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Inflammatory Bowel Disease (Gary Lichtenstein, Section Editor)

# The Gut Microbiome as a Target for IBD Treatment: Are We There Yet?

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## Abstract

*Purpose of review* This review aims to highlight recent research on the gut microbiome in IBD and the application of microbiome-modulating therapies for the treatment of IBD including the use of the microbiome as an indicator for disease severity and treatment response.
*Recent findings* Despite the high number of gut microbiome studies and emerging evidence supporting the gut microbiome's involvement in disease pathogenesis, no single microorganism has been identified as a pathogenic agent in IBD. Retrospective studies and meta-analyses on antibiotic use in ulcerative colitis and Crohn's disease and long-term outcomes are conflicting. Similarly, the use of probiotics for the treatment of IBD remains inconclusive; however, some encouraging results are emerging as microbial concoctions are optimized to include beneficial bacterial strains. Fecal microbial transplantation (FMT) is currently emerging as one of the more promising microbiome-modulating IBD therapies.

FMT studies in ulcerative colitis have shown improved remission rates compared to placebo; however, relatively small study sample sizes and varied treatment methods, limit definitive conclusions.

*Summary* With clear evidence of an IBD gut dysbiosis, novel therapies to treat and prevent disease relapse will undoubtedly require a microbiome-modulating approach. The complexity and variability of IBD disease pathogenesis (disease phenotype, gut microbiome, host genetic susceptibility, and environmental factors) will likely require a personalized and multidimensional treatment approach where microbiome-modulating therapy is coupled with other therapies to target other IBD disease components.

## Introduction

Inflammatory bowel disease (IBD) is a group of chronic inflammatory gastrointestinal diseases and a global public health concern. In Western countries, the prevalence of IBD exceeds 0.3% and in newly industrialized countries, the incidence is rapidly increasing [1•]. The two main clinical entities of IBD include Crohn's disease (CD) and ulcerative colitis (UC). While a defined etiology has yet to be established for either CD or UC, there is a probable role for dysbiosis of the gut microbiome. In addition, several other pathogenic factors including environmental stimuli, host susceptibility genes and an aberrant immune response all contribute to disease pathogenesis [2]. Despite decades of research aimed to better understand IBD, much remains unknown and as a consequence, progress towards the development of effective intervention has—unfortunately for those suffering from the disease—advanced at a disappointingly slow pace. In this review, we highlight current research on IBD gut microbiome and summarize recent reports on therapies targeting the microbiome for the treatment of IBD.

# Latest findings in the inflammatory bowel disease gut microbiome

Since the advent of next-generation sequencing and the development of computational methods to analyze highly complex biological sequence data, the role of the gut microbiome in IBD has been intensely researched and well documented. Many studies have characterized the IBD gut microbiota (typically the bacterial members), and its reduced bacterial diversity and richness compared to healthy controls [3–6]. Importantly—and lamentably—the question of whether gut dysbiosis observed in IBD is a cause or consequence of disease remains unresolved. Although no single microorganism so far is consistently implicated in the observed gut dysbiosis, common dysbiosis trends are consistently reported. For example, several independent studies report a notable decrease in some genera of the Bacteroidetes (e.g., *Alistipes* and *Barnesiella*) and Firmicutes (e.g., *Faecalibacterium*, *Oscillibacter*, *Agathobacter*, *Ruminococcus*) [4, 6, 7] with a specific reduction in anti-inflammatory microorganisms such as *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii* [8]. Conversely, an

enrichment of overall *Enterobacteriaceae* [7, 9] including *Escherichia coli* [5, 6, 10–12] and *Fusobacterium* [7, 13–15] have been commonly reported in IBD patients. Moustafa et al. [6] observed an increased prevalence of virulence markers from both *E. coli* and *Clostridium perfringens* in IBD individuals compared to healthy controls; a substantially higher amount of virulence factors, identified through shotgun metagenomics sequencing, were also observed in CD compared to UC. These virulence factors include enterotoxin, hemoglobin protease, hemolysin A, hemolysin B, hemolysin C, hemolysin D, cytotoxic necrotizing factor 1, invasion protein IbeA, secreted autotransporter toxin, and Tir domain-containing protein. It remains to be seen whether a similar trend exists with the mucosal-associated microbiota. These findings suggest that the functional potential of these virulence factors may play a critical role in IBD pathology.

