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CRITICAL REVIEW

Fecal microbiota transplantation: the power of poop

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ABSTRACT
Fecal microbiota transplantation (FMT), a procedure involving the transfer of stool from healthy donors to patients, has demonstrated success in re-establishing gut microbiota homeostasis and facilitating the recovery of metabolic and immune function. Based on positive results from numerous clinical trials, current North American and European clinical guidelines recommend FMT as a treatment option for recurrent *Clostridium difficile* infections. Ongoing investigations into FMT's efficacy in the treatment of other conditions, such as multiple sclerosis and inflammatory bowel disease, may expand the application of FMT to a myriad of diseases. Nonetheless, challenges regarding biosafety concerns and public perception need to be addressed before FMTs can be considered for broader applications.

INTRODUCTION

Fecal microbiota transplantation (FMT) is a procedure that transfers stool from a healthy donor to the gastrointestinal tract of a patient with altered gut microbiota. This process aims to restore the normal gut microbiome and to suppress pathogenic bacteria without the use of antibiotics.[1]

The first step of FMT is to collect a stool sample from a healthy donor. The donor may be a relative, a spouse, or an unrelated stranger.[1] After a donor has been recruited, their stool and serum will be screened for the presence of infectious agents such as human immunodeficiency virus to reduce the risk of disease transmission. Donor history will also be assessed; donors with active infections, recent exposure to antibiotics, or chronic gastrointestinal conditions will be excluded. If the donor meets the eligibility criteria, the collected stool sample will then be emulsified in a sterile saline solution and administered to patients after removing particulates.[1,2]

Currently, the main application of FMT focuses on the treatment of recurrent *Clostridium difficile* infections (rCDI), a condition characterized by chronic gastrointestinal inflammation unresponsive to antibiotic treatments.[1] Numerous clinical guidelines from North America and Europe have recommended FMT as a treatment option against rCDI.[3,4] Additionally, the applicability of FMT for the management of many other gastrointestinal and non-gastrointestinal disorders, including irritable bowel disease (IBD), slow-transit constipation, and multiple sclerosis, is currently under investigation.[1] Despite its potential, FMT also faces challenges such as biosafety precautions and stigma within the general population.

THE HUMAN GUT MICROBIOTA

The human gut microbiota is comprised of over 35,000 bacterial species and microbes, including archaea, viruses, and protozoa.[5,6] These microbes play important roles in nutrient metabolism, immune development, and immune protection.[7] Under normal conditions, the gut microbiota maintains a homeostatic equilibrium that rests on a symbiotic relationship between the microbial community and the animal host.[6] Disruption of the commensal flora is associated with inflammatory gastrointestinal disease, colon cancer, and diabetes.[6] However, evidence has yet to identify a causal relationship between dysbiosis and the aforementioned conditions. Nevertheless, there has been a building interest from the medical community to treat these diseases by restoring the normal gut microbiota through FMT.[8] This interest is promoted by the potential for FMT to act as an alternative to antibiotic treatments, which has been shown to collaterally disrupt and decrease the biodiversity of the gut microbiome, ultimately placing patients at higher risk for future infections.[9,10]

FECAL TRANSPLANTS & CLOSTRIDIUM DIFFICILE INFECTION

C. difficile infection (CDI) manifests as abdominal pain, fever, and diarrhea secondary to colon inflammation and damage from toxins excreted by the bacteria.[11] *C. difficile* is transmitted primarily through spores in feces, a process that can be facilitated by cross-contamination in healthcare institutions and between healthcare professionals.[11] In fact, CDI is the most common hospital-acquired infection in Canada.[12] Patients can become susceptible to CDI as a result of indiscriminate use of proton-pump-inhibitors and antibiotics harmful to the gut microbiota. For example, reductions in bifidobacteria populations have been shown to decrease host immune protection.[5] Additionally, older patients are more likely to contract CDIs and require hospital admissions in order to manage the increasing complexity of their conditions. In Canada, an estimated 37,900

cases of CDI were reported in 2012, with $281 million in direct and opportunity costs.[12] Case mortality rates range from 6-30% with a general upward trend since as early as 1995.[13]

For mild cases of CDI, individuals can reasonably recover without medical intervention.[10] In severe cases with risks of organ failure or toxic megacolon, surgery is needed to remove diseased and necrotized portions of the colon.[13] For the majority of cases gauged as moderate in severity, antibiotics are considered first-line therapies.[13] However, in recent years, more CDI patients have presented as antibiotic-resistant, with higher rates of severe, recurrent, and chronic cases. Accordingly, FMTs were introduced as a safe, inexpensive, and more effective alternative to the standard of care.[11,13] Randomized control trials with a combined pool of over 600 participants determined that FMTs, compared to placebo or first-line treatment with the antibiotic vancomycin, cured diarrhea in 59% more CDI patients.[14]

