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Microbial-Based and Microbial-Targeted Therapies for Inflammatory Bowel Diseases

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Abstract

Inflammatory bowel diseases (IBD), including Crohn's disease, ulcerative colitis and pouchitis, are chronic, relapsing intestinal inflammatory disorders mediated by dysregulated immune responses to resident microbiota. Current standard therapies that block immune activation with oral or biologic agent immunosuppression or surgical resection are generally effective, but each therapy induces a sustained remission in only a minority of patients. Furthermore, these approaches can have severe adverse events. Recent compelling evidence of a role of imbalanced of microbiota (dysbiosis) driving immune dysfunction and inflammation in IBD supports the therapeutic rationale for manipulating the dysbiotic microbiota. Traditional approaches using currently available antibiotics, probiotics, prebiotics, and synbiotics have not produced optimal results, but promising outcomes with fecal microbiota transplant (FMT) provide a proof of principle for targeting the resident microbiota. Rationally designed oral biotherapeutic products (LBP) composed of mixtures of protective commensal bacterial strains demonstrate impressive preclinical results. Resident microbial-based and microbial-targeted therapies are currently being studied with increasing intensity for IBD primary therapy with favorable early results. This review presents current evidence and therapeutic mechanisms of microbiota modulation, emphasizing clinical studies, and outlines prospects for future IBD treatment using new approaches, such as LBPs, bacteriophages, bacterial function-editing substrates and engineered bacteria. We believe that the optimal clinical use of microbial manipulation may be as adjuvants to immunosuppressive for accelerated and improved induction of deep remission and as potential safer solo approaches to sustained remission using personalized regimens based on an individual patient's microbial profile.

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Keywords

pouchitis; fecal microbiota transplantation; probiotics; prebiotics; synbiotics; diet; live biotherapeutic products; dysbiosis; microbiota

Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD), ulcerative colitis (UC) and pouchitis, are chronic intestinal inflammatory disorders characterized by dysregulated immune responses to enteric resident microbiota in genetically susceptible hosts [1-3]. Based on the requirement of microbiota colonization to develop colitis in germ-free (GF) susceptible rodents [4-7], gut microbiota play a crucial role in the pathogenesis of IBD [1,3,8]. Microbiota include potentially pathogenic microbes driving inflammation (pathobionts), as well as, potentially beneficial microbes inducing protective immune responses (commensals) [1,9,10]. However, most IBD patients exhibit unbalanced gut microbiota profiles (dysbiosis), with expanded potentially pathogenic Proteobacteria (especially Enterobacteriaceae that include *E. coli* and *Klebsiella*), Fusobacteria, *Ruminococcus gnavus* and *Candida tropicalis* [11] and reduced potentially protective Firmicutes (especially *Faecalibacterium prausnitzii,* Ruminococci and *Clostridium* clusters IV and XIVa) [12,13] (Table 1). The immunologic consequences of dysbiosis and its causal role in experimental colitis provide a strong rationale for therapeutically modifying the enteric microbiota in patients with IBD [1,3,8,14]. Current primary therapies in IBD, such as corticosteroids, methotrexate, 5-aminosalicylic acid (5-ASA), JAK inhibitors, anti-tumor necrosis factor (TNF)-α, anti-interleukin (IL)-12p40 antibody, and anti-integrin antibodies and surgical resection etc, mostly target effector immune responses [15-17]. These therapies can induce remission in many IBD patients, but can have severe adverse events with impaired quality of life (QOL). Microbiota-based therapies, including fecal microbiota transplant (FMT), probiotics and prebiotics, are suggested to be safe and can potentially correct the dysbiosis driving the dysregulated immune response [1,3,18]. Recent success of FMT in recurrent or refractory *Clostridium difficile* (rCDI) [19] achieved a major breakthrough in microbial-based therapy, which is being studied with increasing intensity as IBD primary therapy with favorable reported results [20]. In response to this trend, the United States Food and Drug Administration (FDA) created a new category, live biotherapeutic products (LBPs), for “live organisms, such as bacteria, which are applicable to the prevention, treatment, or cure of a disease or condition of human beings” and issued a guidance for clinical trials [21]. This review provides an overview of current microbial-based and microbiota-targeted therapies (Tables 2-5) and prospects for future treatments in IBD (Table 6) (Figure 1).

Microbiota in IBD: The rationale for therapeutic microbial manipulation

In general, ‘microbiota (or microbes)’ includes bacteria, fungi and viruses (mostly bacteriophages) while ‘microbiome’ refers to microbiota and their genes and metabolites [1,22,23]. The huge number of microbial cells in the distal intestine (10^{14} bacteria/g), species (approximately equal to human cells), genes (outnumber human genes by 100-fold),

bacteriophages (outnumber bacteria by 10-fold) and their weight (1−2 kg) [13,22,24,25], are considered a ‘superorganism’ and ‘forgotten organ’ [26,27]. The colonic lumen contains the densest bacteria concentration in the human body (10^{11}–10^{14} bacteria/g), followed by oral (10^8/g), ileum (10^7−10^8/g), jejunum (10^4/g), duodenum (10^3/g) and stomach (10^1/g) [22,23,28]. An individual’s enteric bacterial composition varies greatly and each individual harbors 100−150 diverse intestinal species [22,29]. This diversity allows humans to obtain a variety of benefits, such as digesting various foods (especially fiber), producing vitamins and other protective metabolites, activating homeostatic gut and systemic immune responses and preventing colonization by exogenous pathogens [1]. However, the diversity of bacteria in IBD patients is significantly decreased [12,13,30,31], whereas fungi and bacteriophages are expanded [11,31-33]. Furthermore, the composition and function of enteric microbiota in IBD patients is frequently disrupted, characterized by expanded potentially pathogenic microbes and reduced protective microbes producing short chain fatty acids (SCFAs) [12,13,34-39]. This microbial imbalance, termed as ‘dysbiosis’, was first noted in the intestine of IBD patients [12,13,30,34-38], but recently oral dysbiosis is also reported [40-42], the latter indicating that dysbiosis can be independent of local inflammatory processes. Although more careful assessment is needed in various patient subsets using modern detection techniques, consistent changes occur in CD and UC (Table 1). The link between this dysbiosis and gut inflammation is supported by many experimental studies. CD-associated adherent-invasive *Escherichia coli* (AIEC) invade epithelial cells and replicate within macrophages and can cause chronic experimental colitis [43,44]. Another Enterobacteriaceae, *Klebsiella pneumoniae* isolated from a CD patient, induces experimental colitis with high Th1 response compared to other control strains and species [42]. *Fusobacterium varium* strains from UC patients invade epithelial cells compared to strains from healthy controls and induce experimental colitis [45]. Alternatively, certain *Clostridium* species and *F. prausnitzii* are putative anti-inflammatory microbes. Clostridia are dominant intestinal microbes, accounting for over 60% of mucosa-associated bacteria [46]. A subset of resident *Clostridium* species produce SCFAs and can induce colonic regulatory T cells (Tregs) or IL-10-producing B cells and macrophages to protect against experimental colitis [47-50] with reduction in the abundance of Enterobacteriaceae [50]. *F. prausnitzii* another major SCFA producer, induces IL-10 production by human and murine dendritic cells [51]. Indeed, IBD-derived fecal bacteria stool did not induce colonic Treg in GF mice [9]. Interestingly, most expanded bacteria in IBD are aerotolerant species (aerobes or facultative anaerobes), such as *E. coli*, *F. varium*, *Haemophilus*, *Enterococcus faecalis* and Neisseriaceae. In contrast, the majority of reduced bacteria are obligate anaerobes, such as *Clostridium* clusters IV, XIVa, XVIII and *F. prausnitzii*. This trend gives rise to the ‘oxygen hypothesis’ wherein disruption in anaerobiosis indicates to a role for oxygen in intestinal dysbiosis [52]. Recent studies support this hypothesis by showing that *Clostridium* strains inhibit dysbiotic Enterobacteriaceae expansion by reducing luminal oxygen via activation of epithelial PPAR-γ [53,54]. Notably, decreased PPAR-γ gene expression is associated with IBD pathogenesis [55]. Dysbiosis of fungi and bacteriophages in IBD were also noted recently [31-33] with interactions between C. tropicalis, *E. coli* and *Serratia marcescens* [11]. Further investigations may determine the significance of elevated anti-fungus antibody in many CD patients [56]. A causal association between dysbiosis and IBD is further supported by results from recent FMT trials, as a shift of the recipient’s dysbiotic microbiota

towards the donor's non-dysbiotic microbiota is associated with clinical response [57-60]. In addition to its causal role in driving inflammation, microbiota influence efficacy of certain immunomodulatory therapies, including anti-TNF-α [61,62], steroids [63] and PD-1-based treatments [64]. Understanding microbial dynamics is necessary for optimal current and future IBD therapies, particularly personalized management. Technologic developments and ongoing human microbiome projects have improved the culture of previously 'unculturable' human microbiota [65], access to more extensive multi-omics databases [66] and gene catalogues established by metagenomic sequencing [12,24].