The large observed inter-individual variation of gut microbiome composition in IBD patients has been corroborated by many studies, and has considerably frustrated the search for compositional biomarkers that are diagnostic for IBD. However, the absence of specific taxa in the gut microbiome may serve as biomarkers for IBD. For example, the absence of *Roseburia* and *Faecalibacterium* (e.g., *F. prausnitzii*)—both butyrate producers—and an enrichment of *E. coli* may be predictive of an ileal CD phenotype [9]. Another butyrate-producer, *Alistipes*, was also found to be substantially depleted in IBD patients compared to healthy controls [6], thus highlighting the potential importance of acetate-to-butyrate converting organisms for gut homeostasis [6, 9, 16•]. IBD treatment in some individuals may also contribute to the dysbiosis reported in some studies given that recruitment of treatment-naïve IBD patients is challenging with most individuals being subjected to treatment therapies upon diagnosis.

In an effort to apply a more holistic approach to understanding IBD etiopathogenesis, an increasing body of research is investigating the effect of host genetics on the gut microbiome. Researchers have identified four distinct host loci that were significantly associated with changes in relative abundance for particular genera including *Faecalibacterium*, *Rikenellaceae*, *Lachnospira*, and *Eubacterium* [17••]. A marked decrease in *Roseburia* has been observed in both IBD patients and healthy individuals with a high genetic risk for IBD, thus suggesting that a microbial dysbiosis may precede the development of IBD [16•]. Other studies have conflictingly shown the influence of environmental factors to outweigh that of host genetics [17••].

Despite the ability to infer the abundance of microorganisms through DNA sequencing, metabolic activity from microbiomes is incompletely captured using metagenomics approaches alone. Increasingly, metatranscriptomics studies are being applied [18••] alongside metagenomics to better inform our understanding of IBD disease pathogenesis. For example, Schirmer et al. [18] applied metagenomics and metatranscriptomics approaches on paired stool samples from CD and UC patients in addition to non-IBD individuals. Interestingly, results from this study demonstrate that in many cases, taxon abundance does not correlate well with metabolic activity. This suggests that although some taxa may appear elevated in abundance, their metabolic activity may show a different trend. The authors, as others have reported found that *F. prausnitzii* was reduced in CD; relative pathway abundance analysis showed a high variability of metabolic functional potential across both IBD and non-IBD individuals. The authors also reported elevated RNA levels of *Ruminococus*

*gnavus* levels relative to healthy controls, which were not reflected in the DNA sequence data, suggesting that seemingly small shifts in DNA relative abundance in these organisms may impart significant impact on disease imposed by large changes in metabolic activity. In other cases, some taxa well represented by their relative abundance in the metagenomics data were nearly undetectable in the metatranscriptomics data. The authors speculate that the discrepancy may be explained by dormant or inactive microorganisms in the gut being captured by the metagenomics approach [19].

Other important microorganisms until now have been widely overlooked in IBD. These include fungi, archaea, and viruses. As a consequence of improved sequencing technologies, an increasing amount of studies are evaluating the lesser recognized microorganisms of the IBD gut microbiome. These studies have evaluated both adult and pediatric IBD fungal profiles (fecal and mucosal); in either group, fungal diversity results are increased [7], decreased [20–22], or not significantly changed [7, 20, 23], and this is largely dependent on biological specimen type (mucosa or stool) and experimental method used to assess diversity. In adult cohorts, *Candida* species including *C. albicans* [20], *C. tropicalis*, and *C. glabrata*—an important fungal pathogen associated with a pro-inflammatory response [7, 24] in addition to *Gibberella moniliformis, Alternaria brassicola, Aspergillus clavatus*, and *Cystofilobasidiaceae* [7] are increased in IBD, whereas *Saccharomyces cerevisiae* (Ascomycota) and *Malassezia sympodialis* (Basidiomycota) are decreased [20]. In a fecal fungal microbiota study, Sokol et al. observed a significant association between the Basidiomycota-to-Ascomycota abundance ratio and IBD disease phenotype and severity. IBD patients had a much higher Basidiomycota-to-Ascomycota ratio in comparison to healthy controls and in IBD flares vs. IBD remission, suggesting that this ratio may be used as a fungal dysbiosis index. The gut environment is a complex ecosystem and it is expected that any dysbiosis or perturbations can have substantial impact on its homeostasis and networks of interactions including host-microbiota, bacteria-bacteria, and inter-kingdom. Murine studies have shown that a disruption in the bacteria-fungi abundance triggered by antibiotics can lead to an expansion of the fungi, thereby initiating an inflammatory response [20, 25]. Interestingly, this finding is also supported by the absence of fungal diversity differences in treatment-naïve pediatric CD individuals against healthy controls [23].

