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MICROBIOTA AND IBD

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Abstract: The current article is a review of the most important, accessible, and relevant literature published between April 2019 and March 2020 on the gut microbiota and inflammatory bowel disease (IBD). The major areas of publications during the time period were in the areas of human studies as well as mechanistic insights from animal models. Most papers focussed on the bacterial component of the gut microbiota although some papers described aspects of the virome and mycobiome. Over 130 relevant papers were published in the reporting period.

Keywords: Inflammatory bowel disease, Microbiome, Microbiota, Colitis models,

HUMAN STUDIES

Several studies were published which compared IBD microbiota profiles with healthy controls, including a systematic review[1]. Sampling strategies included comparison of faecal *vs.* mucosal samples, and active *vs.* uninflamed colonic sites[2-6]. A consistent reduction in microbial richness (alpha-diversity) was confirmed in all sequencing studies[2,4-6], with increases in Proteobacteria (including *Enterobacteriaceae*, *Acidaminococcus*, *Veillonella*) and a reduction in Firmicutes (including *Roseburia sp.* and *Faecalibacterium prausnitzii)* confirmed, similar to previous studies. Specific comparison between faecal and mucosal microbiota signatures indicated that mucosal signatures were often more useful in discriminating between health and disease, compared to faecal microbiota profiles[4]. A Dutch study assessed the stability of CD patients' overtime, concluding that temporal stability of the CD microbiota community structure was lower than healthy controls but was not affected by disease activity. While IBD has been associated with gut microbiota composition changes, the impact of gut microbial metabolome, the molecular interface between host and microbiota, are less-well understood. Franzosa et al[7] performed shotgun metagenomic and untargeted metabolomic profiling of IBD patients and non-IBD controls. A number of differentially abundant metabolite features were identified in the IBD cohort; including enrichments for sphingolipids and bile acids, and depletions for triacylglycerols and tetrapyrroles which reflects perceived adaptation to oxidative stress. Integrating the metagenomic and metabolomic datasets identified 122 robust associations, highlighting potential mechanistic relationships that are impacted during IBD. A further study[8] from the same group, published in Nature, further interrogated the functional dysbiosis seen in IBD. The study, which is the publication of the Human Microbiome Project 2 initiative, details the development of IBDMDB, as part of the Integrative Human Microbiome Project and one of the first integrated studies of multiple molecular features of the gut microbiome that have been implicated in IBD dynamics. Using an extensive multi-omic approach they identified an increase in facultative anaerobes at the expense of obligate anaerobes, as well as molecular disruptions in microbial transcription (for example, among clostridia), metabolite pools (acylcarnitines, bile acids, and short-chain fatty acids). Paralleling the reduced species richness associated with IBD, metabolite pools were also reduced in IBD patient samples. Active disease was marked by increases in temporal variability, with characteristic taxonomic, functional, and biochemical shifts. Finally, integrative analysis identified microbial, biochemical, and host factors central to this dysregulation.

Alterations in bile acid metabolism are commonly highlighted in the context of IBD. However, detailed comparison of bile salt transformation genes (BSTGs) in the gut microbiome of heathy and IBD subjects requires further investigation. Based on metagenomic data, Das et al[9] were able to show that IBD patients harboured significantly less BSTGs compared to healthy subjects. A significant number of BSTGs originated from Firmicutes members, which are known to reduce in IBD.

Other publications which looked at IBD microbiota profiles, stratified cohorts based on the inflammatory marker IL-13[10] or based on vitamin K levels[11]. IL-13 is an important pathological factor in both adult and paediatric UC, whilst vitamin K, which is partly synthesised by gut bacteria, may therefore correlate with altered microbiota profiles. Stratifying their adult UC cohort based on IL-13 levels identified different clinical-pathological characteristics; Butera et al[10] showed that high IL-13 mRNA patients were generally diagnosed younger and had a more extensive colitis compared to the low IL-13 mRNA group. The high IL-13 group had a higher abundance of *Prevotella* whilst the low IL-13 group had increased *Sutterella* and *Acidaminococcus*[10]. Wagatsuma et al[11] showed that vitamin K deficiency was associated with reduced microbiota diversity, reduced *Ruminococcaceae* and *Lachnospiraceae* abundance compared to vitamin K sufficient CD patients.

A Danish study[12] described the gut microbiota profiles of IBD patients after 7 years of disease duration. The study showed a significant difference in microbiota profiles in UC patients with active disease compared to inactive disease. Firmicutes levels were lower in active UC, as well as lower overall alpha-diversity. Firmicutes levels were also lower in CD patients with aggressive disease along with an increase in Proteobacteria abundance.

Differences in the gut microbiota of newly diagnosed paediatric CD patients from Poland was also reported during this reporting period. Eighty-two children were included in the study (64CD: 18 HV), as reported previously[13], a reduction in microbiota diversity and species richness was detected in newly diagnosed patients compared to controls. An increase in *Enterococcus* abundance and a reduction in *Bifidobacterium adolescentis, Roseburia faecis, Faecalibacterium prausnitzii, Gemminger formicilis, Ruminococcus bromii* and *Dialister* were all detected.

Patients with IBD frequently have impaired psychological function. Microbiota changes are also thought to be associated with psychological conditions, including anxiety and depression. Recently attempts have been made to determine whether microbiota changes in IBD correlate with patient well-being and quality of life (QoL). A prospective study of psychological comorbidities, QoL and microbiota composition was performed in 171 participants within the Swiss IBD cohort study[14]. All participants were in remission at the time of analysis. A reduced species richness was seen in IBD patients with increased perceived stress scores compared to those with lower perceived stress scores. A significant reduction in species richness was also seen with increasing anxiety scores in UC patients and with increasing depression in CD patients. The majority of taxonomic changes associated with anxiety and depression were observed with the Firmicutes phylum. No clear patterns of microbial composition changes were apparent for QoL measures. The Swiss IBD cohort study was also used to investigate dietary restrictions – namely vegetarian and gluten-free diets and their influence on IBD course and microbiota composition[15]. Despite IBD patients believing that restricting their dietary habits, by following vegetarian and gluten-free diets would reduce their disease symptoms, such an association was not born out by the data analysis. Following a meat-eating diet resulted in dramatic alterations in gut microbiota profiles; with lower species richness demonstrated in CD patients whilst the opposite was seen in UC patients. Higher abundance of *Bacteroides, Faecalibacterium* and *Sutterella* were seen in meat-eating individuals, whilst higher levels of most Firmicutes were detected in non-meat-eating IBD patients.