Antibiotics

Antibiotics, antimicrobial substances active against bacteria, are widely used treat complications of IBD (bacteremia, abscess, opportunistic and surgical site infections) [1]. Antibiotics are also used as primary therapy for inducing or maintaining remission based on the hypothesis that certain bacteria cause IBD, the pathologic similarities between CD and *Mycobacterium avium* subspecies *paratuberculosis* infection and isolation of this organism in some CD patients [67]. IBD is considered to be caused by intricately intertwined gut microbiota, host genes, immune system and environmental factors rather than a specific infectious colitis [1,3]. However, as potential pathobionts are expanded in dysbiotic IBD intestines, targeted antibiotic therapy is a rational strategy. Unfortunately, most antibiotics decrease overall bacterial diversity and inhibit not only pathobionts but also beneficial bacteria, which can lead to overgrowth of pathogenic bacteria (*C. difficile*), fungi (candida) and bacteriophages [32]. Despite their inhibitory effects, some antibiotics increase protective bacteria [68-70] and modulate host immune functions [71]. This section updates clinical efficacy of antibiotics in IBD (Table 2) and their therapeutic mechanisms.

Ulcerative colitis

Two meta-analyses of antibiotic therapy for active UC demonstrated improved remission rates overall (64% vs 48% placebo) [72,73]. With a broad variety of different agents and protocols (vancomycin, metronidazole, tobramycin, ciprofloxacin, amoxicillin, ethambutol, tetracycline and rifamycin), it is difficult to choose optimal antibiotic agents. Of note, all randomized controlled trials (RCTs) using intravenous antibiotics failed to achieve therapeutic benefit over control treatment. In contrast, most oral antibiotics achieved clinical response except for 2 RCTs of ciprofloxacin. Two RCTs of a promising 2-week triple antibiotic primary therapy cocktail including oral Amoxicillin, Tetracycline and Metronidazole (ATM) showed significantly improved remission rates, clinical and endoscopic scores [74,75]. This regimen, designed based on susceptibility testing of *F. varium* [75], significantly reduced mucosal *F. varium* abundance in Japanese UC patients [76]. Further, a new RCT of the ATM triple cocktail versus AT cocktail, excluding metronidazole, has been initiated (ClinicalTrials.gov identifier: NCT03986996), given metronidazole's potential negative effect on gut barrier function and poor patient acceptance. Only a few reports address the long-term outcomes of antibiotics: one trial reported that 7 days of oral tobramycin significantly improved remission rates at 1 week (74% vs 43% placebo) [77], but no statistical difference in relapse rates at 2-year follow-up (24% vs 12%) [78]. Another trial showed 6 month-oral ciprofloxacin improved endoscopic and histological

appearances at early 3 month, but the benefit disappeared by 6 and 12 months [79]. In contrast, the ATM cocktail therapy demonstrated significantly higher remission rates and lower clinical and endoscopic scores at both intermediate (3–5 months) and long-term (12–14 months) follow-ups [74,75].

Pouchitis

All three RCT (including metronidazole, rifaximin and ciprofloxacin) showed therapeutic benefit, matching widespread clinical use. Three meta-analyses including RCTs and cohort studies support the favorable results [80-82]. A meta-analysis concludes that antibiotics and biologics (anti-TNF-α) are more beneficial for chronic refractory pouchitis than are corticosteroids, bismuth, elemental diet and tacrolimus [81]. Furthermore, ciprofloxacin is suggested to be more effective than metronidazole [82]. Ciprofloxacin reduced *Clostridium perfringens* and *E. coli* and did not affect abundance of anaerobic bacteria, while metronidazole reduced *C. perfringens*, but not *E. coli*, and reduced anaerobic bacteria in a cohort study [83], indicating that ciprofloxacin is more active against pathogenic species and less harmful to beneficial species. Major concerns with sustained or intermittent use of antibiotics include antibiotic resistance and side effects, such as tendon rupture with ciprofloxacin and peripheral neuropathy with metronidazole. Regarding antibiotic-dependency observed in many pouchitis cases, a recent clinical trial proposed a unique hypothesis that antibiotics enrich antibiotic-resistance in non-pathogenic species, which might prevent colonization with pathogenic species as long as antibiotics are used [84]. Based on this, a new RCT is currently underway that alternates antibiotics short-term with dietary interventions to support growth of beneficial species to avoid progression to antibiotic-dependent disease (NCT04082559).

Crohn's disease

A meta-analysis of studies designed to maintain remission after surgical resections demonstrates significant benefit of antibiotics alone and as adjuvants to immunomodulators (azathioprine or 6-mercaptopurine) or anti-TNF-α therapies [85]. However, three meta-analyses suggest that the benefit of antibiotics is weak for overall treatment of CD [80,86,87]. However, anti-*Mycobacterium* agents (especially rifamycin-containing regimens), demonstrate some benefit for inducing remission [73,88] but do not induce a sustained remission to support clearance of a pathogen [89,90]. Long-term responses have been studied in a few reports, indicating that the protective effects of antibiotics wane over time; Aberra *et al.* suggested efficacy over 60 days [90,91]. Multiple additional RCTs of rifamycin for active CD (NCT02240108, NCT00603616, NCT02240121, NCT02620007) (Table 6) and prevention of postoperative CD recurrence (NCT03185624, NCT03185611) are ongoing or recently completed (NCT01951326). One of these trials specifically targets CD-associated *E. coli*-colonized patients (NCT02620007). Other agents, including ciprofloxacin and metronidazole alone or in combination, also show remission induction [72,73]. Given the fungal dysbiosis in CD, an ongoing RCT investigates whether addition antifungal fluconazole to an antibiotic cocktail can improve remission rates is underway (NCT02765256). For specific conditions such as anal or internal fistula, ciprofloxacin and metronidazole reduce drainage [73], improve symptoms and improve fistula closure rates [92-94]. For abscesses, the first choice is surgical treatment, but frequently emergency

surgery can be avoided by antibiotics and percutaneous drainage [95]. Although meta-analyses of antibiotics in IBD are quite positive, clinical use of these agents are largely restricted to patients with active pouchitis and septic complications of CD. This disparity is in part due to publication bias that favors publication of positive results.

Therapeutic mechanisms

Several mechanisms mediate therapeutic actions of antibiotics. (1) ***Inhibiting pathobionts***. Each antibiotic has a unique spectrum against bacteria and most antibiotics inhibit pathogenic species and decrease overall bacterial diversity. Long-term metronidazole eliminates Bacteroides, with bacterial concentrations correlated with disease activity [96]. Ciprofloxacin is effective against enteric pathogens and most Gram-negative Enterobacteriaceae. Although rifamycin does to alter the overall microbiota composition in IBD patients [71], it reduces bacterial attachment [71]. (2) ***Increasing beneficial bacteria***. Despite many antibiotics reducing beneficial species, such as *F. prausnitzii* [84], some antibiotics can increase protective species. For example, rifamycin increases *Lactobacillus* [70], *Bifidobacterium* and *F. prausnitzii* [69]. (3) ***Modifying bacterial metabolites***. Shifts in microbiota composition alter microbial metabolites, with increased SCFAs and other beneficial products [12,69] that correlate with clinical response in IBD patients [69,97]. (4) ***Immunomodulatory effect***. Rifamycins, ciprofloxacin, metronidazole and macrolides have mucosal immunomodulatory effects [71,98-100]. Specifically, rifaximin is a gut-specific agonist of the human pregnane X receptor (PXR) that helps maintain mucosal homeostasis [71,99].

