Fecal microbiota transplantation and metagenomic medicine

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INTRODUCTION

Have you ever had a gut feeling that you were not alone? Before you get up to lock the doors, consider that our gastrointestinal tract, in particular the distal colon, is home to trillions of bacteria and other microorganisms collectively referred to as the microbiome. Fortunately, most of the microbiota are not harmful, but instead provide physiological functions such as digestion and immune system development. Importantly, the intestinal microbiome acts as a front line defense against potential pathogens entering our gut. An important clinical example that highlights this is an infection by a bacterium called *Clostridium difficile*, which usually causes a diarrheal/colitis syndrome, but in some cases may progress into a life-threatening pseudomembranous colitis or a colonic distension called toxic megacolon. Although healthy individuals are resistant to the ingested spores, cases of *C. difficile* infection (CDI) are on the rise because of antibiotic treatments that disrupt the protective microbiota. To compound this problem, there are reports of increased incidence and mortality rates, metronidazole resistance, and the emergence of hypervirulent strains (e.g. BI/NAP1/PCR 027). This ‘epidemic’ has forced us to critically evaluate how we manage CDI cases, especially taking into consideration the inherent dilemma that antibiotic therapy itself is causing this infection.

What can be done? The standard treatment includes discontinuation of the infecting antibiotics and adding other antibiotics (metronidazole, vancomycin). Other additional therapies now include oral bacteriotherapy/probiotics, toxin binders, vaccination, and even performing surgical bowel resection. However, despite additional medical therapy, there are some patients (15 - 35%) that continue to have chronic recurring disease or a severe presentation. For these patients, there has been a last ditch protocol that focuses on replacing the disrupted microbiome through a procedure called fecal microbiota transplantation (FMT). Although this procedure has been around for over 50 years, it is not a mainstream practice even though it has been found to provide safe, relatively inexpensive, and rapid relief with potential long term protection. This is likely due to disinterest from patients (the ‘yuck’ factor), physicians (‘natural’ approaches without good evidence tend to be presumptively dismissed), and researchers. In this article, I will provide a fresh perspective of FMT and discuss how it is becoming an increasingly attractive option in light of our improved understanding of the colonic microbiome.

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FMT works on the principle of taking the bacteria in a healthy donor’s stools and introducing them into the patient’s colon in order to restore a ‘healthy’ intestinal microbiota population. Historically, FMT has been studied and performed in veterinary medicine to treat various disorders in farm animals (transfaunation). The first instance of FMT in humans was in 1958, when a team of physicians in Colorado successfully treated four patients with pseudomembranous colitis. At the time, three of these patients had severe life threatening post-operative colitis that was unresponsive to conventional treatments. In a final attempt, the physicians pioneered the FMT procedure and the patients miraculously recovered and were discharged after several days. It would be much later in 1978 when *C. difficile* was identified to be a cause of antibiotic-associated diarrhea/colitis, which was then followed by the first report of a successful FMT in a CDI case in 1981. While FMT was originally performed by a crude colonic retention enema of homogenized stool samples obtained from closely related or intimate donors, the procedure has been refined through the 1990s. Nowadays, most studies use standardized donor screening and stool collection, cryoprotectant processing and freezer storage, and instillation with a nasogastric/nasoduodenal tube or guided infusion with a colonoscope or upper tract endoscope. However, the basic engraftment principle applied in 1958 is so simple that there are even published ‘do-it-yourself’ guidelines that rely on easily acquired items (e.g. kitchen blender, enema bag) and a healthy friend.

Today, the main indication for FMT is severe refractory CDI or chronic disease with a history of recurrence and a failure of multiple antibiotic regimens. While the evidence is limited to case series and reports of chronic CDI, recent systematic reviews have found an astounding 89-92% clinical resolution of the diarrheal syndrome in over 300 cases reported in the literature. These numbers are encouraging, but only recently has there been interest in conducting a randomized controlled trial (Fecal trial, 2008 - ongoing).