Currently, limited information exists on the potential role of the gut microbiota in extra-intestinal manifestations (EIMs) of IBD. Around 40% of IBD patients experience EIMs, which usually affect joints, skin, eyes or hepatobiliary system, with joint pain being the most common. Muniz Pedrogo et al[16] undertook a cross-sectional study to look at gut microbiota differences associated with IBD-associated arthropathy (IBD-A). No microbial biomarkers were identified for IBD-A, the study also did not confirm previous studies demonstrating an increased abundance of Proteobacteria. From predicted functional analysis, the study did however find that IBD-A was associated with a higher abundance of bacterial genes encoding tyrosine metabolism pathways.

Gut microbiota alterations have been reported in primary sclerosing cholangitis (PSC), a chronic progressive biliary system disease. Typically, up to 80% of PSC patients also have co-occurring IBD, with 2-8% of IBD-patients also developing PSC. A two-centre study assessed the microbial signature of PSC and PSC-IBD patients, in an attempt to better understand potential pathological significance[17]. Only limited microbial composition differences were identified between PSC and PSC-IBD patients, leading the authors to conclude that the PSC and not the colitis was the main driver of the dysbiosis. Further evidence of microbiota changes in PSC were reported by Quraishi et al[18]. In a small cohort of patients [PSC-IBD (n=10)], UC (n=10) and healthy controls (n=10), RNA-seq, immunophenotyping and microbial profiling of colonic biopsies was reported. Using inferred functional profiling of the microbiota, PSC-IBD was associated with a dysregulated bile acid metabolism with multi-omic integration indicating PSC-IBD was associated with alterations in functional networks associated with bile acid metabolism as well as cancer regulation.

Pouchitis is a common complication following ileal pouch-anal anastomosis (IPAA), estimated to affect up to 50% of patients, with a strong negative effect on QoL. Significant discrepancy exists between patient reported symptoms and endoscopic appearance of the pouch; it is also unclear whether clinical symptoms correlate with microbiota profiles. In a cohort of 233 patients who has undergone IPAA surgery, the composition of the mucosa-associated microbiota differed depending upon their clinical symptoms[19]. Patients with active inflammation also had reduced levels of Bacteroidetes. Patients who did not have active inflammation but had clinical activity also had reduced Bacteroidetes abundance. The study data also suggested that microbiota composition was associated with stool frequency, with a decrease in Bacteroidetes relative abundance seen in patients with the highest stool frequency. Further analysis of pouchitis patients was undertaken to explore whether diet and microbiota alterations contributed to pouchitis pathogenesis[20]. Patients in the lowest fruit consumption tertile (<1.45 servings per day) had the highest rate of pouchitis. Fruit consumption also correlated with microbial diversity and the abundance of various genera, including *Faecalibacterium* and *Lachnospira* as well as *Ruminococcaceae* members.

According to traditional Chinese medicine (TCM), UC can be divided into two disease syndromes Pi-Xu-Shi-Yun (PXSY; a deficiency syndrome) and Da-Chang-Shi-Re (DCSR; a sthenia syndrome). To date, defining microbiota differences between PXSY and DCSR phenotypes has not been undertaken. In a cohort of 93 subjects (30 healthy controls; 32 PXSY phenotype and 31 DCSR phenotype) microbiota composition analysis of faecal samples was undertaken[21]. The study showed that the genus *Streptococcus* was significantly increased in UC patients, in particular the DCSR phenotype, whilst *Lachnoclostridium* was increased in the PXSY group. A further study of TCM – Shen Ling Bai Zhu San (SLBZS) treatment a 10-herb composition was also shown to alter microbial community structure in the murine gut. SLBZS was shown to reinstate structural changes induced by colitis, to inhibit *Corynebacterium* and *Helicobacter* - 2 potentially pathogenic genera and to also increase numbers of the SCFA-producing bacterial genus *Blautia*[22].

The tripartite relationship between diet, the gut microbiota and IBD was explored in a study from China[23]. In a cohort of 322 participants (280 IBD: 42 healthy controls), macro and micronutrient intake and gut microbiota profiles were analysed to provide a correlation network to identify key biomarkers of IBD. Dietary intake of many vitamins and minerals were lower/deficient in IBD patients compared to healthy controls. Increased levels of *Halomonas, Lactobacillus, Shewanella* (CD), *Bdellovibrio* and *Rhodobacter* (UC) and *Bacteroides fragilis* (CD and UC) were noted. Compared to healthy controls, 22 microbial species in the UC group and 37 species in the CD correlated to diet and metabolites.

The impact of IBD treatment on microbiota composition was also the focus of several studies[24]. A small study looking at mucosa-associated microbiota profiles in Chinese CD patients (n=9) before and after induction therapy and comparing findings to healthy controls (N=6) was published[25]; although information on what induction therapy was used was not provided. Sixty-five genera were differentially abundant between active and quiescent disease states; remission was associated with reduced levels of *Fusobacteria* and increases in potential beneficial bacteria including *Lactobacillus, Akkermansia, Roseburia, Ruminococcus* and *Lachnospira.* Confirming previous studies, microbial richness increased from active disease>remission>healthy. Cruz-Lebron et al[24] compared faecal microbiota populations in Bra-

zilian CD patients treated with corticosteroid or anti-tumour necrosis factor immunotherapy (anti-TNF). An increase in Proteobacteria abundance was seen in anti-TNF patient samples alongside concomitant decrease in Bacteroidetes. Corticosteroid treatment was associated with an increased abundance of Actinobacteria. Whilst the findings from this Brazilian cohort are in agreement with previous North American/European studies, the study design did not control for disease severity with would be implicit in the different treatment modalities. Anti-TNF therapy was also the focus of a second study which analysed the faecal microbiota profiles of 2 European prospective cohorts to assess the impact of anti-TNF as well as anti-$\alpha 4\beta 7$ integrin therapy[26]. Anti-TNF therapy shifted IBD patient faecal microbiota profiles towards that of healthy controls. *In silico* metabolic profiling highlighted that metabolite exchange was significantly reduced at baseline in IBD patients and was associated with later clinical remission. Predicted butyrate synthesis, subsequently verified by metabolome analysis, was also associated with clinical remission following anti-TNF therapy. A recent study[27] also looked at microbial metabonomic profiles to assess whether metabonomic and metataxonomic profiling was useful in identifying predictive biomarkers of anti-TNF response in CD. Collecting various biological samples (blood, urine and stool) from luminal CD patients prior to commencing anti-TNF therapy and also following 3-months of treatment, highlighted that several metabolic biomarkers involved in lipid, bile acid and amino acid pathways may well serve as useful biomarkers for predicting treatment response.