Clinical concerns

Safety: In clinical trials IBD patients exhibited no increased risk of severe adverse events with antibiotics compared to placebo [86], but safety issues must be considered. Anti-*Mycobacterium* therapy has more frequent adverse events, such as rashes and skin pigmentation, but not increased withdrawal rate [88]. Long-term use of metronidazole can cause peripheral neuropathy [80,101].

Risk of resistance: Probably due to higher antibiotic exposure, the prevalence rates of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and extended-spectrum beta-lactamases (ESBL)-producing *E. coli* are significantly higher among IBD patients [102].

Risk of CDI: Antibiotics increase CDI infection in IBD patients [103] through decreased lactate-producing bacteria numbers and increased succinic acid [104] although others reported rare CDI in CD patients [105]. Antibiotic-resistant probiotics may prevent CDI after antibiotic therapy [106].

Effective protocols: While oral antibiotics appear to be effective as adjunctive therapy for IBD flares based on their direct effects on luminal bacteria and mucosal immune function, the benefits of intravenous antibiotics is not proven [107]. For fulminant colitis, such as toxic megacolon at risk for severe bacteremia, especially when receiving corticosteroids, intravenous broad-spectrum antibiotics appear to be reasonable [108]. The most effective

therapy duration remains unclear, but Ledder provides recommendations [109]. The short-term benefit (induction of remission) of antibiotics is promising, while the long-term benefits (maintenance) appear low with increased toxicity or antibiotic resistant bacteria [78,90,91]. Sequential maintenance approaches, such as protective nutrients, probiotics or FMT, need to be considered after induction of remission with antibiotics.

Risk of dysbiosis: Compelling epidemiologic evidence indicate that multiple early childhood exposures to antibiotics carry higher risk of developing CD [1]. It is unclear whether this risk is due to antibiotics themselves, an infection that required antibiotic use, or early IBD symptoms.

Conclusions

Despite the many different antibiotics, protocols and endpoint assessments in clinical trials with publication bias, oral antibiotics provide a promising primary or adjuvant therapy for inducing remission of IBD. Specific pathobiont-targeted strategy have recently emerged as an area of interest (*F. varium*, *AIEC*, *C. perfringens*), supporting future personalized antibiotic use. For active UC, the oral ATM cocktail is promising. For active pouchitis, ciprofloxacin > metronidazole are effective. For active CD, rifamycins are promising. Given the negative potential effects of long-term use such as host toxicity and antibiotic-resistance, short-term use followed by alternative maintenance therapies, such as probiotics, prebiotics, diet, standard immunotherapies, etc. should be considered.

Standard probiotics and LBPs using resident protective microbiota

Probiotics are living microorganisms such as bacteria or yeast with beneficial health effects [110], which included LBP [21]. Since Metchnikoff first published the concept of probiotics (Yogurt containing *Lactobacillus bulgaricus*) in 1907, many probiotic strains have been studied in clinical trials including IBD [108,110] (Table 3). Probiotic strains used in IBD trials have mostly belonged to two genera, *Bifidobacterium* and *Lactobacillus*, and isolated from limited sources (Yogurt, milk etc.) [108,110]. Recently, a variety of LBP candidates (*Clostridium*, Firmicutes spores, *Bacteroides*, *Roseburia*) isolated from healthy human microbiota have been investigated [1,3].

Ulcerative colitis

A meta-analysis of 18 RCTs in UC patients, including pediatric, demonstrates therapeutic benefit over placebo [111]. Also another meta-analysis including Chinese-based RCTs supports the use of adjuvant probiotics with 5-ASA in active UC [112]. Multiple strains have been investigated with favorable results (Table 3). A systematic sub-analysis suggests *Bifidobacterium*-containing probiotics significantly benefit active UC [113]. Because different strains have different metabolomic and immunomodulatory activities and provide complementary help, a cocktail of different strains may be more efficient than a single strain. Indeed, VSL#3, a cocktail of 8 strains, *Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii* subspecies *bulgaricus*, *Bifidobacterium longum*, *B. breve*, *B. infantis* and *Streptococcus salivarius* subspecies *thermophilus*, improved remission and relapse rates [111,112]. Additional RCTs of VSL#3 (NCT03415711) and *L. rhamnosus* (NCT04102852)

in active UC are underway. More recently, a SERES Therapeutics (Boston, MA) cocktail of purified Firmicutes spore (SER-287) from feces of healthy screened donors was tested in a Phase 1B RCT in active UC [114-116]. Treatment arms included 6 days of vancomycin pretreatment followed by 8 weeks of SER-287 either daily or weekly or placebo pretreatment followed by weekly SER-287 vs placebo/placebo. Vancomycin improve engraftment of microbes from SER-287 [114] and improved remission rates (placebo/placebo daily: 0%, vanco/SER287 daily: 40%, placebo/SER287 weekly: 13.3%, vanco/SER-287 weekly: 17.7%) and endoscopic scores [115]. SER-287-treated remitters exhibited widespread transcriptional shifts from baseline, with by decreased expression of inflammatory genes and increased expression of homeostatic mediators [116]. These promising results led to a Phase 2B, 3-arm RCT in active UC (NCT03759041). Based on improved engraftment of SER-287 by vancomycin pretreatment, two patient groups receive different doses of SER-287, both following short courses of oral vancomycin. In pediatric UC, 2 RCTs demonstrated that oral VSL#3 [117] or rectal *L. reuteri* ATCC55730 [118] significantly improved clinical and endoscopic scores. Long-term follow-up data are limited, but a 2-year-follow-up showed promising results [119].

Pouchitis

Meta-analyses indicate that probiotics significantly induce remission and prevent relapse in pouchitis [80,120,121]. A RCT of oral *C. butyricum* MIYAIRI showed improved relapse rates (11% vs 50%) [122]. Gionchetti and colleagues reported strikingly decreased relapses (15% vs 100% placebo) in recurrent pouchitis after 9 months of oral VSL#3 therapy [123], but these positive results were not replicated in the USA [124]. In naive ileal pouches within a year after surgery, VSL#3 prevented onset of pouchitis over placebo (10% vs 40%, $P<0.05$) [125]. Microbial analysis revealed that the probiotic enriched Lactobacilli and Bifidobacteria and increased bacteria diversity while reducing fungal diversity [126]. In contrast, probiotics containing *Lactobacillus* and *Bifidobacterium* did not improve pouch dysfunction nor pouchitis activity [127].

Crohn's disease

In contrast to UC and pouchitis, several meta-analyses in CD suggest very weak or no benefit of standard probiotics [111,128] with benefits limited to maintaining remission after surgery [111,129,130]. However, there is a strong strain-specific effect [131]; VSL#3 improved endoscopic features [129,130] and decreased mucosal inflammatory cytokine levels [129]. *E. coli* Nissle1917 and other *Lactobacillus* strains tested in RCTs lacked benefit [111,128-130,132], but significantly induced of Treg numbers in peripheral blood [132]. *Bifidobacterium* strains, some of which are included in VSL#3, have not been tested alone, but the combination with prebiotics (synbiotics) significantly improved remission rates, clinical activity and histological scores in CD patients with active disease compared to placebo [133].

Therapeutic mechanisms

Most orally administered current probiotics pass through, although *E. coli* Nissle1917 [134] can colonize, the intestine and perform several documented protective functions [135,136]. Subsets of resident microbiota have extensive evidence of preventing and treating