Limited studies have attempted to deeply characterize the gut virome in IBD due to methodological and analytical challenges. Most of IBD gut virome studies have focused on bacteriophages (the overwhelming majority of viruses within the gut). In one such study, a significant expansion in the bacteriophage *Caudovirales* was observed in IBD individuals [26]. In contrast, characterization of the eukaryotic virome in one study reported high levels of *Herpesviridae* transcripts from inflamed colonic mucosa of CD and UC patients. More recently, using a treatment-naïve CD and UC cohort (and gut mucosa), Ungaro et al. [27] reported higher levels of *Hepadnaviridae* transcripts among UC patients and *Hepeviridae* among CD patients. The UC virome was characterized by low levels of *Polydnaviridae* and *Tymoviridae*, while low levels of *Virgaviridae* were associated with CD. The authors suggested that eukaryotic viruses are associated with intestinal inflammation and highlighted the importance of biomarker discovery and development of antivirals for the treatment of IBD.

# Manipulating the gut microbiome in the treatment of inflammatory bowel disease

Despite the increasing knowledge of gut dysbiosis in IBD and the increasing reports pertaining to particular species that are either higher or lower in persons with IBD, these findings have yet to be harnessed into a robust disease altering therapy.

## Antibiotics

A meta-analysis suggested that antibiotics were an effective therapy in both UC and CD [28]. However, considering that the studies included different antibiotics with different microbial susceptibilities, it is difficult to conclude anything from this meta-analysis other than the possibility that altering the gut microbiome in some way may be beneficial. Additionally, the endpoint of mucosal healing was not an endpoint assessed in this meta-analysis; rather, the use of the CDAI was the primary focus. In the case of antibiotics, the alteration would be a reduction in particular microorganisms. There is the possibility that antibiotics could also be harmful over the long term. Data have shown that a course of ciprofloxacin can alter the gut microbiota for several months [29]. Recently, a study reported on the use of azithromycin in treating children with mild to moderate CD [30••]. Thirty-five children were randomized to azithromycin 7.5 mg/kg 5 days/week for 4 weeks and then 3 days/week for another 4 weeks together with 8 weeks of daily metronidazole 20 mg/kg. Thirty-eight children were randomized to metronidazole 20 mg/kg alone daily for 8 weeks. The authors claimed that a placebo treatment was not possible due to regulatory hurdles in a multinational investigator initiated trial. At 8 weeks, the remission rate based on the Pediatric Crohn's Disease Activity Index was 66% in the azithromycin/metronidazole group and 39% in the metronidazole alone group ($p = 0.025$). The number needed to treat for remission was 3.7. There was no objective mucosal healing data although fecal calprotectin declined significantly in the azithromycin group ($p = 0.001$) but not in the metronidazole alone group ($p = 0.33$). The remission rate seems high for the metronidazole group alone, though the reported total remission rate of 66% is extraordinary. Hence, it is difficult to know whether the high reported remission rates were secondary to participants having milder disease or simply reflected a contribution of a placebo effect provided by the addition of azithromycin as participants were not blinded to its use. While there were no endoscopic data, the fecal calprotectin levels were significantly reduced in the azithromycin group. However, the range at week 8 (737–2867 μg/g) suggested that all those randomized to azithromycin likely still had active intestinal inflammation. No microbiome data were provided.

In a retrospective cohort study of 354 patients with IBD admitted to an academic Boston hospital in 2009–2014, antibiotics (not administered for the treatment of sepsis) provided no additional benefit in CD when used together with intravenous corticosteroids [31]. Antibiotic use reduced the need for short-

term medical rescue therapy but did not influence long-term outcomes in UC. The long-term outcomes included length of stay, need for surgery, or therapy escalation at 1 year or rehospitalization. Ciprofloxacin and metronidazole were the antibiotics used in the vast majority of cases. While this study suffers from the usual biases of retrospective studies, it is one of the largest studies to date to explore the use of antibiotics as an adjunctive therapy in hospitalized IBD patients, and does not show much, if any, role for this practice.

There is limited evidence but considerable clinical experience using antibiotics to treat perineal fistulas and pouchitis [21]. Despite the absence of firm evidence guiding the use of antibiotics in treating luminal CD and UC some experts still advocate for their selected use [32].