The impact of IBD therapies on the fungal component of the microbiota (mycobiome) is currently limited. Jun et al[28] assessed the effect of 5-aminosalicylic acid (5-ASA) on the gut mycobiome in a cohort of 57 UC patients, including 20 treatment-naïve subjects. Whilst there was no significant difference in mean age between the treatment-naïve and 5-ASA groups, there were significant sex-dependent differences (60% *vs*. 24% male respectively). Ascomycota was the dominant phylum in all samples, following 5-ASA treatment, Ascomycota and *Wickerhamomyces* levels increased whilst *Scytalidium, Fusarium, Morchella* and *Paecilomyces* all decreased in both inflamed and uninflamed mucosae. The bacteria/fungal dynamic was seen to be interrupted in inflamed mucosae with 5-ASA treatment seeming to restore the bacteria/fungal status.

Fungal microbiota signatures were also assessed in PSC[29]. Faecal microbiota signatures of PSC patients with and without UC were assessed alongside healthy subjects which showed that alongside altered bacterial diversity, PSC patients also have dysbiotic fungal signatures, including increased species richness, increased *Exophiala* abundance, and decreased *Saccharomyces cerevisiae* levels. Correlation network analysis also indicated that PSC patients exhibited a strong disruption in bacterial/fungal networks, suggesting an alteration in interkingdom crosstalk.

Alterations in intestinal virome communities are also important in UC pathogenesis. To add to the current knowledge, Zuo et al[30] performed a deep metagenomics sequencing study of virus-like preparations alongside bacterial community analysis (16S rRNA sequencing) of rectal mucosa from 167 subjects (91 UC: 76 healthy controls). UC mucosal samples comprised a high abundance but low diversity of *Caudovirales* bacteriophages. *Escherichia* and *Enterobacteria* phage were also present in higher numbers in UC mucosa samples compared to healthy controls. In addition, interkingdom correlations between viruses and bacteria were significantly depleted in UC patient samples.

MECHANISTIC STUDIES

Repolarisation of immune cells, including macrophages, in response to bacterial stimuli is an area of increasing interest. A study[31] exploring the link between *Fusobacterium nucleatum* and proinflammatory M1 macrophage polarisation in the context of colitis development was undertaken. *F. nucleatum* levels are increased in UC patients with *F. nucleatum* load positively correlating with M1 macrophage levels, Mayo scores, as well as CRP and IFN-γ levels. *F. nucleatum* feeding in a DSS-induced colitis model resulted in increased M1: M2 macrophage ratios. The study also delved into the molecular mechanisms which showed that *F. nucleatum* induced macrophage mobilisation promoting skewing towards an M1 phenotype occurs *via* the AKT2 signalling pathway. Activated macrophages can then secrete large quantities of inflammatory factors, such as TNF-α, IFN-α, and MCP-1, which in turn recruit more macrophages

into sites of inflammation, damage the mucosal barrier, promote bacterial translocation and eventually lead to increased disease progression.

Based on the intricate relationship between the gut microbiota and the host immune system, characterising of microbial signatures associated with immune cells and comparing these signatures to mucosa-associated signatures may shed new light on IBD aetiology. Using a new approach that allowed isolation of lamina propria cells from mucosal biopsies followed by magnetic-bead based cell sorting; Dheer et al[32] was able to show that phagocyte-associated microbiota was enriched in Proteobacteria, with CD and UC patient phagocyte-associated microbiota showing different microbial composition from their mucosal sample counterparts but also distinct disease centric profiles.

Predictive metabolomic approaches continue to be an essential step towards understanding how gut microbial metabolism affects IBD patient health. However, all approaches have limitations based on poorly annotated databases and insufficient rigorous (independent) validation. A new computational framework, called MelonnPan (Model-based Genomically Informed High-dimensional Predictor of Microbial Community Metabolic Profiles) was applied MelonnPan to two independent gut metagenome data sets comprising >200 patients with Crohn's disease (CD), ulcerative colitis (UC), and healthy control (HC) participants[33]. Both cohorts had independent metagenomic and metabolomic datasets. MelonnPan successfully predicted a large number of experimentally identified metabolites, significantly outperforming existing prediction tools.

CLINICAL STUDIES PEDIATRICS

A longitudinal study analysing the microbiome in paediatric patients diagnosed with Crohn's Disease (CD) was undertaken by Kasal et al[34]. Within this cohort (204 CD) first diagnosis, relapse, remission, and control samples were found to have differing microbial composition. Five bacterial species (*Clostridium symbiosum, Clostridium clostridioforme, Megamonas funiformis, Eubacterium fissicatena*, and notably *Hespellia porcina*) showed strong association with relapse and another ten (*Brachyspira aalborgi, Klebsiella pneumoniae Morganella morganii, Lactobacillus gasseri, Akkermansia muciniphila, Bacteroides eggerthii, Enterococcus casseliflavus, Shigella sonnei, Lactobacillus casei, Pseudoflavonifractor capillosus*) with remission. Additionally, it could be seen that the microbiota of patients in remission (post-treatment) did not return to a healthy state, nor did the microbiome of relapse patients' return to the profile seen at first diagnosis. This supports the idea that disease induces long-term changes to the gut microbiota. Interestingly, gender-specific differences were also observed in the CD first diagnosis group, hypothesised to be due to hormonal influences on the microbiota[34]. The Lancet published a study which used a cohort of 428 treatment naïve children diagnosed with Ulcerative Colitis (UC) to develop a clinical prediction model for 52-week corticosteroid-free remission. This was defined as clinical remission, with no corticosteroid use, for four weeks or longer immediately before week 52, no medical therapy beyond mesalazine, and no colectomy. The secondary outcome was escalation to anti-TNFαtherapy within the 52 weeks. Additional outcomes were escalation to immunomodulators only, and colectomy. The primary model developed used baseline clinical and laboratory factors, as well as week 4 response to standard therapy to predict treatment success. Rectal gene expression and gut microbial factors were found to improve the ability to predict clinical outcomes, beyond initial disease severity and laboratory characteristics, and provide insight into the biological reasons for disparate patient courses[35].