experimental colitis mediated by well-documented mechanisms [1,48,50,137]. Several comprehensive reviews more extensively document protective effects of probiotics and commensal bacteria [135,136]. The protective mechanisms of traditional probiotics and LBPs include the bacteria themselves (DNA, cytoplasmic and cell wall contents) and their metabolites, such as organic acids, SCFAs, lactic acid that stimulate homeostatic immune and mucosal protection [1,138]. (1) ***Inhibiting pathobionts***. Certain protective bacteria inhibit resident potentially pathogenic microbiota, such as Enterobacteriaceae [50,139], *Fusobacterium* [50] and Bacteroideceae [140]. Many pathobionts adhere intestinal epithelial cells to induce inflammation, i.e. AIEC and *F. varium* [45,141,142]. Probiotic *E. coli* Nissle1917 and *L. johnsonii* La1 can compete for ecologic niches, epithelial binding and nutrients with pathobionts and inhibit their adhesion and proliferation [143]. Furthermore, decreased luminal pH by organic acids (SCFAs etc.) produced by probiotics and protective resident bacteria [144], anti-bacterial peptides (bacteriocins) [145] and bile-acids modulated by probiotics [146] can inhibit pathobionts. In addition to these bacterial cross-talk, probiotics and resident bacterial species can indirectly (via host cells) affect pathobionts: mucosal PPAR-γ signaling activated by probiotic *Clostridium* and VSL#3 reduce luminal oxygen and inhibit aerobic Enterobacteriaceae [53,147]; *E.coli* Nissle1917 induces defensin production by epithelial cells through flagellin-toll like receptor binding (TLR) [148]. (2) ***Increasing beneficial resident bacteria***. Probiotics and LBTs can increase growth of other resident beneficial bacterial species and improve the intestinal eco-system [50,123,149]; increase Lactobacilli [126,139], Bifidobacteria [123,126,149], *S. thermophilus* [123] and bacterial diversity [126], while reducing fungal diversity [126]. (3) ***Improving mucosal barrier function***. *Bifidobacterium* strains strengthen epithelial barrier function in UC [150]. SCFAs provide the main energy source of colonic epithelial cells, improve mucosal barrier function and activate colonic Tregs [151,152]. However, in clinical studies, some probiotics work without elevating SCFA [153]. Other protective bacterial metabolites include indoles that bind aryl hydrolase receptors, PXR and sphingolipids [135]. TLR and NOD2-recognition pathways mediate some bacterial protective functions [154]. (4) ***Mucosal and systemic immunomodulation***. Probiotics and resident bacteria can induce anti-inflammatory cytokines (IL-10, TGF-β etc.) and mucosal and systemic regulatory cells (Treg, IgA^+ and regulatory B cells) and attenuate inflammatory cytokines (IFN-γ, IL-12p40, TNF-α etc.) [47,48,118,132,154-156].

Clinical concerns

Safety: Probiotics are well-tolerated with low rates of adverse effects [157,158] although rare cases of sepsis, endocarditis and liver abscess with use of *Lactobacillus* and fungemia by *S. boulardii* have occurred, primarily in hospitalized and severely ill or immunocompromised patients with intravenous catheters [158].

Optimal protocols: Resident microbiota compete with exogenous microbes. Therefore, antibiotic pretreatment seems reasonable to improve engraftment of exogenous probiotics and LBTs. SERES's RCT demonstrates that pretreatment with vancomycin enhances engraftment of Firmicutes spores [114,115]. Some papers suggest that beneficial effects require 10^6–10^8 probiotics/g stool [159]. Given that only 20% of probiotic cells survive [160,161] and stool weight is 1kg, 5×10^8–10^{11} probiotic cells administration may be

required. However, lower doses may be sufficient for resident LBT strains that proliferate in the intestine. The rectal route (enema) can be considered for pouchitis and pouchitis. D'Inca *et al.* compared oral versus enema with *L. casei* GG in active UC and showed a significant advantage of the rectal route for reducing mucosal inflammatory cytokines and modifying the microbiota (*Lactobacillus* increased, Enterobacteriaceae decreased) [139]. Matthes *et al.* showed that *E. coli* Nissle1917 enemas are effective in a dose-dependent manner in active UC patients [162].

Conclusions

Some standard probiotics benefit UC and pouchitis activities. In contrast, the benefits of probiotics for CD seem to be strain specific and limited in maintaining remission after surgery for CD patients. However, VSL#3 containing *Bifidobacterium*, *Lactobacillus* and *S. salivarius*, have more beneficial effects. These positive reported results are subject to publication bias. Although clinical trials of LBTs are just beginning, providing protective resident microbiota to reverse dysbiosis and restore homeostatic microbial community structure and function is an attractive approach that will be actively investigated in the near future.

Prebiotics

Prebiotics are food ingredients that are selectively fermented by host microbes to confer a health benefit. Examples include dietary fiber and oligosaccharides naturally contained in fruits, vegetables and grains [163]. IBD patients are traditionally advised to lower their fiber intake and sometimes fast during flares to reduce mechanical stimulation of the damaged mucosa [164]. However, many studies of various dietary fiber and oligosaccharides suggest favorable results as an emerging treatment approaches (Table 4). Their ability to increase potentially beneficial bacteria and beneficial metabolic effects (SCFAs etc.) have been verified in humans and murine models [163,165].

Ulcerative colitis

Many studies focus on QOL, symptoms and bacterial metabolites in UC treated with various prebiotics. Psyllium, germinated barley foodstuff (GBF), lactulose and oligofructose-enriched inulin significantly improve QOL and symptoms in UC patients [166-169]. Intake of psyllium and wheat bran significantly increased fecal butyrate [170,171]. A large RCT with psyllium demonstrated equivalent effectiveness to 5-ASA to maintain remission in UC [171] and a crossover trial in active UC is underway (NCT03998488). GBF contains low-lignified hemicellulose that are efficiently fermented by colonic microbiota [161,165]. GBF reduced CRP [172] and improved clinical and endoscopic scores in active UC in an uncontrolled long-term study [173]. Supplemental oligofructose-enriched inulin with 5-ASA significantly reduced fecal calprotectin (4-fold change) at day 7 compared with 5-ASA alone [168]; a RCT is underway (NCT03653481). A RCT of Synergy1, composed of equal proportions of fructo-oligosaccharide and inulin in active UC has been completed without published results (NCT02093767) and an additional RCT in inactive UC is currently recruiting (NCT02865707). Curcumin, the biologically active component of turmeric with anti-inflammatory and antioxidant effects, can support the growth of protective bacteria

[174], so is a promising prebiotic. A large RCT in UC improved remission rates with clinical and endoscopic scores compared to controls [175]. Additional RCTs of curcumin have recently been registered in pediatric (NCT02277223) and adult (NCT02683759) UC patients. Fucosyllactose modifies microbiota [176]; 2 RCTs are underway (NCT03847467, NCT03847467). Glycomacropeptide can modify microbiota and metabolites, reducing Proteobacteria and increasing SCFAs [177]; the first RCT is recruiting UC patients (NCT02825914).

Pouchitis

Two cross-over studies focused on disease activity. Three weeks of inulin supplementation significantly improved clinical and histological scores from baselines associated with increased butyrate levels and reduced pH, *B. fragilis* and increased secondary bile acids levels [178]. However, the same treatment protocol failed to show significant benefit although a slightly increased butyrate level correlated with reduced disease activity [179]. One possible explanation is variable microbiota in individuals, since efficacy of prebiotics can depend on abundance of resident Bifidobacteria [180].

Crohn's disease

Restricted dietary fiber did not improve symptoms need for surgery or hospitalization in CD patients [181]. On the contrary, fiber-rich diets significantly reduced surgery in active CD [182] and prevented relapse during remission [183]. Two recent RCTs using oligofructose-enriched inulin inhibited disease activity of active CD associated with increased SCFAs [184] and *B. longum* and reduced *R. gnavus*, a potential pathogen in CD [185]. An additional RCT is underway (NCT03653481). 2 RCTs are underway (NCT03847467, NCT03847467) testing fucosyllactose a prebiotic that modifies microbiota [176].

Therapeutic mechanisms

Prebiotics are substrates fermented by resident microbiota to organic acids (SCFAs), CO_2, H_2 and methane gas [163,165]. (1) ***Increasing beneficial bacteria***. Prebiotics enriched Bifidobacteria [185,186], lactobacilli [186], *F. prausnitzii* [187] and *Clostridium* clusters IV and XIVa [188]. (2) ***Inhibiting pathobionts***. Prebiotics can decrease Proteobacteria [177], *Bacteroides* [178,186], *R. gnavus* [185] and Candida [186]. (3) ***Improving mucosal barrier***. SCFAs improve mucosal barrier function by providing a key nutrient for colonic epithelial cells [47,48,135], while inulin prevents mucus defects [189]. (4) ***Mucosal and systemic immunomodulation***. Some prebiotics induce Tregs [47,48,135], likely through SCFA production, and intestinal IgA [190]. (5) ***Absorption of toxic substances***. Dietary fiber can adsorb toxic substances, cholesterol, bile acids, and provide bacterial scaffolds to benefit inflammation [191].

Clinical concerns

Safety: Because prebiotics derive from natural foods, prebiotics are considered to be safe [166,167,169,192]. There were no severe adverse events reported in RCT, although a few food-allergy events occurred [192,193]. Of note, psyllium may cause gastrointestinal obstruction, especially at stenotic sites [192,193] and has not used in CD trials.

