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The Gut Microbiota and Gut Disease

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The relationship between the structure and function of the gastrointestinal microbiota, health, and gut disorders is increasingly recognised. This has been facilitated by recent advances in sequencing technologies that allow for deeper and more complex examination of this vast ecosystem. As a consequence, microbial manipulation and microbiota-targeted therapies (MTTs) are now emerging.

This complex microbial community includes bacteria, protozoa, archaea, fungi, and viruses. Shotgun metagenomic sequencing of faecal flora enables detection of microbe abundance and taxonomic profiling of organisms down to species and strain level by gene sampling. Additionally, new bacterial culturing techniques have enhanced our ability to characterise bacteria phenotypically and add to the precision of metagenomic sequencing through enhancing reference genome databases[1]. These new technologies enable functional analysis through metabolomic, transcriptomic and proteomic profiling that extends far beyond the reach of conventional methods. The functional roles of, and interrelations between, community members and their direct interactions with the host immune system can be analysed[2].

The bacterial component consists of five major phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria and Verrucomicrobia. Their functions include digestion of dietary residues, maintenance of epithelial integrity and function, host protection through maintenance of the mucosal barrier, and interaction with the host immune system[3]. Physiological functions derived from the gut microbiota reach distant organs through the circulation of several metabolites and the gut "endocrine" system[3].

Microbiota development begins *in utero* and takes shape in the early years of life. Its maturation evolves according to environmental factors including geographical location, mode of delivery, antibiotic exposure and breastfeeding[4]. After the first few years of life the microbiota becomes more stable and 'adult-like' in its composition. Diversity and composition vary between individuals, and within individuals, and may fluctuate over time depending on environmental conditions[4]. This makes the establishment of normal reference ranges challenging and despite advances in sequencing and culturing technologies this aspect of defining "normal" remains a difficult area to examine.

The structure and function of the gut microbiota may play a key pathophysiological role in the rapid rise of metabolic and immune-mediated disorders that has occurred in 'western' populations over the last 50 years, and more recently in the developing world[3]. Epidemiological studies suggest that a

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wholly genetic basis is unlikely for these conditions and implicate impaired gastrointestinal microbial homeostasis. Pathobionts are over-represented in these conditions, suggesting that environmental changes allow commensals with pathogenic potential to proliferate and dominate, rather than extrinsic "culprit" pathogenic organisms "infecting" the host[3].

Studies of germ-free animals has provided further insights into the microbiota-host immune system interface. Germ-free mice have impaired development of gut-associated lymphoid tissue, decreased IgA production, defective T cell regulation and a lack of antagonising organisms[3]. The infusion of microbiota from diseased to germ-free mice has led to the transfer of disease phenotypes, including inflammatory bowel disease (IBD), obesity, diabetes and primary sclerosing cholangitis (PSC)[5-7]. Disruption to the microbiota-host symbiotic relationship appears to lead to the manifestation of disease[3].

Microbiota targeted therapies manipulate the gastrointestinal microbiota in disease states in order to reduce the antigenic drive, restore the balance between pro and anti-inflammatory organisms, and alter the intestinal biochemical milieu. The goals are to restore gut microbial homeostasis, diminish dysregulated immune responses and confer beneficial effects on the microbiota's functional integrity[8]. These therapies include probiotics, prebiotics, synbiotics, antibiotics, faecal microbiota transplantation (FMT) and dietary interventions.

Extensive evidence implicates key changes in the gut microbiota in different organ systems. This review focuses on the microbiota in gastrointestinal disorders and the emerging evidence around MTTs in clinical care.

Inflammatory bowel diseases

The pathophysiology of inflammatory bowel diseases (IBD) is multifactorial. Genome-wide association studies have identified more than 200 predisposing genes, many of which are involved in the recognition and handling of gut microbes[3, 9]. Epidemiological studies have implicated environmental factors that influence the microbiota including geography, antibiotic exposures, smoking and diet[10]. An altered microbiota-host immune system interface leads to intestinal inflammation in animal models. A germ-free environment prevents the development of colitis[11], which is reversed with

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bacterial colonisation and, the transfer of suspected pathobionts and human IBD microbiota [12]. Faecal diversion, through the use of a stoma, is a standard treatment approach in Crohn's disease.