Three separate papers on the impact of enteral nutrition (EEN) on the microbiome were published. One comparing commensal bacterial strains (*Bifidobacteria, E. coli,* and *Lactobacilli)* ability to grow, *in vitro,* on three different kinds of enteral nutrition. All strains (n=19) grew to counts greater than CFU/ml. Comparing the growth of pure commensal bacterial strains on the different formulas, no significant differences in *Bifidobacteria* or *E. coli* growth could be seen although *Lactobacilli* growth differed. Additionally, the study analysed the total counts of anaerobic bacteria seen in faecal samples from 15 children with CD before and after 6 weeks of EEN treatment. A comparably reduced amount of cultured *Bifidobacteria* was observed in children with CD. Overall anaerobic bacterial numbers seemed unaffected before and after treatment, but individual shifts in commensal microbial bacteria could be seen[36]. The effects of EEN

vs. steroids was examined in a cohort of 19 patients with new-onset active CD. Both groups reached remission at a similar rate, but assessment at week 8 showed increased *Ruminococcus* and an increased proportion of *Clostridium* in patients with EEN-induced remission. Additionally, mucosal healing rate increased compared to patients with steroid-induced remission[37]. As EEN, currently, is the sole dietary treatment for CD there is a need for novel treatment options. Svolos and colleagues looked at individualized food-based diets (CD-TREAT), with similar composition to EEN, and their effect on the gut microbiome, inflammation, and clinical response in three different cohorts (25 CD adults, 5 CD kids, rat model). In adults, the CD-TREAT diet was found easier to comply with and with similar effects on fecal microbiome composition, metabolome, mean total sulfide, pH, short-chain fatty acid, and butyrate. Similarly, in children 80% showed clinical response, 60% entered remission, and overall a decrease in fecal calprotectin was seen. The human results were replicated in the animal model, where CD-treat was seen to produce similar changes in bacterial load, short-chain fatty acid levels, microbiome, and ileitis severity[38].

Presence of antibodies to *Saccharomyces cerevisiae* (ASCA) can be seen in up to 60% of patients with CD, but associations with gut microbiota is so far unexplored. During this period an Australian study investigated the microbial diversity and clinical characteristics of ASCA positive and negative CD patients. ASCA status was found to have no effect on the alpha and beta diversity but compared to noninflammatory bowel disease controls an overall decrease in diversity was observed. Microbial richness was similar across the groups, with *Ruminococcus torques* and *Yersinia entercolitica* significantly associated to ASCA-positivity and *Enterobacter cloacae* and *Faecalibacterium prausnizii* to ASCA-negativity. Additionally, in this cohort of patients ASCA positivity was associated with older age, ileocolonic disease, and long-term risk of surgery[39].

In Gut, two independent papers within paediatrics IBD were published during the reporting period. Tan et al[40] demonstrated the benefit of oral vancomycin (OV) in 17 children with primary sclerosing cholangitis ulcerative colitis. Overall, OV improved Paediatric Ulcerative Colitis Activity Index (PUCAI) scores and decreased faecal calprotectin to <200. Normalisation of histological inflammation was also observed in nine patients. Importantly, no vancomycin-resistant *Enterococcus* was acquired during the treatment. The second study investigated infants born to mothers with IBD by inoculating germ-free mice with stool from mothers and infants (with and without IBD). Maternal samples were collected each trimester and following delivery, while infant stool was collected at five different timepoints. In IBD positive mothers the first and second trimesters was characterised by lower αdiversity and changed microbial composition. In infants, maternal IBD status was found to be the main predictor of microbial diversity, with enrichment in Gamma Proteobacteria as well as a loss of *Bifidobacteria* seen. In the mouse model with IBD-associated dysbiosis fewer class-switched memory B-cells and regulatory T-cells were found in the colon[41].

The effect of faecal microbial transplantation (FMT) on paediatric cohorts was also reported on during this period. Following FMT, body mass index (BMI) in children with *Clostridioides difficile* infection or UC was calculated every third month for a year, analysing treatment effect on weight. No statistically significant change was seen[42]. As FMT is a new treatment option for paediatric CD patients, there is a need for a defined protocol – which Pai and colleagues aimed to develop. A pilot study to assess outcomes of FMT using both colonoscopic infusions and oral capsules was proposed. The primary outcomes of the study would be to asses feasibility (including, patient recruitment, sample collection, and rates of adverse events) whiles the secondary outcomes would address clinical efficacy (including change in clinical response, change in urine metabolome and change in microbiome)[43].

CLINICAL STUDIES/FMT

As the administrative route of FMT moves towards decreased invasiveness, more studies are analyzing the use of nasogastric delivery and oral capsules. A prospective pilot study protocol to assess clinical response, acceptability, and safety of nasogastric *vs.* colonoscopic delivery was published. The STOP-Colitis pilot trial, which is yet to be completed aims to determine the feasibility of using one of the administrative routes in a future randomized double blind placebo-controlled FMT trial[44]. A further study protocol for a randomised con-

trolled trial investigating the effect of a low FODMAP diet on UC patients and their gut microbiota was also published[45]. Three independent studies focused on long-term administration of FMT *via* oral capsules in UC cohorts. Overall improved disease symptoms, without need for therapy escalation, and high patient tolerance were reported[46-48]. Cold et al[46], evaluated the use of multidonor FMT capsules in seven patients, receiving 25 capsules daily for 50 days, directly following completion of treatment and six months after. A transient improvement in symptoms was seen, with short term improved faecal calprotectin levels and stool microbial diversity as well as an improvement in quality of life measurements[46]. As a maintenance treatment, after colonoscopic administration, FMT was reported to be well tolerated in 13 patients receiving ten capsules weekly for six weeks[47]. In another patient cohort with active UC, capsule based long-term multi-donor FMT was found to be safe and effective in modulating microbial diversity and structure. Administration via capsules was also found to increase safety and cost effectiveness, due to decreased invasiveness[48]. The majority of the clinical FMT studies published during the reporting period focused on FMT for UC patients, with the general consensus being that FMT is a safe and effective treatment option for this cohort. By analyzing pooled studies long-term safety and efficacy could be determined, with current improvements in donor stool preparations as well as the increased use of colonic transendoscopic enteral tubing found to have reduced adverse events[49].