Tolerability: Clinical use is limited by high participant dropout due to bloating and discomfort among IBD patients [184].

Conclusions

Improved beneficial bacteria community structure and metabolism by prebiotics are documented in human volunteers and IBD patients, but relatively few clinical RCTs have been conducted. Although more high quality and disease activity-focused clinical studies are needed, prebiotic therapy is a promising safe and physiologic treatment and maintenance approach to IBD, perhaps in combination with LBPs.

Prebiotic diets

Diet greatly affect microbiota composition and metabolism and IBD dysbiosis is associated with diet [194-196]. Many rigorously designed RCTs have been newly registered. Exclusive enteral nutrition (EEN) is used as first-line therapy for inducing remission in CD with mucosal healing and histological improvement [194,197]. This approach is most widely used in pediatric patients. Responses may be partially attributed to EEN-mediated microbial changes, despite decreased diversity [32]. The Mediterranean style diet (MSD), Asian and semi-vegetarian diets increase beneficial bacteria [198], potentially reduce pathobionts [199] and may benefit IBD patients [200], leading to a RCT investigating the effectiveness of MSD in UC (NCT03053713). The specific carbohydrate diet (SCD), consisting of mostly meat, fruits, vegetables, nuts, oils, and honey with the elimination of grains, has shown efficacy in a retrospective IBD study [201] leading to multiple RCTs, investigating its effects microbial profile and clinical outcome (NCT02858557) (NCT02412553) and efficacy in pediatric (NCT02610101, NCT03301311) and adult (NCT03058679, NCT02412553, NCT02858557) IBD and comparison vs MSD (NCT04082559, NCT03058679). Other promising diets are under investigation, such as the fasting-mimicking diet in UC (NCT03165690), Mashiha in IBD (NCT02796339); the low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet in UC (NCT02469220). Several of these diets, including SCD and low FODMAP, are low in fiber and prebiotics, so they may affect symptoms more than disease efficacy. A better understanding of prebiotics may provide improved advice for patients' food choices.

Synbiotics

Synbiotics are mixtures of probiotics and prebiotics that beneficially affect the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract by selectively stimulating the growth and/or by activating the metabolism of one or a limited number of health-promoting bacteria, thus improving host welfare [163]. Given that IBD patients harbor less beneficial intestinal bacteria (Table 1), administration of synbiotics may improve treatment with probiotics or LBPs. Indeed, some papers demonstrated that the benefit of prebiotics depends on baseline abundance of resident protective species [180]. However, clinical studies of synbiotics are limited (Table 4). Ishikawa *et al.* demonstrated that Bifidobacterial strains plus galacto-oligosaccharide synbiotics improved endoscopic scores and decreased inflammatory markers in treated UC patients [202]. Furrie *et al.* detected higher numbers of total Bifidobacteria on the mucosal

surface in active UC patients fed a synbiotic containing *B. longum* and Synergy1 than in those taking placebo [203]. In CD, *B. longum* plus Synergy1 was effective [133]. Overall, prebiotic therapy appears safe and promising, but RCTs are needed to assess the efficacy of dietary/prebiotic interventions. The concept of combined therapies is supported by observations that partial EN plus an exclusion diet high in fiber and fresh fruits and vegetables was better tolerated and induced a more sustained remission in pediatric CD patients compared with standard EEN therapy [197].

FMT

After the breakthrough success of FMT therapy in rCDI in 2013 [19], several accessible fecal banks have been established (OpenBiome etc.) and multiple clinical studies have been performed in IBD patients. This section updates FMT clinical trials in IBD (Table 5), which have been extensively reviewed [57,204,205].

Ulcerative colitis

After initial success of FMT for induction of remission in UC in 1989 [206], four RCTs and several case series have provided promising results. Three out of four RCTs demonstrated a significantly improved clinical, endoscopic and histological scores [58,59,207] although clinical response rates (24–32%) are not as dramatic as in FMT for rCDI (93%). In the unsuccessful RCT [60], the FMT group showed a higher clinical remission rate over controls (41% vs 25%) without statistical significance, likely due to limited subject numbers. However, clinical efficacy was strikingly different with different donors [58]. Indeed, pooled analyses show effectiveness of FMT for active UC [57,204,205]. Bacterial taxa analyses revealed that FMT significantly improved bacterial diversity, which correlates with clinical responses [59,204]. Interestingly, several bacteria taxa associated with remission after FMT, such as *Clostridium* clusters IV and XVIII, while the presence of Proteobacteria (Sutterella spp) and *Fusobacterium* species was associated with lack of remission [59]. Ishikawa *et al.* modified the *Fusobacterium*-targeted antibiotic ATM cocktail (tetracycline replaced by fosfomycin, AFM cocktail) and showed that the pre-AFM+FMT combination improved outcomes [208]. Moreover, they showed that the reduced abundance of Bacteroidetes by AFM antibiotics pretreatment was clearly restored in FMT responders, but not non-responders. Bacteroidetes is one of the symbiotic taxa [209], that can inhibit *C. perfringens* [145] and induce Treg [47,48,137]. Two RCTs investigating antibiotics prior to FMT are currently underway (NCT02606032, NCT02033408). Based on limited long-term follow-up reports, the effects of FMT seem to gradually decrease over 3 months [210,211]. However, some responders exhibit long-term remission (>1–2 years) [207,212]. Multiple RCTs are underway in several countries.

Pouchitis

Herfarth *et al.* demonstrated the difficulty of engraftment of FMT: one out of six patients showed successful engraftment and remission [213]. This could be due to several factors, including donor selection, the dose, frequency and route of administration of FMT, and the pouch microenvironment. Pouches are constructed from the small intestine where potentially beneficial Firmicutes bacteria such as Clostridia are rarely detectable in normal conditions.

Of note, Stallmach *et al.* showed impressive clinical benefits and engraftment by multiple FMT in antibiotic-refractory pouchitis patients [214]: all 5 patients who received FMT achieved clinical response (4/5 remission) and 3/5 patients maintained remission with sequential FMTs. A RCT is currently recruiting (NCT02049502).

Crohn's disease

Although some case series showed less benefit of FMT in CD patients compared with UC [212,215], many promising case reports and series describe induction of CD remission [204]. Meta-analysis of 6 prospective and uncontrolled trials [204] shows 52% clinical remission rate with publication bias. For adult CD, 58–87% clinical responses were reported [216,217]. Responders showed greater improvement in microbial diversity with a significant shift in fecal microbial composition towards their donor's profile than non-responders and increased lamina propria Tregs following FMT [216]. FMT via nasogastric tube induced remission in 77.8% of pediatric CD patients 2 weeks after FMT with evidence of engraftment [218]. As seen in UC, responders of FMT in CD showed rapidly improved symptoms and clinical activity several weeks after FMT, but this effect diminished over several months after FMT [216-219] with return to bacterial composition patterns close to pre-FMT levels [219]. To maintain the clinical benefits from FMT, Li *et al.* suggested performing the next course of FMT less than 4 months after the previous FMT, based on the large scale clinical trial [220]. Multiple RCTs are currently underway.

Therapeutic mechanisms

The therapeutically relevant components of FMT remain elusive [221]. Increased bacterial diversity is clearly associated with successful response of FMT in IBD [59,204,216]. Further, the recipient microbiota after successful FMT resemble donor microbiota, likely due to implantation of donor bacteria and/or donor feces promoting growth of resident bacteria that resemble the donor's species [221]. Although several potentially relevant species are reported [59], more data are required to support the protective species. FMT is a complex material containing bacteriophages, fungi and metabolites as well as bacteria [59]. Given the therapeutic benefits of filtrated-FMT in rCDI studies [222], cell-free components (bacteriophages and metabolites) in FMT need to be included as research targets. A RCT of filtrated-FMT in UC has been registered (NCT03843385).

Clinical concerns

Safety: FMT is safe and well tolerated in IBD clinical trials [57,204,223-225]. Importantly, two bacteremias (one death) by ESBL *E. coli* were reported in immunocompromised patients who received donor stool harboring these strains [226]. Exclusion criteria now include ESBL-producing species. Fecal banks are one source for donor stool.