Crohn's Disease

Altered microbiota in Crohn's disease is associated with an impaired epithelial mucosal barrier, dysregulated immune responses and inflammation[13]. A microbial signature, studied in treatment-naïve paediatric cohorts, has been characterised by deceased diversity on both faecal and mucosal tissue sampling[14, 15]. A distinct mucosa-associated microbial profile was reliably associated with a diagnosis of Crohn's disease in a large cohort, which was characterised by increased abundance of *Pasturellaceae*, *Veillonellaceae, Neisseriaceae, Fusobacteriaceae,* and *Enterobacteriaceae,* and reduced abundance of *Firmicutes*, including *Faecalibacterium* and *Ruminococcus* species, *Lachnospiraceae,* and *Roseburia* species[14]. Regardless of disease location, ileal and rectal biopsies had similar power to discriminatory between Crohn's disease and healthy controls[14]. These observed bacterial changes may be causative in the pathogenesis or reflect the presence of inflammation.

A number of specific organisms have been proposed as key to the inflammatory process. Most recently *Proteus mirabilis* has been shown to be of increased abundance in Crohn's disease compared to controls, and to possess many of the functional characteristics necessary to produce inflammation. [16]. In a murine model *Proteus mirabilis* caused intestinal inflammation, and when co-cultured with epithelial cells resulted in invasion, cytokine production and cell necrosis[16].

Non-bacterial components of the microbiota also play a role in IBD pathogenesis. More recent metagenomic analyses have revealed an increased abundance of *Caudovirales* bacteriophages and *Candida* species[15]**.**

In a paediatric cohort, evaluation of the interaction between the intestinal microbiota and host have demonstrated an altered proteome characterised by reduced mitochondrial protein expression and H_2S detoxification. Further evaluation in animal models has demonstrated an increase in intestinal permeability and confirmed the colitogenic potential of these mitochondrial perturbations[13].

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Antibacterial treatments shed further light on the role of the microbiota contributing to inflammation in Crohn's disease. Imidazole and quinolones contribute therapeutic benefit in perianal fistulae[17]. Imidazoles decrease early post-operative Crohn's disease recurrence[8, 18]. In a large Australian RCT, short-term clinical benefit for inducing remission with anti-*Mycobacterium* agents including clarithromycin, rifabutin and clofazimine was demonstrated but the response was not maintained in the long term [19], however reanalysis by intention-to-treat showed a significant difference favouring the anti-*Mycobacterium* therapy arm after 12 and 24 months[8, 20].

Despite the identification of *in vitro* metabolic and immunological benefits of pre- and probiotics,[21, 22] clinical studies have not consistently confirmed efficacy. *Saccharomyces boulardii* showed efficacy in the prevention of relapse, which was later refuted by a larger double-blind RCT[8]. Studies of *E. Coli* Nissle 1917, different *Lactobacilli* and VSL#3 have not showed any clinical benefit[8].

Dietary therapy is becoming more central to Crohn's disease management, with the benefits attributable, at least in part, to changes in the gut microbiota.

Exclusive enteral nutrition (EEN), that is specially formulated liquid diet with food exclusion, is the best-established dietary treatment in Crohn's disease[8, 23]. A recent controlled trial of combined formulated enteral nutrition with phasing-in of particular whole foods demonstrated superiority compared to exclusive enteral nutrition[24]. Microbiota analysis demonstrated an association between achieving remission and a significant decrease in Proteobacteria in both dietary intervention arms [25]. In a paediatric cohort a preliminary small observational cohort study demonstrated benefit from a whole food diet mimicking the composition of exclusive enteral nutrition[23].

Central to dietary therapy in Crohn's disease is the exclusion of food additives[26]. Emulsifiers commonly used in ultra-processed food have been shown in animal studies to produce destruction of the protective enteric mucous layer, via effects on the gut microbiota[27]. In vitro studies examining a range of food additives have demonstrated that they can diminish the abundance and viability of protective gut organisms such as *Faecalibacterium prausnitzii*, and enhance the abundance and pathogenic activity of proinflammatory organisms such as *Proteus spp*[28].