A prospective clinical study looked at using FMT in a cohort of 20 UC patients, administering five rounds of treatment *via* gastroscopy. Levels of inflammatory markers (erythrocyte sedimentation rate, ESR), C-reactive protein, colonic musical score, Mayo scores, diarrhea score, abdominal pain score, pus and blood stool score, bloody stool score, musical manifestation scoring were all measured before and after treatment. Diarrhea score, abdominal pain, and bloody stool score showed a significant downward trend following FMT. A decrease in clinical index scores for intestinal mucosal lesions and Mayo scores could also be discerned. Using 16S rDNA sequencing, differences in patient and donor intestinal microbiota profiles was also determined[50]. In a cohort of nine UC patients, FMT, as an adjuvant treatment, was found to be well tolerated in UC and recurrent UC, with multiple infusions improving results[51]. FMT was also shown to promote maintenance of steroid free clinical remission to a higher degree than placebo in 61 UC patients in clinical remission. Furthermore, higher endoscopic and histological remission could be seen[58]. A study from China aimed to elucidate the extent and process of microbial engraftment in IBD patients (UC *vs.* CD) after single dose FMT-treatment. Three days following FMT a universal increase in *Bacteroides* was seen, together with individual changes in microbiome composition. Marked differences in colonization success were observed between UC and CD recipients who shared a donor, with UC retaining a higher amount of donor specific single site allelic variations (SNVs). Overall gut metagenomic profiles, on species and strain level, showed that CD presented lower bacterial colonization than UC after treatment. Additionally, different bacterial strains were found to display disease-specific displacement advantages under the two disease statuses[52]. New donor screening guidelines were proposed, after two UC patients with recurrent *Clostridioides difficile* infection tested positive for *Clostridium perfringens* following FMT treatment[53]. Two independent studies focused on FMT in pouchitis. A pilot study, with 19 patients enrolled, was published by Selvig et al[54] which assessed the effect of single FMT administration by pouchoscopy. The treatment was found to have a tolerable short-term safety profile and was associated with a decrease in bowel movement, but no major endoscopic or histological changes were reported. In a small study of three Japanese patients with chronic pouchitis the efficacy of FMT was found to be safe but with limited effect, with one patient showing clinical response but no patients reached clinical remission[55].

FMT as a novel treatment is being explored in PSC patients because of the known interactions between genes, mucosal immunity, immune tracking, and the microbiome. A pilot clinical trial demonstrating FMT safety in ten patients with PSC was conducted by Allegretti et al[56], showing improved alkaline phosphatase levels as well as increased bacterial diversity and engraftment in all ten participants (9 UC, 1 CD). The observed increase in bacterial diversity persisted 24 weeks following administration, indicating that single FMT may be sufficient to induce engraftment in PSC. Single dose colonoscopic administration of FMT was also studied in a group of ten patients with CD. In this cohort FMT was found to have a modest effect, with two participants requiring escalation of therapy due to adverse events. General trends showed more *Lachnospiracae* in the responders and increased *Ruminococaceae* and *Bacteroides* in non-re-

sponders[57]. Further studies are needed to fully evaluate FMT safety in these two conditions. A large study by Paramsothy et al[58] enrolled 81 patients with active UC, administering colonoscopic infusion of FMT - followed by intensive multidonor FMT *vs.* placebo enemas and optional open-label FMT. Stool samples were collected at screening, twice during the treatment period, and eight weeks following completion. Large bowel biopsy samples were also collected at entry, at completion of blinded therapy, and at the end of open-label FMT when applicable. After FMT an increased microbial diversity and altered composition could be seen, with the greatest diversity seen in those who achieved remission. Notably patients in remission had enrichment of *Eubacterium hallii* and *Roseburia inulivorans,* as well as increased levels of short-chain fatty acid biosynthesis and secondary bile acids. In patients that did not achieve remission an enrichment of *Fusobacterium gonidiaformans, Sutterella wadsworthensis* and *Escherichia* species could be seen, together with increased levels of heme and lipopolysaccharide biosynthesis. Associations between donor stool contents and outcomes were also seen, with *Bacteroides* associated with patient responding to FMT and *Streptococcus species* associated with non-responders[58].

A study[59] looking at persistent diarrhea in CD patients after confirmed mucosal healing was published. This large study (215 IBD patients and 48 controls; 590 tissue biopsies) showed that in IBD patients, despite endoscopic evidence of disease improvement/remission, microbial community composition in CD patients remained dysbiotic with lower alpha-diversity scores in patients with residual symptoms, including persistent diarrhea.

A further study using human tissue samples (21 CD) and an *in vivo* mouse model, looked at changes to intestinal mucosa (inflamed CD *vs.* non-inflamed CD) upon contact with healthy donor stool suspension. Microbial load in mucosal samples were found to impact treatment outcome, with initial low load shifting in composition towards that of the donor stool (increased relative count of *F. prausnitzii*) and inducing secretion of anti-inflammatory cytokine IL-10. Initial high load was shown to be less prone to capture donor microbes (again, specifically *F. prausnitzii*) and were associated with induction of pro-inflammatory immune response. These findings indicate that stratification of FMT recipients, on the basis of tissue microbial load, could be used as a strategy to ensure successful colonisation[60]. Another smaller study analysed the response to FMT in CD patients. In this randomised, single-blind, sham-controlled pilot trial the patients received either FMT or placebo treatment after entering clinical remission using oral corticosteroid treatment[61]. None of the subjects reached the primary endpoint, >60% similarity with donor microbiome at week 6, but a statistically non-significant increased rate of steroid free clinical remission could be seen in the FMT group. Notably, lack of microbial engraftment was associated with failure to maintain clinical remission. Due to the cohort size further studies are needed to elucidate the therapeutic effect of FMT in patients with CD.

