and its potential applications are developed is dependent upon how efficiently the medical use of human feces is regulated. The current regulatory guidelines, which treat human feces as a drug, create a disincentive for research, restrict access to care, and fail to evaluate the long-term risks associated with the process. Classifying stool as a body tissue would begin to address these various issues.

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