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Although exclusive enteral nutrition is clinically effective, and thought to mediate benefit through microbial alterations, the nature of the latter remain unclear[29]. Reduced abundance of suspected pathogenic bacteria has been reported, but reduced abundance of the anti-inflammatory *Faecalibacterium prausnitzii* has also been demonstrated[29]. The role of food additives, including emulsifiers, present in EEN, is unclear[27].

An alternative approach to selective microbial changes is faecal microbiota transplantation, the replacement of a patient's luminal stool with stool from "healthy" donors. Two small randomised controlled trials (RCTs) in Crohn's disease are not sufficient to confirm therapeutic benefit [30, 31]. Following corticosteroid induction, faecal microbiota transplantation demonstrated a trend towards higher steroid-free clinical remission than sham FMT[30]. In another study comparing gastroscopic to colonoscopic infusion, without a placebo arm, no clinical difference was observed between the two routes of delivery[31].

Ulcerative colitis

Specific susceptibility genetic loci are associated with ulcerative colitis[9]. Environmental factors associated with pathogenesis include intake of red meat, while the consumption of fruit and vegetables, appendicectomy, smoking, and poor living conditions are associated with a decreased risk[10]. The unifying mechanism by which these factors are thought to modify risk is through changes in the gut microbiota.

The observed microbial signature associated with ulcerative colitis is distinct from both Crohn's disease and "healthy" controls. However some compositional changes are similar, including decreased diversity and abundance of *Firmicutes*, and increased representation of genera from the *Proteobacteria* phylum[15]. Increased *Alistipes massiliensis, Ruminococcus gnavus, Escherichia coli*, *Helicobacter* and *Campylobacter* species have been identified in ulcerative colitis compared to healthy controls[32].

The contribution of dietary factors to disease pathogenesis in ulcerative colitis, and their capacity to alter the intestinal microbiota, are not well established and not part of standard care. Noncomparative studies evaluating exclusion diets, and randomised trials evaluating the low FODMAP diet, have shown improvement in clinical indices but not mucosal inflammation[23]. Elimination diets have not shown

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efficacy for the maintenance of remission in ulcerative colitis[23]. Small randomised trials have shown improvement in clinical and endoscopic disease activity with curcumin supplementation[23].

The impact of food additives on the microbiota and subsequent influence on the development of ulcerative colitis has been borne out in a small randomised, placebo-controlled trial that showed an increased relapse rate in patients randomised to capsules containing carrageenan, a food additive frequently used in dairy and meat products [33].

Probiotics have been shown to confer anti-inflammatory effects, positive immune regulation, and enhanced intestinal barrier function[8]. VSL#3, a probiotic mixture of seven bacterial species, has shown efficacy in the treatment and prevention of pouchitis, and as an adjunct to 5-ASA treatment in mild to moderate ulcerative colitis. *Escherichia coli* Nissle 1917 has shown equivalence to 5-ASA in maintaining remission[8]. Open label-controlled studies evaluating different combinations of *Bifidobacteria* and *Lactobacillus* species have also shown relapse prevention and improvement in clinical indices[8]. Despite these studies, however, probiotics have not become part of standard care in ulcerative colitis.

Faecal microbiota transplantation has been established as an effective therapy in ulcerative colitis. Four randomised controlled trials have evaluated faecal microbiota transplantation for inducing remission in ulcerative colitis[34]. Two initial studies were preliminary[35, 36], Rossen et al's study was the only trial evaluating nasogastric FMT administration (two infusions). The clinical and endoscopic results were not significantly different between study arms. Four serious adverse events occurred, two in each group, including suspicion of a small bowel perforation in a patient in the FMT arm who was subsequently found to have severe small bowel Crohn's disease [35]. Moayyedi et al's study, comprising weekly FMT or autologous stool enemas for 6 weeks demonstrated a statistically significant difference in clinical remission [34]. The two subsequent definitive studies entailed multi-donor FMT administered by colonoscopic infusion followed by FMT enemas[37, 38]. These two trials achieved almost identical rates of clinical remission, with more than half of all patients receiving FMT experiencing clinical improvement (Figure I)[38]. Engraftment of the particular bacterium *Eubacterium hallii* was associated with response, and *Fusobacterium gonaidiaformans* with a lack of response, to faecal transplantation[39]. One placebo-controlled study has evaluated faecal microbiota transplantation maintenance therapy and demonstrated endoscopic and histological efficacy[40].