A meta-analysis of four randomized control trials and two cohort studies was undertaken, investigating general clinical remission, clinical response, and steroid-free remission of FMT in UC cohorts. FMT was found to be significantly more effective than placebo on clinical remission and clinical response but no significant differences could be seen on steroid-free remission or serious adverse events[62].

One dietary intervention study was also published, looking at the effect of 8 week mango intake[63]. This small study (10 IBD patients), showed that mango intake reduced IBD disease activity and mitigated intestinal inflammation through proinflammatory cytokine reduction (IL-8, GRO and GM-CSF) as well as increasing the abundance of various beneficial bacteria which can indirectly impact on SCFA level production through bacterial cross-feeding mechanisms.

ANIMAL STUDIES/FMT

A number of studies investigated the effect of FMT on the outcome of colitis in the past year[64-68]. Spalinger et al[66] showed in their first study that protein tyrosine phosphate non-receptor type 22 (PTPN22) variant 619W, which is associated with IBD, affects intestinal inflammation by modulating the gut microbiome. They investigated the therapeutic effect of co-housing DSS treated mice with healthy mice, thereby allowing for transfer of the normal microbiota to colitic mice[67]. Co-housing resulted in quicker mucosal recovery and normalisation of the gut microbiota. DSS-treated mice housed with other DSS-treated mice as opposed to healthy WT

mice, had an increase in *Akkermansiaceae*. Gavage of caecal contents from healthy to colitic mice had the same effect, but they were not able to determine individual species associated with this faster recovery. However, the same recovery was not observed in PTPN22 $^{-/-}$ mice, as their microbiota did not normalize and was distinct form healthy WT, even after co-housing. The study highlights the importance of host genetics and environment on gut microbiota composition.

Another study[64] revealed that FMT provided a therapeutic effect on DSS-induced colitis by reducing the expression of pro-inflammatory genes and increasing the expression of IL-10. This was associated with an increase in more beneficial bacteria, and subsequent decrease in species that are over-represented in human IBD, including *Parabacteroides goldstenii, Bacteroides acidifaciens, Escherichia-Shigella*, and *Blautia* genera. A further study[69] used both single-donor intensive and nonintensive FMT experiments using stool from either IBD patients in remission or healthy non-IBD controls in a mouse model of Crohn's disease (CD)-like ileitis (SAMP1/YitFC mice). The findings highlighted variability in the development of ileitis with stool from remission patients is not necessarily inducing IBD-like pathology. The authors therefore highlight the need for a more personalised approach to patient screening in order to ascertain the inflammatory potential of an individual's gut microbiota.

ATTENUATION OF COLITIS USING DIET OR DIET CONSTITUENTS

The vast majority of animal studies used dextran sulfate sodium (DSS) to induce colitis in rodents, because the clinical and histopathological features of DSS-induced colitis reflect those seen in IBD. A total of 20 studies published in the past year reported that dietary components or extracts attenuated DSS colitis in mice. One study used rats instead of mice[70]. These studies investigated the effects of Chinese herbal preparations or tea[71-76]; flower and plant constituents[77-83]; fruits or their derivatives[84-86]; honey constituents[70,87]; mushroom[88]; dietary manganese[89]; fucose[90]; cellulose[91] and iron[92]. In general, these studies report an improvement in gut microbial community composition or dysbiosis, decreased inflammation, and a decrease in disease activity indices (DAI). Only one study between our search dates reported an exacerbation of DSS-induced colitis, when animals were fed animal protein, which promoted inflammation and enhanced innate immune responses[93].

Another study[94] reported mixed results for dietary fibres, cellulose, inulin and pectin. They used IL-10 receptor neutralization to mimic acute and chronic colitis, to assess the effect of different fibre types on the gut microbiota and disease activity. They found that dietary pectin protected against colitis, whereas inulin promoted it. Inulin consumption was associated with an increase in gamma-Proteobacteria, as well as bacteria that metabolise fibre into SCFA, including *Lachnospiraceae, Ruminococcaceae*, and *Clostridium* cluster XIVa. Inulin feeding was associated with increased butyrate production, while pectin was associated with increased acetate. Interestingly, when they suppressed intestinal and caecal butyrate using hop beta-acids, they observed an attenuation of chronic colitis. These results are counter-intuitive, and require further evaluation, because SCFAs are thought be anti-inflammatory.

Slc5a8, is a sodium monocarboxylate transporter for SCFAs. Sivaprakasam et al[95] showed that under low-fibre diet conditions in Slc5a8-null mice, bacterial dysbiosis resembles that of mice with an inflammatory condition. Two other DSS colitis studies analysed SCFA profiles and found increased levels in mice treated with either *Pleurotus eryngii* (mushroom) or cinnamon essential oil[81,88], including an increase in SCFA-producing bacteria (*Alloprevotella* and *Lachnospiraceae_NK4A136_group*)[81]. Increased levels of SCFA were associated with attenuation of colitis in the mice given dietary supplements.

One study[80] conducted metabolomics, showing that gluco-related metabolism and bile acid metabolism, which requires bacteria, were increased when colitic mice were given gallic acid, a plant phenol found in fruits and vegetables. Mice not treated with gallic acid lacked beneficial species of bacteria such as *Lactobacillaceae* and *Prevotellaceae* and had increased Proteobacteria. An expansion of Proteobacteria, including *E. coli*, is often observed in mice with DSS-induced colitis and humans with IBD. Proteobacteria levels were shown to decrease with supplementation of multiple dietary constituents[73,82,92], or was not reported to be increased with dietary supplementation.

Findings from other studies reporting an attenuation of colitis with dietary supplement included: an improvement in intestinal permeability when DSS-treated mice were provided sufficient dietary manganese[89]; a decrease in pro-inflammatory cytokine production when mice with DSS-induced colitis were provided with a dietary supplement, including daphnetin[72] and *Bruguiera gymnorrhiza*[82]. Daphnetin was found to regulate Treg/Th17 balance, and *Bruguiera gymnorrhiza* suppressed NF-kappaB activation, suggesting that the immune system and inflammation play a role in tipping the microbial communities to a dysbiotic state.