Effective donor: FMT success depends on microbial diversity and composition of the donor's stool, leading to the proposed existence of FMT 'super donors' [58,212,227]. The optimal microbial characteristics of donor feces have not defined in IBD. A family member is often chosen as a donor. Because siblings and relatives share similar gut microbiota because of similar lifestyles, diets and genetics [228,229], they may not be optimal donors if the goal is to modulate the recipient's microbial composition. Switching donors rescued

non-responders in a rCDI trial [19]. Whether donors can be optimized by various methods is under investigation.

Optimal protocol: Engraftment is important factor of efficacy in FMT [230]. A 2018 meta-analysis of FMT protocols indicated that fresh or frozen donor stools, delivery route, and antibiotic pretreatment have no impact on FMT efficacy in IBD [205]. Multiple administrations appear more effective rather than single FMT [205]. Costello *et al.* demonstrated marked benefit of anaerobically prepared FMT [207], while Cui *et al.* established a laboratory preparation of fecal materials [217]. Vermeire *et al.* demonstrated that increased CRP levels at week 2 were an early marker of failure [212], which could allow early rescue therapy in those IBD patients that will not benefit from FMT or guide repeat FMT with a different donor. Because mucosal inflammation reduces microbial diversity and increase pathobionts [231], pre-treatment with immunosuppression to reduce local inflammation and antibiotics to eliminate competing native microbiota may improve engraftment of beneficial species.

Conclusions

Successful FMT have been reported primarily in UC patients. A few positive results exist for CD and pouchitis from case reports and open-label studies. Ongoing multiple RCTs and efforts to optimize protocols, engraftment, donor and recipient selection and matching the optimal donor with individual recipients based on microbial sequencing could improve FMT as a primary therapy. However, we continuously need to consider possible transmission of ‘undefined’ infectious agents in human stools, in contrast to the safety of defined therapeutic LBP cocktails.

Emerging options (bugs as drugs)

This section discusses recent and ongoing pre-clinical studies, technologies and emerging therapeutic concepts [1-3].

Rationally-defined human-derived bacterial consortia - LBPs

A potentially better, more consistent therapeutic approach uses well-characterized, rationally defined and orally-delivered LBPs from resident bacterial species from the intestine of healthy subjects. The most advanced LBP for IBD investigation is a *Clostridium* cocktail. Atarashi *et al.* isolated 17 *Clostridium* strains from healthy human stool screened for induction of $FOXP3^+$ murine $CD4^+$ Tregs [48]. These strains protected several experimental colitis models with high production of SCFAs and induction of colonic IL-10-producing Tregs [48]. All 17 strains belong to *Clostridium* clusters IV, XIVa or XVIII, which are reduced in IBD patients [13,30]. Administering these strains is designed to restore a normal ecology in IBD patients [232]. Based on these results [40] and mechanistic preclinical studies that identified additional mechanisms beyond the Treg and SCFA pathways, such as correcting dysbiosis and altering non-SCFAs metabolites [50], Janssen Research & Development and Vedanta initiated a Phase 1 clinical study in healthy volunteers. Many other LBTs based on different *in vitro* and *in vivo* screening methods are in development and should reach clinical trials soon.

Screening LBPs

Choosing protective resident bacterial strains has been performed *in vivo* by reductionist [48] and combinatorial [233] approaches in gnotobiotic mice by screening for Treg activation and *in vitro* with cell lines and human blood lymphocytes [234]. However, results of *in vitro* studies do not always predict *in vivo* effects [235]. Peran *et al.* showed that a specific strain of *Lactobacillus salivarius* prevented colitis in a TNBS rat model [236]. This strain was selected from 30 laboratory strains for eliciting the highest IL-10/IL-12 and IL-10/TNFα ratios in macrophages. Unfortunately, no strains exhibiting a moderate or low IL-10/IL-12 profile were included in the *in vivo* study. Similarly strains ranked on their induction of *in vitro* IL-10/IL-12 cytokine induction closely matches their *in vivo* attenuation of experimental colitis [234,237]. Our group established a novel *in vivo/in vitro* combined method using gnotobiotic IL-10-reporter mice to measure individual resident bacterial strain induction of IL-10/IFNγ ratios, with high ratio strains preventing and reversing experimental colitis induced by low IL-10/IFNγ-inducing strains [10].

Substrates from microbiota

Although SCFAs are an important anti-inflammatory substrate in microbe-microbe and microbe-host interactions [144], many other candidate bacterial metabolites affect microbiota and host responses to attenuate mucosal inflammation. Because microbial-based therapies have strong strain- and donor- specific effects [131], purified substrates from defined microbes may provide more consistent results. Examples of established protective bioactive substances produced by probiotic and resident bacteria include p75/p40 from *L. rhamnosus* that acts through an EGFR-dependent mechanism [238], polyphosphate from lactobacilli [239], lactocepin from VSL#3 [240], polysaccharide-A from *B. fragilis* [137], an anti-inflammatory protein from *F. prausnitzii* [241] and kangfuxin liquid extracted from *Periplaneta americana* dried worms [242]. Most investigators focus on ‘beneficial’ strains to discover a new therapeutic microbial-based tool. In contrast, a unique product from a ‘pathogenic’ *E. coli* strain, QBECO, is used to immunize hosts (Qu Biologics). Interestingly, purified major macromolecules of an inactivated pathogenic strain of *E. coli* isolated from a patient with an *E. coli* infection restored the immune system’s ability to respond productively to invading bacteria in the gastrointestinal tract and rebuild normal barrier function. QBECO treatment improved endoscopic and histological scores in active UC [243] and CD patients cohort [244]. A RCT in CD patients is ongoing [245].

Editing microbiota

Improved understanding of microbiology and metabolic functions suggests ways to modify or block bacterial functions (enzymes and surface molecules) that provide virulence traits. In mice, tungstate treatment, which inhibits molybdenum-cofactor-dependent microbial respiratory pathways, inhibit Enterobacteriaceae expansion and experimental inflammation [246]. Of note, this effect on microbiota was observed only during inflammation. Additional approaches to selectively inhibit pathobiont numbers and functions in IBD include blocking AIEC epithelial attachment through FimH (NCT03709628) and pathobiont-specific bacteriophages (NCT03808103).

Bacteriophages, yeasts and engineered bacteria

Virus (mostly bacteriophages targeting specific bacteria) improves intestinal homeostasis and protects against intestinal injury and pathogen infection [247]. This is potentially clinically relevant, since specific bacteria-targeted bacteriophages may act without affecting beneficial resident bacteria. A RCT examining therapeutic effects of a bacteriophage against AIEC is recruiting CD patients (NCT03808103). Interestingly, bacteriophage DNA can induce colitis and activate IFN-γ responses [248], so clinical toxicity must be examined. Probiotic yeast, including *Candida glabrata*, produce chitin that reduces bacteria/fungus overgrowth and attenuate DSS colitis with activation of PPAR-γ and induction of IL-10 [249,250]. Although genetically engineered organisms must be carefully handled, several unique bacterial strain express anti-inflammatory substrates such as IL-10, IL-35, trefoil factors, elafin [251-254].

Screening patients: personalized treatment

Based on the heterogeneity of individual IBD patient's microbiota and patient therapeutic responses, a pilot RCT investigating effects of personalized microbiota-based therapy (antibiotics and prebiotics) is underway in pouchitis (NCT04082559). As described above, efficacy of probiotics, prebiotics and FMT (and anti-TNFα therapy) depends on a patient's microbiota [255]. Therefore, the best strategy for personalized management of IBD is to identify intestinal microbial profiles prior to beginning therapy or in non-responders [2] to guide optimal microbiome-based therapies.

Conclusions

Microbial-based and microbial-targeted therapies for IBD are emerging with favorable results. The rational for correcting the established dysbiosis in CD, UC and pouchitis patients is well established. Certain antibiotics are promising short-term primary therapies with relatively safety. However, the risk of resistant bacteria and CDI and their uncertain long-term benefit/ toxicity profiles limit maintenance use of antibiotics. FMT is also a promising primary therapy with well-designed RCTs underway. However, the risk of transmission of 'unknown' pathogens and long-term benefits remain unclear. A major limitation is variable responses from different donors. In contrast, LBPs, prebiotics and diet are well-defined, safe for long-term use and could be designed for personalized use based on the microbial community structure of individual recipients. Hopefully, these new generation microbial-related therapies will be validated by high quality preclinical and clinical trials. A major discussion point is the best clinical applications for microbial therapy in IBD. Current studies concentrate on single agents inducing remission of active UC. However, we believe that preventing relapse after achieving clinical remission with corticosteroids or biologic therapies in UC or CD patients or with antibiotics in chronic relapsing or antibiotic-resistant pouchitis might be more important areas to investigate. Other clinical needs possibly fulfilled by microbial-based therapies are to use these agents as adjuncts to standard biologic or immunologic therapies to hasten or increase the frequency of deep remission or to maintain quiescent disease after removing the more toxic immune-suppressing agent. Long-term use of this physiologic approach to restore microbial homeostatic function would, in theory, be less toxic and more acceptable to patients (and physicians) who are concerned

about risk of infection and neoplasia with sustained immunosuppression. We advocate use of concomitant companion diagnostic tests to profile an individual's microbiota to guide optimal personalized microbial therapies, determine best timing of intervention and ultimately prevent disease onset in high risk individuals.