One possible objection to FMT is the concern for safety as there is the possibility for transmitting infections during the procedure. This is a valid concern for any attempt to administer foreign microbiota as evidenced in trials of *Saccharomyces boulardii* probiotic treatment in CDI patients, which had rare reports of sepsis and fungemia. Surprisingly, in a systematic review of 376 cases of FMT in cases of CDI and other indications, there has not been a report of a major adverse event including transmitted infection. Still, the possibility has been taken into consideration by developing protocols such as extensive donor screening in order to prevent transmission of enteric pathogens and provide reconstitution of ‘healthy’ microbiota.

FMT TREATMENT FOR OTHER DISEASES

Ulcerative colitis (UC) and Crohn’s disease are both types of idiopathic inflammatory bowel disease (IBD) that are possible candidates for FMT treatment because of the possible pathophysiologic role of the colonic bacteria. The first report of FMT in UC treatment was 1989 by Bennet and Brinkmann, in which Bennet, who suffered from persistent UC, successfully treated himself. Another report near the same time used FMT to treat a variety of non-CDI associated colitis syndromes with some
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degree of success. In 2003, there was a landmark study on treating UC, which documented a case series of six patients with chronic UC who underwent FMT. All of the patients in the study went into remission and at 1-13 years of follow-up, none of the patients had any evidence of active disease, indicating that the FMT treatments were associated with a lengthy remission period or possible cure. While the evidence is far from definitive, it does support the idea that FMT can be used to treat other diseases that involve the colonic microbiota. These diseases might include chronic constipation, obesity, metabolic syndrome/insulin insensitivity, irritable bowel syndrome, allergic disease, and potentially indirect neuropsychiatric alterations.

PERSONALIZED METAGENOMIC MEDICINE

A lack of rigorous testing and abundance of biased anecdotal reports has made it difficult for FMT to become widely accepted. However, this may begin to change because of insights drawn from recent microbiome research. To start off, consider the question: what makes each person unique? Of course, many would say that it is a combination of genetic, epigenetic, and environmental factors, but traditionally few would consider the microbiome as a significant influence. Yet, while genetic sequence variations between individuals comprise a miniscule fraction of our genome, the differences in microbiota populations have been estimated to be as high as 50%. Moreover, the microbiome is easily amendable to change and is also believed to demonstrate dynamic alterations with normal ageing, geography, and environmental changes.

Within this spectrum of variation within the population, there is the possibility that the microbiome may contribute to disease susceptibility. Although many studies have experimentally implicated a role of the colonic microbiome in various diseases, there is a need for population based studies to establish an association between different microbiota populations and specific diseases. To accomplish this, we can take advantage of next generation sequencing (NGS) technologies. Already this year, there are several sequencing platforms (e.g. Nanopore, MiSeq, Ion PGM-proton) touted to be able to provide extremely rapid and cost-effective genetic sequencing capability. Using NGS, we can realistically envision mapping out the human metagenome, which comprises all of the microorganism genomes within the microbiome. Currently, there are various initiatives supported by the International Human Microbiome Consortium (IHMC) including the NIH Human Microbiome Project (HMP) and the European Metagenomics of the Human Intestinal Tract project (MetaHIT), which will perform metagenomic sequencing of hundreds of individuals. One of the ground-breaking results has been the classification (like blood typing) of individual intestinal microbiomes into 3 major ‘enterotypes’. In addition, at the recent IHMC congress, there were presentations showing metagenome-wide association with both metabolic syndrome and type 2 diabetes. Although much of the work is in the early stages, the future of personalized medicine may someday involve individual metagenomes used as a pertinent factor in diagnosis, disease management, and determinants of health. In this scenario, FMT could be used to treat people with disease-associated microbiomes.

While FMT began as a last ditch therapy for pseudomembranous colitis and CDI, our increasing understanding of the microbiome may mean that FMT has a role in treating other diseases. History has shown a lack of interest in FMT, but the anticipation from metagenomic research and the urgency of the CDI epidemic may be the much needed push for new advances. On an optimistic note, Kahn and colleagues report that patients with UC are in favour of moving forward with FMT, suggesting that patients may not be as adverse to the idea as what we might think. With any luck, we may see substantial developments in the years to come.

REFERENCES