Studies employing other methods of colitis induction also demonstrated attenuation of colitis when a dietary constituent was introduced. One study used the *Citrobacter rodentium*-induced colitis model, and showed that supplementation with quercetin, a flavonoid found in plants, suppressed pro-inflammatory cytokine production and was associated with increased levels of *Bifidobacterium, Bacteroides, Lactobacillus*, and *Clostridia*, with a concurrent reduction in *Enterococcus* and *Fusobacterium*[96]. Supplementation with milk oligosaccharides also provided anti-inflammatory effects and led to an increase in *Ruminococcus gnavus* and propionate in IL10$^{-/-}$ mice[97]. Another study used acetic acid to induce colitis and found that supplementation with a purified polysaccharide from *Hericium Erinaceus* (monkey head mushroom), EP-1, reduced the extent to which microbial communities changed after colitis was induced, and was associated with increased SCFA production and reduced inflammation. Another model of colitis; the 2,4,6-Trinitrobenzenesulfonic (TNBS)-induced rat model, was used to assess the effect of *Myrciaria jaboticaba* (Brazilian Berry) peel aqueous extract, EJP, on the outcome of colitis[98]. EJP treatment decreased colitis symptoms, such as weight loss, colon length, and markers of inflammation. The caecal microbiome of colitic rats treated with EJP had increased levels of *Lactobacillus*, and, Enterobacteria levels remained unchanged relative to healthy animals. Butyrate and acetate production were also increased in EJP-treated animals when compared to animals treated with a common IBD anti-inflammatory medication, mesalazine. Both mesalazine and long-term EJP treatment protected against oxidative damage.

A further study assessed both the *Citrobacter rodentium*-induced colitis model and a TNBS mouse model to evaluate the immunomodulatory properties of 2 potential probiotic strains, a *Bifidobacterium animalis* spp. *lactis* Bl5764 and a *Lactobacillus reuteri* Lr5454 strain[99]. Whilst both strains were shown to ameliorate colitis symptoms in the models, the mechanism of action of the strains was very different, highlighting the need to assess specific strains rather than implying functional potential from other strains.

Animal studies investigating the effect of bioactive dietary constituents mostly report some benefit in the context of colitis. It is unknown whether this is due to negative studies not being published. It is likely that many of these dietary compounds will be trialled in humans with IBD.

OTHER COMPOUNDS AND FACTORS THAT ATTENUATE ANIMAL COLITIS

As with diet, the vast majority of studies investigating the effect of compounds on the outcome of colitis report positive results and use the DSS model of colitis. Compounds found to attenuate DSS-induced colitis included bacterial beta-glucuronidase, nitrate, acetylcholinesterase inhibitor pyridostigmine bromide, aquaporin 4 deficiency, probiotics obtained from stool of healthy individuals, unconjugated bilirubin, platinum nanoparticles, prescription opioid, phloretin antioxidant, and butyrate-releasing xylan derivatives[94,100-108].

The vast majority of bilirubin released into the gut through bile is in the conjugated form. Beta-glucuronidase catalyses the deconjugation of conjugated bilirubin. The diverse gut microbiota beta-glucuronidase (GUS) enzymes are the main source of glucuronidase in the gut. The study by He et al[100], which explored the role of beta-glucuronidase in DSS colitis, found that beta-glucuronidase attenuated DSS-induced colitis, coupled with a marked decrease in the digestive proteases trypsin and chymotrypsin, reduced bacterial translocation, attenuated weight loss, increased gut barrier function, and reduced inflammation. Further work is needed in order to determine whether or not beta-glucuronidase confers benefits in humans with IBD. Singh et al[94], found that increased mucus production was associated with acetylcholine availability, which was increased by Pyridostigmine bromide (PB). PB treatment was associated with attenuated DSS-induced colitis, and protected against the loss of particular bacteria, including commensal *Clostridia* and *Flavobacteria* in DSS-treated mice. However, it also increased levels of taxa that may not be as beneficial, such as *Fusobacteria* and *Erysipelotrichia*.

Only one study used a non DSS model of colitis. Pagano et al[109] used a DNBS model of colitis and showed that cannabidivarian (CBDV), a non-psychoactive phytocannabinoid, attenuated inflammation via transient receptor potential ankyrin type-1 (TRPA1), which plays a role in inflammation. DNBS plus CBDV treatment was associated with a trend toward a reduction in Firmicutes, while CBDV treatment alone (without colitis) was associated with a significant increase in Bacteroidales. They also went on to show that CBDV attenuated colitis in DSS-induced colitis.

A study assessing the impact of age on mucosal barrier function was also reported during the assessment period[110]. Using mouse models at different ages, Liu et al[110] were able to show that expression of tight junction proteins reduced with increasing age alongside compositional differences in the gut microbiota. Aging also led to a more severe disease presentation following DSS challenge.

METHODOLOGICAL CONSIDERATIONS FOR IBD RESEARCH

A few studies added to our understanding of the importance of having methodologically robust animal protocols and designs to study the microbiota in colitis. These studies highlighted the role of environment on the pattern of inflammatory lesions[111], the role of sex differences in the microbiota of mice[112], the importance of sampling fecal contents from the correct anatomical location to show disease association[113]. Son et al[112] showed that there were sex differences in the microbiota of WT female and male mice, but not IL10$^{-/-}$ mice. Proteobacteria was significantly increased in female IL10$^{-/-}$ mice than female WT mice. At the species level, *Lactobacillus murinus, Bacteroides acidifaciens*, and *Helicobacter hepaticus* were significantly increased in IL10$^{-/-}$ mice compared to WT mice. PICRUSt (predicted functional) analysis showed that the relative abundance of beta-glucuronidase (K01195) was higher in female IL10$^{-/-}$ mice than that in female WT mice.