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SER-287, a second-generation FMT therapy, has shown promised in this space. This oral formulation of *Firmicutes* spores has recently demonstrated safety and clinical efficacy in mild-to-moderate ulcerative colitis in a phase 1b double blinded randomised trial, with and without vancomycin preconditioning [41].

Colorectal Cancer

Colorectal cancer has well established molecular, genetic and environmental mechanisms contributing to its aetiology. There is emerging evidence that the microbiota contributes to the development of this cancer. Germ-free and antibiotic treated mice develop less tumours. Animal models also have microbial signatures that are associated with carcinogenesis and the pathways through which it develops[42]. Studies are currently underway to identify microbial biomarkers for early cancer detection.

Metagenomic data of faecal samples and mucosa-adherent microbiota from cancer subjects show enrichment of *Fusobacterium*, *Porphyromonas*, *Peptostreptococcus* and *Prevotella*, as well as altered fungi (mycobiota)[42]. Functional analysis has revealed an association with altered secondary bile acid production and a shift to amino acid degradation, the significance of these changes is not known[42].

The role of diet in carcinogenesis is closely linked to intestinal bacteria, as carcinogens arise from dietary sources; some organisms detoxify dietary compounds, others utilise dietary substrates to induce DNA damage. Observational studies implicate a “westernised” dietary pattern that is high in animal protein and fat, and low in fibre, as a risk factor for the development of colorectal cancer[43]. A large systematic review showed that improved diet quality is consistently associated with reduced colorectal cancer risk[43].

In preclinical studies probiotics, prebiotics and synbiotics reduce inflammation, induce tumour cell apoptosis and restore microbiome homeostasis. Additionally, antibiotics can eliminate pro-tumorigenic bacteria[44]. However, very few randomised trials addressing the value of these

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interventions in treating colorectal cancer have been undertaken, largely because of the perceived risk of inducing further negative microbial changes, possible interaction with immunotherapy, and the risk of bacterial translocation in immunosuppressed patients. Additionally, cohort studies have implicated prior antibiotic exposure as a risk factor for the development of colorectal cancer[44].

Compared to other microbial targeted therapies, FMT is less selective in its modulation of the microbiota. Animal models have shown resistance against colorectal tumorigenesis with FMT, but there have been no human clinical studies[44].

***Clostridiodes difficile* infection**

Clostridiodes difficile (*C. difficile*) is a conditional pathogenic bacterium, whose spores germinate when the balance of gut microorganisms is disrupted. Susceptibility to *C. difficile* infection has been associated with perturbed microbiota and bile acid composition [45]. Antibiotics are the most common predisposing cause, but other causes of disturbed microbiota that allows the organism to proliferate and dominate include gastric acid suppression with proton pump inhibitor therapy and histamine 2 receptor antagonists.

Although antibiotics are the main risk factor for *C. difficile* colitis, antibiotics to which the organism is sensitive remain first line treatments, including metronidazole, vancomycin, and fidaxomicin[46]. Limitations of antibiotic for the treatment for *C. difficile* infection include high recurrence rates, adverse drug reactions, their contribution to the development of resistant strains and the potential precipitation of further gut dysbiosis[46].