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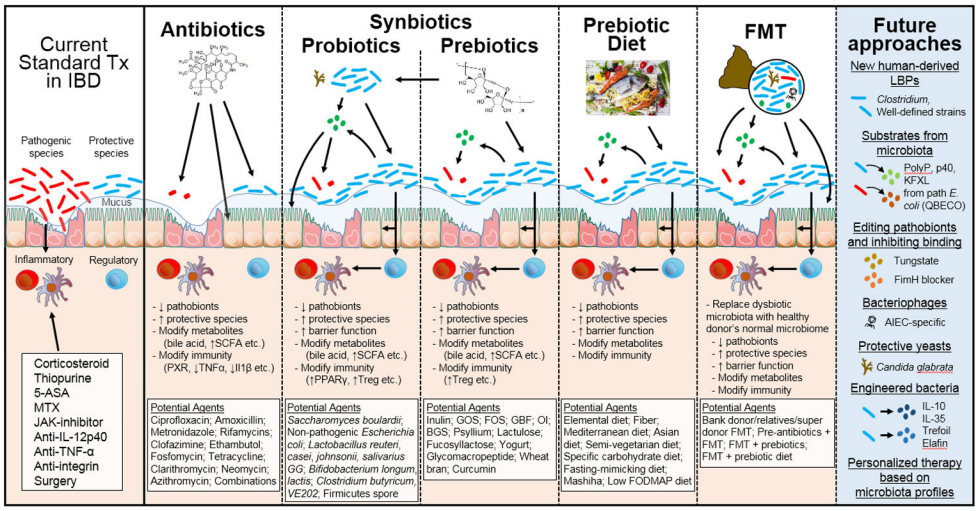

Figure 1.

Graphic overview. The concept of manipulating microbiota to correct dysbiosis is a relatively new approach to treating inflammatory bowel disease (IBD). This review updates the status of current microbial-based and microbial-targeted therapies and prospects for future treatments in IBD. Tx: therapy, 5-ASA: 5-aminosalicylic acid, MTX: methotrexate, JAK: Janus kinase, IL: interleukin, TNF: tumor necrosis factor, SCFA: short chain fatty acid, PXR: pregnane X receptor, PPAR: peroxisome proliferator activated receptor, Treg: regulatory T cell, GOS: galacto-oligosaccharide, FOS: fructo-oligosaccharide, GBF: germinated barley foodstuff, OI: oligofructose-enriched inulin, BGS: bifidogenic growth stimulator, FODMAP: fermentable oligosaccharide, disaccharide, monosaccharide and polyol, FMT: fecal microbiota transplant, LBP: live biotherapeutic product, PolyP: polyphosphate, KFXL: Kangfuxin liquid, path: pathogenic, AIEC: adherent-invasive *Escherichia coli*, Images of antibiotics and prebiotics are adopted from KEGG. Image of prebiotic diet is adopted from Monash University (https://www.monashfodmap.com/blog/a-low-fodmap-mediterranean-style-diet/). Red: aggressive microbial species and cells, blue: protective microbial species and cells.

Table 1

Representative dysbiotic microbiota in IBD

Ulcerative colitis	Pouchitis	Crohn's disease
Bacterial diversity ↓	**Bacterial diversity ↓↑**	**Bacterial diversity ↓**
Proteobacteria ↑	**Proteobacteria**	**Proteobacteria ↑**
Enterobacteriaceae	Enterobacteriaceae	Enterobacteriaceae ↑
E. coli ↑	*E. coli* ↑	Adherent-invasive *E. coli* ↑
		K. pneumoniae ↑
		Pasteurellaceae ↑
		Haemophilus ↑
		Neisseriaceae ↑
Fusobacteria ↑	**Fusobacteria**	**Fusobacteria ↑**
F. varium ↑	*Fusobacterium* ↑	Fusobacteriaceae ↑
Bacteroidetes ↑↓	**Bacteroidetes**	**Bacteroidetes**
Bacteroides ↑	*Bacteroides* ↑	Bacteroiales ↓↑
B. vulgatus ↑		
Firmicutes ↓	**Firmicutes**	**Firmicutes ↓**
Clostridiales ↓		Clostridiales ↓
clusters IV, XIVa, XVIII ↓		clusters IV, XIVa ↓
F. prausnitzii ↓		*F. prausnitzii* ↓
E. rectale ↓	*E. rectale* ↓	*E. rectale* ↓
Ruminococcaceae	Ruminococcaceae	Ruminococcaceae ↓
R. gnavus ↑	*R. gnavus* ↑	*R. gnavus* ↑
clusters I, II, IX, XI ↑		
C. perfringens ↑	*C. perfringens* ↑	
Peptostreptococci ↑		Veillonellaceae ↑
Lachnospiraceae		Lachnospiraceae ↓
Roseburia hominis ↓		Erysipelotrichaceae ↓
Bacilli ↑	Bacilli	Bacilli ↑
E. faecalis ↑	Lactobacilli ↓	Lactobacillus ↓↑
	Actinobacteria	**Actinobacteria**
	Bifidobacteria ↓	Bifidobacteriaceae ↓
Viral diversity ↑		**Viral diversity ↑**
		Caudoviales bacteriopahge ↑
Fungal diversity		**Fungal diversity**
Candida ↑		*Candida* ↑

IBD: inflammatory bowel disease, ↑/↓: increase/decrease in IBD compared to healty, red: increased in IBD, blue: decreased in IBD. References [3,12, 13, 30-39, 60, 84].

Table 2

Antibiotics for IBD (Randomized trials)

Author, year	Disease activity	Case /Control	Base therapy	Agent (s)	Route	Therapy duration	Outcomes, therapy vs control	PMID
Ulcerative colitis								
Dickinson, 1985	active	18/15	Steroid	Vancomycin	oral	7 d	NS	3910524
Chapman, 1986	active	19/20	Steroid	Metronidazole	i.v.	5 d	NS	3536677
Burke, 1990	active	42/42	Steroid	Tobramycin	oral	7 d	Improve clinical and histological score, 74% vs 43%	2104079
Mantzaris, 1994	active	19/20	Steroid	Metronidazole + Tobramycin	i.v.	10 d	NS	8273796
Mantzaris, 1997	active	34/36	Olsalazine, steroid (oral/enema)	Ciprofloxacin	oral	14 d	NS	9068468
Casellas, 1998	active	19/11	Steroid	Amoxicillin	oral	5 d	Improve luminal IL-8 and other inflammatory mediaters	9552221
Turunen, 1998	active	38/45	Steroid, 5-ASA, sulfa	Ciprofloxacin	oral	6 m	Improve endoscopic and histologic scores at 3 mo, but not at 6, 12mo.	9797360
Gionchetti, 1999	active	14/12	Steroid	Rifaximin	oral	10 d	Improve clinical, endoscopic scores, 64% vs 42%	10389700
Mantzaris, 2001	active	29/26	Steroid	Ciprofloxacin	i.v.	10 d	NS	11521989
Ohkusa, 2005	active	10/10	Steroid, 5-ASA, probiotics	Amoxicillin + Tetracycline + Metronidazole	oral	14 d	Improve clinical, endoscopic, and histological scores	16334443
Ohkusa, 2010	active	105/105	Steroid, 5-ASA, immunosuppressant, sulfa	Amoxicillin + Tetracycline + Metronidazole	oral	14 d	Improve clinical, endoscopic, and histological scores	20216533
Turner, 2018	active	16/12	Steroid (i.v.)	Amoxicillin + Vancomycin + Metronidazole + Doxycyclin/ Ciprofloxacin		5 d	Improve clinical score	Abst (a)
Pouchitis								
Madden, 1994	active	11/11		Metronidazole	oral	2 w	Improve stool frequency (73% vs 0%)	8200250
Shen, 2001	active	7/9		Ciprofloxacin vs Metronidazole	oral	2 w	Both improve clinical and endoscopic	11720319