PSYCHIATRIC DISORDERS AND THE COLITIC MICROBIOME

One study in the past year found that intestinal autophagy was associated with pychosocial stress and the outcomes of colitis[114]. Another study by Takahashi et al[115] explored whether or not the biogenic lactic acid bacterium (LAB), Enterococcus faecalis (EF-2001), could reverse depressive-like behaviour in DSS-treated mice. IBD patients have higher rates of depression and anxiety, and Lactobacillus, which converts sugars to lactic acid, are associated with major depressive disorder. They therefore hypothesized that LAB may be beneficial. They treated mice with EF-2001 for 20 days and this was associated with decreased hippocampal and rectal inflammatory cytokines. However, the link between LAB, inflammation and depression remains unknown.

MICROBIOTA REGULATION OF IMMUNE RESPONSES IN IBD COLITIS MODELS

Several studies[65,116-120] investigated the role of the immune system and its association with the microbiome in colitis. Goethel et al[117] conducted a study aimed at determining whether or not the microbiota of Nod2$^{-/-}$ mice responded in the same way to antibiotic treatment as their WT counterparts. They found that recovery of the microbiota of Nod2$^{-/-}$ mice following amoxicillin treatment was delayed, and that reduced microbial diversity was still observed 14 days post-treatment. Nod2$^{-/-}$ mice treated as neonates had increased susceptibility to colitis, but not adult Nod2$^{-/-}$ mice. Neonatal susceptibility was transferrable by FMT, resulting in altered T cell populations and worsened colitis.

Another study[116] used a Nod2$^{-/-}$ mouse model to investigate possible CD1d modulation of DSS-induced colitis. CD1d is expressed on the surface of human antigen presenting cells. Consistent with previous studies, they found that binding of glycolipid alpha-galactosylceramide to CD1d protected against experimental colitis. They also showed that the microbiome of Nod2$^{-/-}$/CD1d$^{-/-}$ mice differed significantly from co-housed WT, Nod2$^{-/-}$, and CD1d$^{-/-}$ mice, with increased colonisation of *A. muris*. They attributed these changes to dysfunction of Paneth cells, including abnormal degranulation, which they observed in the Nod2$^{-/-}$/CD1d$^{-/-}$ mice. Geesala et al[116] showed another plausible link between the immune system, microbiota and colitis. A recently identified serine protease, Rhomboid 5 homolog 2 (RHBDF2), is thought to be a crucial regulator of the mem-

brane-anchored metalloprotease (ADAM) 17, which is capable of cleaving membrane-bound TNF, by releasing it in its biologically active soluble form. Geesala et al[116] revealed that loss of RHBDF2 in IL-10 deficient mice results in a much higher susceptibility to and exacerbation of colitis, and is associated with an exaggerated Th1 immune response, involving CD4+TCRB+Tcells. Concurrent disturbances in the gut microbiota were also observed, including an increase in the mucin degrader *Bacteroides acidifaciens* and the colitogenic pathogen, *E. coli*. Expansion of *E. coli* is often reported in patients with IBD, therefore the loss of soluble TNF through a lack of RHBDF2 may play a role in microbial community disturbances and should be explored further.

Bajic et al[120] investigated whether the gut microbiota is involved in intestinal Reg3B expression. Using broad and selective antibiotic treatments they were able to demonstrate that rifaximin treatment resulted in a reduction in intestinal Clostridial species as well as a reduction in Reg3B expression, butyrate and propionate. SCFA regulation of Reg3B was then assessed using an organoid model which demonstrated that propionate levels directly impacted on Reg3B expression but not butyrate or acetate. Further evidence for the important role of propionate in the context of IBD was reported by Ormsby et al[121] who demonstrated that the presence of propionic acid results in altered virulence and resistance in adherent invasive *E. coli.*

USE OF BACTERIA, VIRUSES, OR THEIR PRODUCTS TO MODULATE COLITIS

The use of single microbes or their products to modulate colitis was explored in eight studies. One of these studies explored the effect of a bioactive bacterial product, SEL001, from *Lactobacillus sakei*[122]. Four studies explored the impact of treatment with single bacterial strains, including *Bacillus lichenformis*[123], *Lactobacillus plantarum*[124], *Lactococcus lactis*[125], *Akkermansia muciniphila*[126]. All studies reported an improvement in gut microbiome community balance. A reduction in pro-inflammatory cytokines was observed in three of the studies[122,124,126], and a reduction in circulating endotoxin and concurrent decrease in Bacteroidetes when L. plantarum strains were administered[123].

One study investigated the role of a single species in inducing rather than treating colitis. Lengfelder et al[127] used a germ free IL10$^{-/-}$ mouse model to investigate the role of *Enterococcus faecalis* in inducing colitis. They showed that *E. faecalis* gene expression and its ability to cause colitis is dependent upon the microbial community in the colon, as it had protective effects when part of a consortia of bacteria, but not when mono-colonisation was performed. *Enterococcus faecium* isolated from patients with UC, but not healthy donors, was also shown to promote colitis in another study, which also used IL10$^{-/-}$ mice[128]. These studies highlight the fact that colitis and IBD are multifactorial diseases involving complex interactions between host and microbes.

One study explored the role of the microbiome in susceptibility to virus induced colitis[129]. Using a gnotobiotic IL10$^{-/-}$ mouse model, this study investigated the ability of bacteria to alter the course of murine norovirus (MNV)-triggered colitis. They found that MNV-induced pathology was dependent on the presence of bacteria, as germ-free and antibiotic treated mice do not develop inflammation after MNV infection. However different consortia of bacteria differentially influenced the outcome of MNV infection. The addition of segmented filamentous bacteria to one consortium abolished MNV-induced colitis, whereas no change was observed for the other consortia. SFB was shown to enhance intestinal barrier function via increased mucus secretion, and higher expression of tight junction proteins, antimicrobial peptides, and pro-inflammatory cytokines. This study highlights the complexity of gut microbial communities and the need to study the effects of multiple organisms within the same ecosystem.

CONCLUSIONS

Despite significant progress in defining the role of the microbiota in IBD, there are still significant knowledge gaps that require further investigation. Additional large longitudinal well-phenotyped cohort studies that include IBD patients of all ages and all disease stages are essential to further elucidate the interrelation ship between the host, the disease and the environment including the microbiota. These studies need to include appropriate controls both in terms of healthy subjects but also be controlled for factors including geography, treatment and diet. In addition, continued appreciation of the collective microbiota is required.

Conflict of Interest

The authors declare that they have no conflict of interests.

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