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The Microbiome and Inflammatory Bowel Disease



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Ulcerative colitis (UC) and Crohn's disease are the two chronic and progressive inflammatory states that commonly define inflammatory bowel disease (IBD). UC is typically characterized by continuous mucosal inflammation that involves that rectum and colon and often presents as bloody diarrhea. In Crohn's disease, inflammation is spotty, transmural and can be observed in any portion of the gastrointestinal tract. IBD affects roughly 1.4 million people in the United States

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and some 2.2 million in Europe.^{5,6} The steadily increasing incidence and prevalence of IBD, as well as the association of IBD and urban living, suggests that environment plays a critical role in the development of these diseases.^{8,13} This hypothesis, in conjunction with the documented variations in gut microbiome associated with industrialization and geography,³ has led researchers to pursue the intestinal microbiota as an avenue for diagnostic and therapeutic intervention.

It is thought that a shift in composition of the intestinal microbiome may contribute to the development of IBD in genetically susceptible individuals. Initially hinted at by studies demonstrating such things as a reduced risk of IBD in breastfed infants or increased risk in

(continued on page 30)

(continued from page 28)

those with low vitamin D levels,^{1,2,10} the new age of bioinformatics has enabled corroboration of this theory. One example of the complex genetic-microbe interplay is a study by Ijaz et al. demonstrating that adult relatives of patients with Crohn's disease had less diverse intestinal microbiota than healthy adults unrelated to IBD patients.⁴

While there is no singular microbe responsible for IBD, gut dysbiosis is clearly implicated.⁵ An overall reduction in microbial diversity has been observed as well as specific, relative increases and decreases in "good" and "bad" microbes.^{5,9,12} In Sartor and Wu's extensive 2017 review, Roles for Intestinal Bacteria, Viruses, and Fungi in Pathogenesis of Inflammatory Bowel Disease and Therapeutic Approaches, the authors distill the latest documented genetic compositional changes in the intestinal microbiome of IBD patients.¹² They identify the overarching theme of the associated dysbiosis as a decrease in known "protective" bacteria such as Bifidobacterium species and an expansion of potentially inflammatory microbes like Proteobacteria, Fusobacterium species, and invasive *E. coli*.¹²

The common treatments for UC and Crohn's, including immunosuppressive therapies, mesalamine, glucocorticoids, and tumor necrosis factor antagonists, rarely induce remission and colectomy is too often an undesirable endpoint. Furthermore, an IBD patient's quality of life can be significantly diminished when treated with conventional therapies.¹⁷ However, like the trend of fecal microbiota transplantation (FMT) for the treatment of *Clostridium difficile* infection, there is promising evidence that a similar approach will prove efficacious in treating UC and Crohn's, especially given the increasingly predictable intestinal microbiome perturbation. In one of the premier studies of alternative treatments for IBD, Moayyedi et al. demonstrate, in a randomized controlled trial, that FMT can induce remission in UC patients.⁷ Researchers used the Mayo score for UC, which includes scores for stool pattern, rectal bleeding, endoscopic findings, and physician assessment (scores ranges from 0-12, with higher scores correlating with increased disease severity) to assess patients. Eligible enrollees were adults

18 years or older with active UC determined by a Mayo score ≥ 4 (with an endoscopic score ≥ 1); remission was defined as a Mayo score < 3 at seven weeks. FMT from healthy donors was completed via retention enemas administered once weekly for six weeks. Overall, 9 of the 38 patients in the FMT treatment arm achieved remission, compared to 2 of the 37 patients in the placebo arm. Moreover, there was no difference in serious adverse events between the two groups. In another promising prospective, uncontrolled study, by Uygun et al. response of UC patients to FMT was examined.¹⁴ Responders were defined as a decrease in Mayo score $\geq 30\%$. 21 patients in the study, 70% of the subjects, were ultimately classified as responders. While 9 patients were categorized as non-responders, there was still improvement in CRP and hemoglobin levels after FMT.

Despite the positive findings mentioned above, there is conflicting data, and in another RCT, Rossen et al.¹¹ did not demonstrate a difference in the remission rate of FMT vs. placebo. However, increased intestinal microbiome richness following FMT has been shown in patients with Crohn's, and there is evidence to suggest that FMT donor species richness determines efficacy of FMT treatment for IBD.^{15,16}

Ultimately, while current data is cause for optimism, more foundational research is necessary to characterize the microbe-gene interaction and define a treatment paradigm. ■

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