Under normal conditions, the gut microbiota exhibits "colonization resistance," a phenomenon by which normal bacteria outcompete and directly attack invading microorganisms to taper their growth.[1] In CDI treatments, antibiotics such as vancomycin kill both *C. difficile* and healthy strains of bacteria.[11] The resulting loss of healthy, commensal bacteria can contribute to rCDI, as pockets of resistant *C. difficile* may remain even after symptoms recede. Consequently, the infection is likely to return with increased severity as well as with an increased likelihood for antibiotic resistance.[11,13] FMT reintroduces commensal microbiota, such as bifidobacteria populations, via healthy feces, thereby re-establishing colonization resistance as a part of the normal immune function in warding off recurrent infections.[1,11]

Since numerous North American and European clinical guidelines already call for the use of FMTs in antibiotic-resistant CDI, there is mounting support for the adoption of FMT as the first-line treatment for CDI.[11] This establishes a need for future clinical trials to focus on optimizing FMT's preparation and administration for effective large-scale deployment.[11]

FECAL TRANSPLANT IN OTHER DISORDERS

FMT's efficacy in treating CDI has drawn attention to its potential to treat similar disorders, including inflammatory bowel disease (IBD), diabetes, and slow-transit constipation.[1] IBD is a chronic inflammatory disorder of the gastrointestinal system.[8] The pathophysiology of IBD is complex, and has been associated with a decrease in the diversity of the gut microbiota and depletion of commensal bacteria.[8,15] Several clinical studies have been conducted evaluating the effectiveness of FMT in treating IBD, but the results are not conclusive. One parallel RCT conducted by Moayyedi and colleagues found a statistically significant difference in remission between patients treated with FMT versus patients treated with a placebo enema.[16] However, another RCT comparing FMT with placebo found no statistically significant differences in remission rates between the groups.[17] Although more research is needed to determine FMT's effectiveness in treating IBD, current research suggests that dysbiosis, or microbial imbalance, is not the sole pathophysiology under IBD. Thus, FMT will likely be limited as an adjunct therapy.[11] Patients with diabetes have also been found to have lower diversity in their gut microbiota, but a causal path for this association has yet to be elucidated.[18] In humans, FMT appeared to improve insulin sensitivity in insulin-resistant patients when assessed 6 weeks after treatment, which sheds light to its therapeutic potential in treating diabetes.[19] However, further developments in the FMT process are needed before it can be reliably used in clinical settings for conditions other than rCDI.[18]

PUBLIC PERCEPTION

While researchers view FMT as an innovative and successful treatment that could be more effective at eradicating infections than first-line antibiotics, there is still significant stigma ftom the general population on the treatment. The media plays a crucial role in educating the public and improving their understanding of FMT. Currently, the media presents FMT as a disgusting but necessary treatment.[20] The "ick factor" is often the first topic discussed when addressing FMT instead of the positive impact it can have on patients. This bias poses significant hurdles to the recruitment of healthy donors.[20] As FMT is being considered as a first-line therapy over antibiotics, there is no longer a need to portray FMT as an outlandish idea. Instead, more rational public discussions regarding the merits and challenges of FMT are required to increase public acceptance and overcome patient non-compliance. Additionally, physician education is also needed as stigma remains among healthcare professionals.

There have been reports in which patients have been turned down by physicians who protested the "ick factor" of the treatment despite emerging evidence that the treatment is superior to antibiotics against rCDI.[20] Education on and destigmatization of FMT are necessary to entertain future discussions on biosafety regulations and policy implementations.

BIOSAFETY

As FMT is a transfer of biomatter between donor and recipient, it carries the risks analogous to that of a blood transfusion. Inadequate screening of donors may contribute to the transmission of parasites, pathogens, or diseases that have fecal links such as colorectal cancer.[20] As the impact of fecal matter in the pathology of some long-term illnesses is still not fully understood, there exists the possibility that FMT may collaterally introduce new conditions into immunocompromised patients. Currently, Health Canada includes a non-exhaustive list of diseases to be screened for as a part of their donation protocol.[21] More research into the link between fecal matter and various conditions needs to be conducted to prevent FMT-based disease transmissions.

CONCLUSION

Despite its relative anonymity and stigma among the general public, FMT is quickly becoming a mainstay treatment for rCDI. There are currently several ongoing clinical trials gauging FMT's effectiveness against various other diseases with consideration of routes of administration, preparation, and storage. This new data will hopefully allow for more nuanced and targeted approaches for both specific diseases and patient types. Internationally, many are following in the footsteps of Western guidelines that have adopted FMTs as a treatment for CDI.[12]

As FMTs move forward into larger and broader applications, there needs to be more policy considerations regarding its use and distribution. With potential for biohazardous contamination and implications in human genetic material, decisions need to be made regarding how FMTs are to be handled in various legal and societal contexts.[12] The scientific community is only beginning to grasp the full identity and power of the human microbiota. Moving forward, it is increasingly important to uphold the dissemination of accurate information and its use in supporting decisions. While clinical guidelines are bound to evidence-based support, the public must be mindful of media representation that falsely interprets scientific findings for sensationalism or fraudulent conflicts of interest.[12]

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EDITED BY JESSICA CHEE & JIM XIE

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