C. difficile infection was the first condition to show benefit from FMT in a randomised controlled trial (Figure II) [47, 48], and has had a dramatic impact on this condition. Because of the simplicity and cost of antibiotics they remain first line treatment. However for the 30 to 50 percent of patients with recurrence in a short time FMT is the next step in therapy, with a cure rate of greater than 90 percent of patients[49]. Most patients require just a single treatment, with the benefit apparent within hours. Most of the remainder will respond to a second dose. FMT has been successfully administered in different doses and routes (per oral via gastroscopy and colonoscopic), with no major differences in

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outcome for these different treatment regimes, due to the high sensitivity of the condition to FMT[46, 49]. FMT for recurrent *C. difficile* infection is recommended by international guidelines as a first line therapy[46, 49]. Meta-analyses have shown no difference in efficacy when comparing fresh to frozen stored FMT, or aerobic to anaerobic prepared FMT, despite reduced viability of bacteria in FMT when freeze-thawed or aerobically prepared[49]. Although FMT for this indication is considered safe, serious FMT-related adverse events have been reported including bowel perforation, aspiration pneumonia [50], and more recently reported transmission of drug-resistant organisms [51].

Emerging bacteriotherapies for *C. difficile*, include stool-derived microbial suspensions containing carefully selected live bacteria in a cryopreservative, purified spores of the *Firmicutes* phylum or the non-toxigenic *C. difficile*, microbe-free faecal filtrates, as well as engineered bacteria and phagotherapy[46].

Irritable Bowel Syndrome

Functional gut disorders encompass biological, psychological and social ("bio-psycho-social") factors. The most common, irritable bowel syndrome (IBS), is characterised by altered bowel habit together with abdominal discomfort and bloating. It has been speculated that in some patients changes in the microbiota may play a role, particularly since the disorder can be precipitated by a definable initiating event such as gastroenteritis or antibiotic exposure. [52].

Lifestyle, pharmacological, and psychological interventions form the proven mainstays of treatment. The low dietary consumption of fermentable carbohydrates, the low "FODMAP" (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet, has demonstrated short and long term symptom relief [53]. The impact on the microbiota appears to represent a shift towards a inflammatory state[54]. A low to moderate strength recommendation has been made for soluble fibre supplementation, the benefit from which may reflect the anti-inflammatory effect of increasing abundance of SCFA-producers[54].

The majority of RCTs examining probiotic formulations have evaluated *Bifidobacterium* and *Lactobacillus* species. Multi-strain formulations have demonstrated a modest improvement in IBS symptoms[55]. Antibiotic therapy has shown some benefit in RCTs, most

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consistently with the non-absorbed, luminally-active rifaxamin in non-constipation predominant IBS[55, 56].

The preliminary data for FMT in IBS are conflicting, however the heterogenous nature of the condition and of FMT trial design make the data difficult to interpret. A meta-analysis of randomised trials reported significant improvements in IBS with endoscopic administration of FMT, but not FMT delivered in capsule form[57]. Of note, in one capsule study donor FMT was associated with worse symptoms than placebo [58]. A recent larger randomised controlled trial evaluating FMT delivered by gastroscopy from a single "super-donor" showed significant clinical efficacy and improved quality of life compared to placebo[59].

Coeliac disease

Coeliac disease, in which ingestion of gluten triggers a T cell-mediated proinflammatory response causing injury to mucosal epithelial cells, occurs in genetically susceptible individuals. Genome wide association studies have revealed coeliac disease associated HLA regions involved in host-microbiota interactions. Additionally, there is an association with environmental factors that influence the gastrointestinal microbiota including breastfeeding, gastroenteritis and antibiotic exposure[60, 61].

In patients with coeliac disease the gastrointestinal microbiota is distinct from healthy individuals, and cohort studies have shown altered microbiota in infants with high risk genetic profiles[61].

A gluten-free diet is the only therapy available at present, but this entails profound dietary and lifestyle limitations, and symptoms often ensue despite apparent good dietary compliance. A gluten-free diet only partially reverses the altered microbial profile. The microbial profile in patients on a gluten-free diet with a persistence of symptoms differs to that of asymptomatic patients[62].

Short-term benefit of a low FODMAP diet in conjunction with a gluten-free diet has been demonstrated in patients with coeliac disease in one RCT[61]. In a systematic review probiotics showed

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no benefit when IBS questionnaires were pooled[63]. Additionally, poor content regulation of these supplements increases the risk of gluten contamination.

