



## **Microbiome Therapy for Recurrent *Clostridioides Difficile* Infection and Chronic Gastrointestinal Disorders**

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Fecal Microbiota Transplantation (FMT), also known as live biotherapeutics product, which had been predominantly utilized by the veterinarians until late 1990's has generated a significant interest for its potential use in various gastrointestinal, psychiatric, neurologic and metabolic disorders within the past several years. Since 2010, there has been an explosion of research, publications and media coverage related to the high efficacy range, 80 – 90% for treatment of recurrent *Clostridioides (Clostridium) difficile* infection (rCDI). The exact mechanisms of its success in curing CDI are yet to be discovered. However, growing evidence suggests that it likely is a synergistic interaction of metabolites, bacteriophages, glycoproteins and bacterial, fungal components of microbiome, which mediate the effects of FMT. Metagenomic studies have shown that patients with rCDI lack protective and diverse colonic microbiome and remain in a state of chronic dysbiosis. Following a successful FMT, the microbiome of a patient with rCDI resembles that of the donor's and remains as such overtime. There is no precise and agreed definition of dysbiosis but is recognized as perturbation of host-microbial interactions which results in compositional changes in the fecal microbiota as determined by clinical criteria of constellation of symptoms, including change in the bowel function (diarrhea, constipation or bloating) in which an alteration of the microbiota is either known based on molecular or culture-based profiling or suspected according to the history, which includes but is not limited to repeated or prolonged use of antibiotics or gastrointestinal infection.

The cause of inflammatory bowel diseases (IBD) is unknown but studies have shown that IBD is a chronic inflammatory disease with altered and decreased microbiota diversity of the gastrointestinal tract when compared to the healthy individuals. Canada has the highest incidence of IBD in the world. The annual total (direct and indirect) health costs is estimated to \$2.8 billion or \$11,900 per person per year.<sup>17</sup> IBD includes Crohn's Disease (CD) and Ulcerative Colitis (UC). While these diseases are collectively referred as IBD, there are distinct differences - most notably the area of the intestinal tract affected and the extent of the inflammation. UC typically affects the colon; the disease usually starts at the anus and may progress upward, and may even involve the entire colon. While in CD, the inflammation tends to occur in patches and may involve any area throughout the entire intestinal tract; however, it most often affects the terminal ileum of the small intestine. Inflammation due to UC involves only the inner intestinal mucosa, while the inflammation in CD disease can extend through the entire thickness of the bowel wall.



The management of CD is challenging due to extra-intestinal manifestations and overlapping symptomology with other inflammatory disorders. Treatment typically targets symptom relief, but patients' ability to tolerate therapy also plays a key role. UC is characterized by lifelong relapsing and remitting colorectal inflammation. The cause of UC is unknown, but is thought to result from an aberrant immune response to environmental factors in genetically predisposed individuals. Metagenomic studies have shown that both patients with UC and recurrent *Clostridioides difficile* infection (rCDI) lack diversity and richness of their colonic microbiota and remain in a state of chronic dysbiosis. While current drug treatments and surgery to remove the colon and rectum can reduce symptoms, they are costly, associated with adverse effects, and do not promote the restoration of healthy gut bacteria. Recent studies have shown that FMT is effective in treating IBD. Recent case series in CD and clinical trials in UC patients have shown FMT to be a potential therapy to induce and maintain clinical remission in subset of IBD patients.

Irritable bowel syndrome (IB) is characterized by chronic, relapsing abdominal discomfort and altered bowel movements – constipation, diarrhea or mixed (diarrhea and constipation). IBS affects approximately 15-20% of Canadians, and its economic and social burden is estimated to be over \$6.5 billion per year in healthcare costs, work productivity losses, and reduced quality of life (QoL). The etiology and pathophysiology of IBS are not yet established but appear to be a complex interplay between the host and environment factors. Currently, there are no evidence-based therapies available to cure IBS. Studies have shown that FMT may be an effective IBS treatment.