## Probiotics

There are no data showing a benefit of probiotics in the treatment of CD [32, 33]. Three studies have shown that *E. coli* Nissle was comparable to low doses of 5-ASA in the treatment of UC. VSL#3, a concoction of eight microbial strains has been shown to improve outcomes in pouchitis and to enhance outcomes in UC when added to 5-ASA. These conclusions were corroborated in a recently published meta-analysis exploring the use of probiotics in IBD [34]. Probiotic studies include a variety of different species, doses, and study duration. Most studies thus far have also focused on bacterial probiotics; however, some speculate that the probiotic yeast may be successful at alleviating inflammation in colitis [35]. Hence, making conclusions about probiotics in general as an intervention may obfuscate the possibility that a purposefully selected strain may be of benefit.

## Fecal microbiota transplantation

Three fully published randomized controlled trials have reported on fecal microbiota transplantation (FMT) in the treatment of UC [36••, 37, 38]. One study was negative while two studies suggested a benefit at achieving remission compared with placebo. The most recent study by Paramsothy et al. [36] reported that 27% of persons receiving FMT versus 8% of those receiving placebo ($p = 0.02$) achieved steroid-free remission and endoscopic response at 8 weeks. These three studies used different methods of FMT administration (nasoduodenal infusion versus enema versus colonoscopic plus enema delivery), dose frequency (daily or weekly), and the creation of the FMT product (fresh or frozen, single donor or pooled donors). It is also unknown whether antibiotic or bowel cleansing preparation prior to FMT enhances outcomes. Two studies suggested that one donor in each study led to better outcomes [36••, 37]. This may be a promising therapy; however, considering the unknowns associated with FMT, encapsulating the desired microorganisms is preferable. Of course, this requires knowledge of what microorganisms are the key ones to administer. Kao et al. [39••] proved that stool could be encapsulated and taken orally in a randomized controlled trial of encapsulated stool versus colonoscopically delivered stool to the cecum in treatment of recurrent *Clostridium difficile* infection (CDI). Both 40 capsules of stool taken orally and delivery of 360 ml of stool into the cecum prevented recurrence in 96% of cases.

Two meta-analyses assessing randomized controlled trials of FMT in UC suggested that FMT was successful at achieving remission with an acceptable

side effect profile [40, 41]. While FMT was nearly three times as likely to achieve remission as placebo and the number needed to treat was only five, in total only 140 persons have received FMT across these studies so the results should not be considered conclusive. In another meta-analysis, authors assessed the risk of a flare of IBD post-FMT and found it to be 14.9% [42]. The risk was higher (22.7%) when the indication for the FMT was CDI in IBD as opposed to the primary treatment of IBD (11.1%). However, the rates of worsening IBD were much lower assessing high quality studies and randomized controlled trials (4.6%).

There is much less known about FMT in pediatric IBD. A single-center open-label study of 21 children with IBD who received a single FMT by endoscopic administration into the duodenum/jejunum and the colon reported that 57% had a clinical response at 1 month and 28% retained some response by 6 months [43]. The authors do not report remission results. It is clear that a single infusion even administered endoscopically throughout the gastrointestinal tract will not provide sufficient response rates. Microbiological data were provided in this study but the clinical results did not provide much in the way of direction for clinicians who might consider FMT in children with IBD. As FMT is an emerging therapy with many associated unknowns, it should only be administered in persons with IBD in a clinical trial setting.

## Microbiome as an indicator of disease severity and treatment response

The diagnosis of IBD is currently performed using invasive endoscopic, radiologic, and histopathologic criteria. The gut microbiome represents a promising non-invasive alternative to current approaches and has been the target of recent research. As discussed, studies associating IBD with the microbiome consistently find reduced diversity relative to healthy controls, making it a reliable, albeit nonspecific measure for following treatment. Compositional differences are more specific than diversity measures but are less consistent, especially at lower taxonomic ranks. Although the gut microbiome composition is remarkably stable within individuals, there exists considerable variation between individuals [44]. The gut microbiome is sensitive to a large number of biological and environmental confounders such as age, sex, lifestyle, antibiotic use, comorbidities, and dietary patterns [45]. Laboratory technical variation including sampling strategy, nucleic acid extraction, sequencing method, and bioinformatics analysis also contributes substantially to observed compositional differences [45]. As a result, no single species to date has been convincingly identified as a biomarker in IBD or any of its component diseases [5, 46]. However, continued interest exists in developing the gut microbiome as a clinical diagnostic test for disease severity and for monitoring treatment response for IBD under conditions where these confounding factors can be controlled.