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Non-alcoholic fatty liver disease / Non-alcohol steatohepatitis / Obesity / Metabolic syndrome

The Western and "developing" worlds currently face epidemics of overweight, obesity, type II diabetes, and metabolic liver disease. The last of these is rapidly overtaking infectious hepatitis as the commonest form of liver disease, and now constitutes the commonest indication for liver transplantation. Substantial evidence links the gastrointestinal microbiota with obesity and the metabolic syndrome, the latter including non-alcoholic fatty liver disease (NAFLD) (Figure III)[64] and non-alcoholic steatohepatitis (NASH). The gut-liver anatomical compartment behaves as a conduit for translocation of bacteria and metabolites from the intestine to the liver, leading to liver damage.

The characteristic microbial profile of patients with obesity and metabolic syndrome is one of reduced diversity and a disproportionate *Firmicutes/Bacteroidetes* ratio, with increased *Firmicutes* and reduced *Bacteroides*[65]. Animal models demonstrate an association between altered microbiota profile and body fat deposition, which has also been identified in infants preceding the development of obesity[4]. Additionally, there is evidence that early life exposure in humans and animals to antibiotics leads to weight gain and increased risk of obesity [66].

Lifestyle interventions such as dietary change are the primary focus of management. Dietary changes result in rapid alteration in the gut microbial population. Bariatric surgery, effective in achieving sustained weight loss and decreasing obesity-related comorbidity independent of weight loss, is thought to act, at least in part, through post-operative changes to the microbiota[67]. This is reflected partly in the *Firmicutes/Bacteroidetes* ratio returning towards a less disproportionate ratio. Microbial changes, however, may relate not just to surgery but also prescribed pre-operative, very low-calorie diets[67].

Probiotics in animal models enhance many metabolic pathways[68]. However, the results of their use in human studies are inconsistent[65, 68]. Similarly, no benefit has been demonstrated with antibiotic therapies

In animal studies, metabolic/obese phenotype is transmissible to germ free animals. Co-housing these mice with those with normal microbiome prevents development of obesity post FMT, consistent with human results that have existing microbiota and exposures [6]. The transfer of microbiota from lean, and post-Roux-en-Y gastric bypass-treated, mice to germ-free mice results in weight loss. Randomised trials evaluating FMT from lean donors into patients with obesity have shown improvement in insulin sensitivity, but without improvement in other biochemical parameters or weight loss[69].

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a progressive disease characterised by inflammation, fibrosis and stricturing of the small and large bile ducts. It occurs mostly in patients with the inflammatory bowel diseases, ulcerative colitis or Crohn's disease. Possible contributing aetiological factors include environmental, immunologic, and genetic factors, in addition to the gastrointestinal microbiota by way of the gut-liver axis[70].

In animal studies, the PSC phenotype has been transferred to germ-free mice via FMT[7]. Additionally, cholangiopathic changes resembling PSC occur with small bowel bacterial overgrowth created by a blind jejunal loop[70].

Three RCTs evaluating antibiotics including metronidazole, vancomycin, rifaximin and minocycline[71], in the treatment of patients with and without coexisting IBD, showed significant improvement in biomarkers including serum alkaline phosphatase (ALP) and total bilirubin. The greatest ALP reduction was achieved with vancomycin. One study also reported an improvement in IBD-related symptoms with vancomycin[71].

In a pilot uncontrolled trial evaluating FMT in 10 patients with PSC, with co-existent ulcerative or Crohn's colitis, 30% of patients demonstrated a reduction of ALP[70].

In light of these preliminary studies, further trials investigating microbiota targeted therapies in PSC are underway. However, the relatively low incidence and prevalence limit large trials.

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Conclusions

Advancing technologies have facilitated progression in the study of the gastrointestinal microbiota and as such, there is mounting evidence for a fundamental relationship between the gut microbial environment, health and disease. An altered gut microbiota may, in certain circumstances, cause an immune response and subsequent disease manifestation. In other situations, the altered gut function is likely to be mediated via non-immune mechanisms.