Progress towards developing a microbiome-based clinical diagnostic for IBD has been most successful for CD. A large-scale European study of 2045 IBD and non-IBD fecal samples identified a microbial signature for CD disease severity consisting of eight genera and an associated presence/absence algorithm with a

sensitivity of around 80%, and specificities for discriminating CD from UC, IBS, anorexia, and healthy control ranging between 90 and 95% [46]. A second large-scale study focusing on mucosal tissue biopsies from children with new-onset CD resulted in the development of a quantitative measure of dysbiosis referred to as the microbial dysbiosis index (MD-index) [47]. The MD-index correlates strongly with disease severity and is consistent with reduced species diversity in CD. These studies demonstrate good progress towards the development of a clinically accepted microbiome-based diagnostic for CD; however, these methods must survive additional validation on larger populations before they can be translated out of the research lab into routine clinical practice.

Beyond its potential value as a non-invasive clinical diagnostic technology, the gut microbiome is useful to monitor IBD disease severity and treatment response in research settings.

The fecal microbiome has been used to monitor the therapeutic efficacy of a variety of dietary therapies [48, 49], including the more promising exclusive enteral nutrition (EEN) diet [50] and the specific carbohydrate diet (SCD) [49]. An increase in microbial diversity was observed for pediatric CD patients ($n$ = 15) enrolled in the EEN diet, and for four of eight pediatric CD patients in the SCD diet, with the remaining four showing no change or a slight decrease in diversity. Both studies showed significant shifts in microbial composition for all patients concomitant with improved clinical outcomes and, for some patients in the SCD study a compositional trajectory towards that of healthy controls. Curiously, in the EEN study, the abundance of *F. prausnitzii*, which is normally thought to have a protective role in CD, was observed to decrease with treatment; however, given that diet is a major confounder of microbiome composition (and the radical nature of the diet itself), this observed decrease is not by itself sufficient to challenge the status of *F. prausnitzii* as a beneficial microbe in CD.

Although the efficacy of FMT in treating IBD has on the whole been underwhelming, there do exist several studies that have used the gut microbiome to monitor the therapeutic outcome of FMT where FMT has successively induced a remission. In a double-blind randomized controlled trial of FMT ($n$ = 38) versus placebo ($n$ = 37) for patients with active UC, significant microbiome changes were observed for the treatment group relative to placebo after 6 weeks [37]. Microbial diversity was enriched, and the active therapy group had microbial profiles more closely resembling their donors. An increase in species diversity and a shift towards the donor profile was similarly observed for treatment responders in other studies of FMT for the treatment of UC [36•, 51].

One noteworthy study used a shotgun metagenomics approach to monitor disease activity over 14 weeks in patients with CD and UC undergoing treatment with anti-integrin therapy with vedolizumab [52]. Consistent with other studies, they found significantly increased diversity in CD patients achieving remission and a similar, albeit not statistically significant trend in UC patients. Additionally, they found 13 significantly enriched pathways in baseline samples from CD patients achieving remission relative to nonremitters, including branched-chain amino acid pathways involved in the biosynthesis of L-isoleucine, L-citrulline, L-threonine, and L-arginine. After 14 weeks, remitters had 15 depleted pathways including several pathways involved in oxidative stress and O-antigen building block biosynthesis. The study is significant since it

highlights how the pathways that associate with disease, which can in theory be supplied by a range of different microbial community compositions, might serve as a more stable and reliable marker of disease than compositional information alone.

Examples of the use of the microbiome to monitor prebiotic and probiotic therapies for IBD are scarce, presumably due to their lack of demonstrated beneficial clinical effects for these interventions [48]. Reports on the use of the nonbacterial component of the gut microbiome for monitoring disease severity treatment are similarly much less abundant than their bacterial counterpart, although some promising early results are now beginning to appear [27]. Further work is necessary to determine whether these components of the microbiome may be useful for monitoring disease severity and treatment outcomes in IBD.

## Conclusions

The therapeutic goal for IBD at present is to induce and maintain remission; thus, there is a need for the recognition and adoption of novel therapeutics that will ultimately cure and perhaps even prevent disease. As IBD occurs due to an interplay between host genetics and immunology, environmental factors, and the gut microbiome, much interest has been aimed at controlling factors proven to be altered. Although, it is not yet wholly clear which altered aspects of gut microbiome in IBD warrant intervention. Researchers and clinicians have great hope that manipulating the gut microbiome will provide an answer to the mystery of IBD and reduce reliance on immunomodulating therapy. Given the heterogeneity of patients, phenotypes and genotypes, a more complex personalized medicine approach to microbiome manipulation will be an aspect to consider in the future.

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## Compliance with ethical standards

**Conflict of interest**
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**Human and animal rights and informed consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

## Publisher's Note



## References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance


1.• Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390:2769–78.

This review updates current epidemiological data on IBD incidence and prevalence from around the world, highlighting the ongoing emergence of IBD in the developing world.

2. de Souza HSP, Fiocchi C. Immunopathogenesis of IBD: current state of the art. Nat Rev Gastroenterol Hepatol. 2016;13:13–27.
3. Gevers D, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, et al. The treatment-naïve microbiome in new-onset Crohn's disease. Cell Host Microbe. 2014;15:382–92.
4. Manichanh C, Rigottier-Gois L, Bonnaud E, Gloux K, Pelletier E, Frangeul L, et al. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. Gut. 2006;55:205–11.
5. Willing B, Halfvarson J, Dicksved J, Rosenquist M, Järnerot G, Engstrand L, et al. Twin studies reveal specific imbalances in the mucosa-associated microbiota of patients with ileal Crohn's disease. Inflamm Bowel Dis. 2009;15:653–60.
6. Moustafa A, Li W, Anderson EL, Wong EHM, Dulai PS, Sandborn WJ, et al. Genetic risk, dysbiosis, and treatment stratification using host genome and gut microbiome in inflammatory bowel disease. Clin Transl Gastroenterol. 2018;9:e132.
7. Liguori G, Lamas B, Richard ML, Brandi G, da Costa G, Hoffmann TW, et al. Fungal dysbiosis in mucosa-associated microbiota of Crohn's disease patients. J Crohns Col. 2016;10:296–305.
8. Takahashi K, Nishida A, Fujimoto T, Fujii M, Shioya M, Imaeda H, et al. Reduced abundance of butyrate-producing bacteria species in the fecal microbial community in Crohn's disease. Digestion. 2016;93:59–65.
9. Willing BP, Dicksved J, Halfvarson J, Andersson AF, Lucio M, Zheng Z, et al. A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. Gastroenterology. 2010;139:1844–1854.e1.
10. Baumgart M, Dogan B, Rishniw M, Weitzman G, Bosworth B, Yantiss R, et al. Culture independent analysis of ileal mucosa reveals a selective increase in invasive *Escherichia coli* of novel phylogeny relative to depletion of Clostridiales in Crohn's disease involving the ileum. ISME J. 2007;1:403–18.
11. Kotlowski R, Bernstein CN, Sepehri S, Krause DO. High prevalence of *Escherichia coli* belonging to the B2+D phylogenetic group in inflammatory bowel disease. Gut. 2007;56:669–75.
12. Fang X, Monk J, Nurk S, Akseshina M, Zhu Q, Gemmell C, et al. Metagenomics-based, strain-level analysis of *Escherichia coli* from a time-series of microbiome samples from a Crohn's disease patient. Front Microbiol [Internet]. 2018 [cited 2018 Oct 18];9. Available from: https://www.frontiersin.org/articles/10.3389/fmicb.2018.02559/abstract. Accessed 1 Nov 2018.
13. Tahara T, Shibata T, Kawamura T, Okubo M, Ichikawa Y, Sumi K, et al. Fusobacterium detected in colonic biopsy and clinicopathological features of ulcerative colitis in Japan. Dig Dis Sci. 2015;60:205–10.
14. Ohkusa T, Okayasu I, Ogihara T, Morita K, Ogawa M, Sato N. Induction of experimental ulcerative colitis by *Fusobacterium varium* isolated from colonic mucosa of patients with ulcerative colitis. Gut. 2003;52:79–83.
15. Strauss J, Kaplan GG, Beck PL, Rioux K, Panaccione R, DeVinney R, et al. Invasive potential of gut mucosa-derived *fusobacterium nucleatum* positively correlates with IBD status of the host. Inflamm Bowel Dis. 2011;17:1971–8.
16.• Imhann F, Vila AV, Bonder MJ, Fu J, Gevers D, Visschedijk MC, et al. Interplay of host genetics and gut microbiota underlying the onset and clinical presentation of inflammatory bowel disease. Gut. 2018;67:108–19.

This study investigated the link between the IBD host genotype and gut microbiome using 16S rRNA sequencing of stool samples and host genotyping data in comparison to healthy controls. A key finding from this study was evidence that a gut dysbiosis commonly associated with IBD may precede disease manifestation. Healthy controls with high IBD genetic susceptibility were significantly associated with a lower abundance of Roseburia.

17.•• Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, et al. Environment dominates over host genetics in shaping human gut microbiota. Nature. 2018;555:210–5.

Using independent cohorts, this study provides evidence that the influence of host genetics on the gut microbiome is likely minimal and report that only a small proportion of the gut

microbiome is heritable; environmental factors impart a much larger effect on the human gut microbiome composition.