Modulation of the microbiota to shift microbial-host interactions towards a health-promoting or disease-countering state is an appealing concept. Dietary interventions entail adding ingredients such as diverse fibre content that promote short-chain fatty acid production and removing dietary components such as chemical additives found in ultra-processed food that disturb the microbiota, causing it to become pro-inflammatory. Diet, and other current, most effective strategies are broadly targeted, such as faecal microbiota transplantation. The benefits of pro- and pre-biotics in the laboratory and animal studies have not consistently translated to human therapy. Antibiotics are effective in targeting particular organisms but may have unintended consequences on commensal microbes.

The most promising microbiota-targeted therapy is FMT, because of its broad and dramatic effects on the entire microbiota. To date, if applied with appropriate screening and applied carefully, it avoids the side effect profile and frequent complications of drug therapies. Efficacy has been demonstrated in a gastrointestinal disease caused by a single pathogen, *C. difficile* infection, as well as in ulcerative colitis. Preliminary data also support its therapeutic role in improving metabolic parameters in obesity, and improving biochemical parameters in PSC. The future lies in defining the therapeutically important components of FMT, so that formulations of enteric organisms and their metabolic products can be manufactured, removing the risks associated with the use of donated stool.

The gut microbiota presents as a huge therapeutic opportunity for health promotion, disease prevention, and the management of a range of gastrointestinal disorders.

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Figure legends

Figure I. Case example of the effect of faecal microbiota transplantation in a patient with active ulcerative colitis.

Baseline colonoscopic appearance of 28-year-old woman with 7-year history of ulcerative colitis demonstrating extensive colitis to the hepatic flexure with an obliterated vascular pattern, superficial ulceration and mucosal bleeding (A) and endoscopic appearance of normal mucosa 8 weeks following faecal microbiota transplantation therapy (B).

Figure II. Case example of the effect of faecal microbiota transplantation in a patient with pseudomembranous colitis.

Endoscopic images of pseudomembranous colitis with mucosal oedema and hyperemia in the transverse colon (A) and sigmoid colon (B); normalised mucosa 4 weeks following faecal microbiota transplantation therapy in the sigmoid colon (C) and rectum (D).

Figure III. Non-alcoholic fatty liver disease histology.

Liver histology (haematoxylin–eosin stain): normal liver (A); non-alcoholic fatty liver disease (B).

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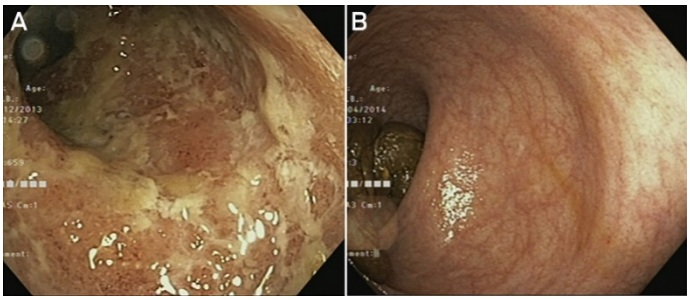

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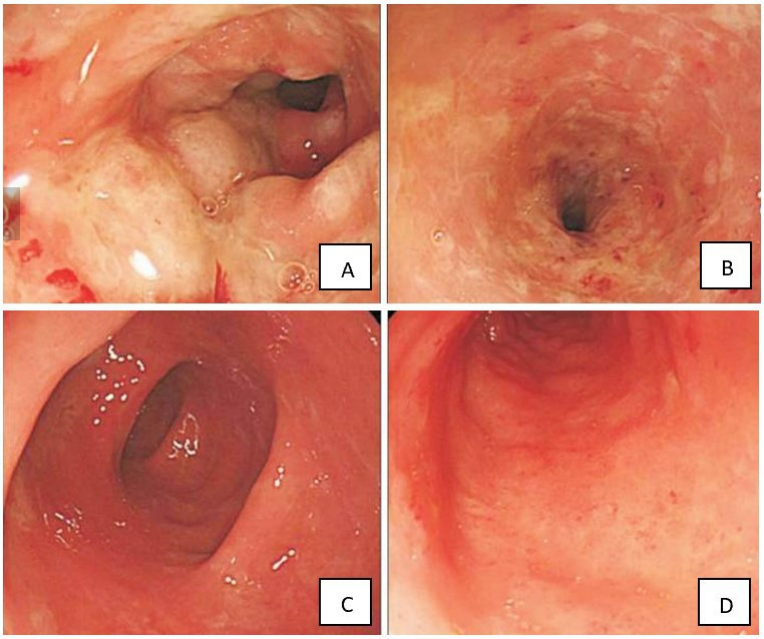