18.•• Schirmer M, Franzosa EA, Lloyd-Price J, LJ MI, Schwager R, Poon TW, et al. Dynamics of metatranscription in the inflammatory bowel disease gut microbiome. Nature Microbiol. 2018;3:337–46.

One of the first studies to combine both metagenomics and metatranscriptomics approaches on fecal samples taken from IBD patients and healthy controls. Their results highlight variability in the sequence data generated from both approaches suggesting that the transcriptional activity may unravel additional disease mechanisms not possible through microbial DNA sequence abundance data.

19. Rehman A, Lepage P, Nolte A, Hellmig S, Schreiber S, Ott SJ. Transcriptional activity of the dominant gut mucosal microbiota in chronic inflammatory bowel disease patients. J Med Microbiol. 2010;59:1114–22.
20. Sokol H, Leducq V, Aschard H, Pham H-P, Jegou S, Landman C, et al. Fungal microbiota dysbiosis in IBD. Gut. 2017;66:1039–48.
21. Chehoud C, Albenberg LG, Judge C, Hoffmann C, Grunberg S, Bittinger K, et al. A fungal signature in the gut microbiota of pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2015;21:1948–56.
22. Mukhopadhya I, Hansen R, Meharg C, Thomson JM, Russell RK, Berry SH, et al. The fungal microbiota of de-novo paediatric inflammatory bowel disease. Microbes Infect. 2015;17:304–10.
23. El Mouzan M, Wang F, Al Mofarreh M, Menon R, Al Barrag A, Korolev KS, et al. Fungal microbiota profile in newly diagnosed treatment-naïve children with Crohn's disease. J Crohn Col. 2017;11:586–92.
24. Seider K, Gerwien F, Kasper L, Allert S, Brunke S, Jablonowski N, et al. Immune evasion, stress resistance, and efficient nutrient acquisition are crucial for intracellular survival of *Candida glabrata* within macrophages. Eukaryot Cell. 2014;13:170–83.
25. Dollive S, Chen Y-Y, Grunberg S, Bittinger K, Hoffmann C, Vandivier L, et al. Fungi of the murine gut: episodic variation and proliferation during antibiotic treatment. PLoS One. 2013;8:e71806.
26. Norman JM, Handley SA, Baldridge MT, Droit L, Liu CY, Keller BC, et al. Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell. 2015;160:447–60.
27. Ungaro F, Massimino L, Furfaro F, Rimoldi V, Peyrin-Biroulet L, D'Alessio S, et al. Metagenomic analysis of intestinal mucosa revealed a specific eukaryotic gut virome signature in early-diagnosed inflammatory bowel disease. Gut Microbes. 2018;0:1–10.
28. Khan KJ, Ullman TA, Ford AC, Abreu MT, Abadir A, Marshall JK, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and Meta-analysis. Am J Gastroenterol. 2011;106:661–73.
29. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. PNAS. 2011;108:4554–61.
30.•• Levine A, Kori M, Kierkus J, Boneh RS, Sladek M, Escher JC, et al. Azithromycin and metronidazole versus metronidazole-based therapy for the induction of remission in mild to moderate paediatric Crohn's disease : a randomised controlled trial. Gut. 2018;68:gutjnl-2017–315199.

This study was a randomized controlled trial of azithromycin plus metronidazole versus metronidazole alone in children with Crohn's disease. The group randomized to azithromycin had a higher remission rate. The remission rate in the azithromycin group was sufficiently high to raise concerns about the impact of lack of blinding.

31. Gupta V, Rodrigues R, Nguyen D, Sauk J, Khalili H, Yajnik V, et al. Adjuvant use of antibiotics with corticosteroids in inflammatory bowel disease exacerbations requiring hospitalisation: a retrospective cohort study and meta-analysis. Aliment Pharmacol Therap. 2016;43:52–60.
32. Ledder O, Turner D. Antibiotics in IBD: still a role in the biological era? Inflamm Bowel Dis. 2018;24:1676–88.
33. Bernstein CN. Antibiotics, Probiotics and Prebiotics in IBD. Nutrition, gut microbiota and immunity: therapeutic targets for IBD. Nestle Nutr Inst Workshop Ser. 2014;79:83–100.
34. Derwa Y, Gracie DJ, Hamlin PJ, Ford AC. Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease. Aliment Pharmacol Therap. 2017;46:389–400.
35. Sivignon A, de Vallée A, Barnich N, Denizot J, Darcha C, Pignède G, et al. Saccharomyces cerevisiae CNCM I-3856 prevents colitis induced by AIEC bacteria in the transgenic mouse model mimicking Crohn's disease. Inflamm Bowel Dis. 2015;21:276–86.
36.•• Paramsothy S, Kamm MA, Kaakoush NO, Walsh AJ, van den Bogaerde J, Samuel D, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet. 2017;389:1218–28.