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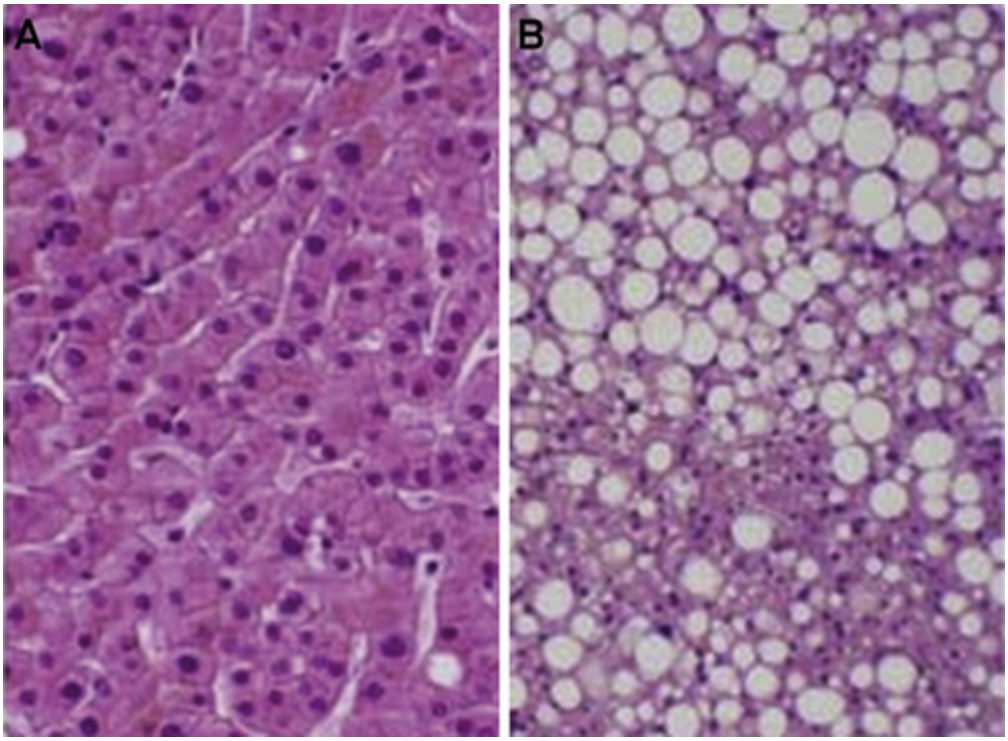

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The Gut Microbiota and Gut Disease

Abstract

The gut microbiota has a key role in the maintenance of good health, and in the pathogenesis of gastrointestinal diseases. These conditions include the inflammatory bowel diseases, colorectal cancer, coeliac disease, and metabolic liver disease. Although the nature of the microbial disturbance in these conditions has not been fully characterised, this has not prevented the development of microbially-based therapies. Microbial-changing therapies may address newly recognised pathophysiological contributors of disease and have the potential to replace or supplement standard therapies. Antibiotics play a role in initial *Clostridiodes difficile* disease and some specific inflammatory disorders. Probiotics have a more limited proven role. Faecal microbiota transplantation is of proven therapeutic benefit in recurrent *Clostridiodes difficile* disease and ulcerative colitis. We review the current literature for microbiota-targeted therapies in gut disorders.

Key words: microbiome; microbiota; gastrointestinal diseases; inflammatory bowel disease; faecal microbiota transplantation

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