This was the most recent published randomized placebo controlled trial of fecal microbial transplantation in the treatment of UC. It suggested a magnitude of benefit similar to that seen in the previously reported Canadian study.

37. Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology. 2015;149:102–9.
38. Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JHA, Duflou A, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology. 2015;149:110–118.e4.
39.•• Kao D, Roach B, Silva M, Beck P, Rioux K, Kaplan GG, et al. Effect of oral capsule– vs colonoscopy-delivered fecal microbiota transplantation on recurrent *Clostridium difficile* infection: a randomized clinical trial. JAMA. 2017;318:1985–93.

This randomized controlled trial showed that encapsulated stool was comparably effective at reducing recurrence of C difficile as colonoscopically administered fecal microbial transplantation.

40. Narula N, Kassam Z, Yuan Y, Colombel J-F, Ponsioen C, Reinisch W, et al. Systematic review and meta-analysis: fecal microbiota transplantation for treatment of active ulcerative colitis. Inflamm Bowel Dis. 2017;23:1702–9.
41. Paramsothy S, Paramsothy R, Rubin DT, Kamm MA, Kaakoush NO, Mitchell HM, et al. Faecal microbiota transplantation for inflammatory bowel disease: a systematic review and meta-analysis. J Crohn Col. 2017;11:1180–99.
42. Qazi T, Amaratunga T, Barnes EL, Fischer M, Kassam Z, Allegretti JR. The risk of inflammatory bowel disease flares after fecal microbiota transplantation: systematic review and meta-analysis. Gut Microbes. 2017;8:574–88.
43. Goyal A, Yeh A, Bush BR, Firek BA, Siebold LM, Rogers MB, et al. Safety, clinical response, and microbiome findings following fecal microbiota transplant in children with inflammatory bowel disease. Inflamm Bowel Dis. 2018;24:410–21.
44. Sommer F, Anderson JM, Bharti R, Raes J, Rosenstiel P. The resilience of the intestinal microbiota influences health and disease. Nat Rev Microbiol. 2017;15:630–8.
45. Debelius J, Song SJ, Vazquez-Baeza Y, Xu ZZ, Gonzalez A, Knight R. Tiny microbes, enormous impacts: what matters in gut microbiome studies? Genome Biol [Internet]. 2016 [cited 2018 Oct 28];17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5072314/. Accessed 1 Nov 2018.
46. Pascal V, Pozuelo M, Borruel N, Casellas F, Campos D, Santiago A, et al. A microbial signature for Crohn's disease. Gut. 2017;66:813–22.
47. Gevers D, Kugathasan S, Knights D, Kostic AD, Knight R, Xavier RJ. A microbiome foundation for the study of Crohn's disease. Cell Host Microbe. 2017;21:301–4.
48. Lane ER, Zisman TL, Suskind DL. The microbiota in inflammatory bowel disease: current and therapeutic insights. J Inflamm Res. 2017;10:63–73.
49. Suskind DL, Cohen SA, Brittnacher MJ, Wahbeh G, Lee D, Shaffer ML, et al. Clinical and fecal microbial changes with diet therapy in active inflammatory bowel disease. J Clin Gastroenterol. 2018;52:155–63.
50. Gerasimidis K, Bertz M, Hanske L, Junick J, Biskou O, Aguilera M, et al. Decline in presumptively protective gut bacterial species and metabolites are paradoxically associated with disease improvement in pediatric Crohn's disease during enteral nutrition. Inflamm Bowel Dis. 2014;20:861–71.
51. Ashton JJ, Colquhoun CM, Cleary DW, Coelho T, Haggarty R, Mulder I, et al. 16S sequencing and functional analysis of the fecal microbiome during treatment of newly diagnosed pediatric inflammatory bowel disease. Medicine (Baltimore) [Internet]. 2017 [cited 2018 Oct 3];96. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5500076/ Accessed 1 Nov 2018.
52. Ananthakrishnan AN, Luo C, Yajnik V, Khalili H, Garber JJ, Stevens BW, et al. Gut microbiome function predicts response to anti-integrin biologic therapy in Inflammatory bowel diseases. Cell Host Microbe. 2017;21:603–610.e3.