Author, year	Disease activity	Case /Control	Base therapy	Agent (s)	Route	Therapy duration	Outcomes, therapy vs control	PMID
							scores. Efficacy: cipro>metro	
Isaacs, 2007	active	8/9	5-ASA, probiotics, NSAIDs	Rifaximin	oral	4 w	Improve remission rate (25% vs 0%)	17567869
Crohn's disease								
Blichfeldt, 1978	active	20/20	Sulfa, steroid	Metronidazole	oral	2 m	NS	345410
Kelleher, 1982	inactive	10/10		Clofazimine	oral	6 m	Improve relapse rate (0% vs 30%)	Abst (b)
Ambrose, 1985	active	18/16/21/17	Steroid, 5-ASA, AZA	Metronidazole vs Cotrimoxazole vs Combined vs placebo	oral	4 w	At 2w, improve symptoms. At 4w, NS	3882364
Dickinson, 1985	active	4/3	Steroid	Vancomycin	oral	7 d	NS	3910524
Sutherland, 1991	active	33/30/36		Metronidazole low dose vs high dose vs placebo	oral	16 w	Improve clinical score Efficacy: high dose > low dose	1916494
Afdhal, 1991	active	25/24	Steroid	Clofazimine	oral	3 m	NS	2007362
Afdhal, 1991	inactive	16/12		Clofazimine	oral	12 m	NS (reduce clinical score)	2007362
Prantera, 1994	inactive	19/17	Steroid tapering	Clofazimine + Rifampin + Ethambutol + Dapsone	oral	9 m	Improve relapse rate	8147352
Graham, 1995	active	7/8		Clarithromycin	oral	3 m	Improve remission rate (71% vs 13%)	Abst (c)
Goodgame, 2001	active	9/9		Ethambutol + Clarithromycin	oral	3 m	NS	11736715
Arnold, 2002	active	25/12		Ciprofloxacin	oral	1 m	Improve clinical score	11837933
Steinhart, 2002	active	66/64		Ciprofloxacin + Metronidazole	oral	8 w	NS	12105831
West, 2004	fistula	11/13	Anti-TNF-α	Ciprofloxacin	oral	12 w	NS (improve fistula 73% vs 39%)	15606395
Rutgeerts, 2005	inactive	38/40	Steroid	Ornidazole	oral	54 w	Improve recurrence rate (8% vs 38%)	15825069
Prantera, 2006	active	25/27/27	Immunosuppressant, 5-ASA	Rifaximin o.d. vs b.d vs placebo	oral	12 w	NS (improve remission rate) Efficacy: o.d.<b.d.	16611272
Selby, 2007	active	102/111	Steroid	Clarithromycin + Rifabutin +Clofazimine	oral	16 w	Improve remission rate (66% vs 50%)	17570206
Leiper, 2008	active	12/10	Steroid, 5-ASA, AZA	Clarithromycin	oral	3 m	At 1 m, improve clinical scores At 3m, NS	18315579

Author, year	Disease activity	Case /Control	Base therapy	Agent (s)	Route	Therapy duration	Outcomes, therapy vs control	PMID
Thia, 2009	fistula	9/2/7	Immunosuppressant, steroid	Ciprofloxacin vs Metronidazole vs placebo	oral	10 w	NS (remission: 30% vs 0% vs 13%)	18668682
Maeda, 2010	fistula	33/41	Steroid, 5-ASA, immunosuppressant, antibiotics, anti-TNF-α	Metronidazole	oral	4 w	Improve clinical score and perianal discharge and pain	20632322
Prantera, 2012	active	104/98/99/101	Steroid, 5-ASA, immunosuppressant, antibiotics, anti-TNF-α	Rifaximin-EIR low vs mid vs high dose vs placebo	oral	12 w	Improve remission rate by mid-dose 800mg/d (62% vs 43% placebo)	22155172
Herfarth, 2013	inactive	17/16	Steroid, 5-ASA, immunosuppressant	Ciprofroxacin	oral	6 m	NS	23511031
Jigaranu, 2014	active	83/83	5-ASA, AZA, anti-TNF-α	Rifaximin	oral	12 w	Improve remission rate (100% vs 84%)	24969283
Levine, 2019	active	35/38 child		Azithromycin +Metronidazole vs Metronidazole	oral	8 w	Improve remission rate (66% vs 39%)	29420227

IBD: inflammatory bowel disease, PMID: PubMed identifier, NS: no statistically significant difference in disease activity, 5-ASA: 5-aminosalicylic acid, sulfa: salazosulfapyridine, AZA; azathioprine, NSAID: nonsteroidal antiinflammator drug, o.d.: once a day, b.d. twice a day, EIR: extended intestinal release. Abst (a): JCC 2018,12,S366, Abst (b): Gut 1982,23,A449, Abst (c): Gastroenterology 1995,108,A826

Table 3

Probiotics for IBD (Randomized trials)

Author, year	Disease activity	Case /Control	Base Therapy	Agent (s)	Route	Therapy duration	Outcomes, therapy vs control	PMID
Ulcerative colitis								
Kruis, 1997	remission	50/53	Sterpod, salicylates	*Escherichia coli* Nissle1917 vs 5-ASA	oral	12 w	Equivalent relapse rate to 5-ASA	9354192
Rembacken, 1999	active	57/59	Steroid, pre-GEM	*Escherichia coli* Nissle1917 vs 5-ASA	oral	3 m	Equivalent remission rate to 5-ASA	10466665
Rembacken, 1999	remission	44/39	Steroid	*Escherichia coli* Nissle1917 vs 5-ASA	oral	12 m	Equivalent remission rate to 5-ASA	10466665
Ishikawa, 2003	remission	11/10	Steroid, sulfa	bifidobacteria-fermented milk	oral	1 y	Improve relapse rate (27% vs 90%)	12569115
Cui, 2004	remission	15/15		BIFICO (Enterococci, Bifidobacteria, Lactobacilli)	oral	8 w	Improve ralapse rate (20% vs 93%) and cytokine profile	15133865
Kruis, 2004	remission	162/165		*Escherichia coli* Nissle1917 vs 5-ASA	oral	12 m	Equivalent relapse rate to 5-ASA (36% vs 34%)	15479682
Tursi, 2004	active	30/30/30	5-ASA	Low balsalazide + VSL#3 vs med balsalazide vs mesalazine	oral	8 w	Improve remission rate (80% vs 77% vs 53%)	15507864
Kato, 2004	active	10/10	Sulfa	bifidobacteria-fermented milk	oral	12 w	Improve clinical, endoscopi and histological scores	15569116
Shanahan, 2006				*Lactobacillus salivarius* UCC118			NS	Abst (a)
Zocco, 2006	remission	65/60/62		LGG vs 5-ASA vs conbination	oral	12 m	Improve relapse-free time (ralapse rate is similar)	16696804
Miele, 2009	active, newly diagnosed child	14/15	5-ASA, steroid	VSL#3	oral	1 y	Improve remission rate (93% vs 36%), relapse rate (21% vs 73%) and endoscopic and histological scores	19174792
Fujimori, 2009	inactive, mild	40/40/40	5-ASA, steroid	*Bifidobacterium longum* vs Psyllium vs synbiotics	oral	4 w	NS (synbiotics significantly improve remission rate)	19201576
Sood, 2009	active	77/70	5-ASA	VSL#3	oral	12 w	Improve remission rate (43% vs 16%) and clinical scores	19631292
Tursi, 2010	active	65/66	5-ASA, MNZ, AZA	VSL#3	oral	8 w	Improve clinical score (63% vs 41%) Remission rate (48% vs 32%, P=0.069)	20517305
Matthes, 2010	active	24/23/23/20	Steroid	*Escherichia coli* Nissle1917	rectal	2w-	Dose-dependent benefit	20398311
Ng, 2010	active	14/14	5-ASA, AZA	VSL#3	oral	8 w	Improve DC cytokine profiles (↑IL-10, ↓IL-12p40) Clinical	20155842

Author, year	Disease activity	Case /Control	Base Therapy	Agent (s)	Route	Therapy duration	Outcomes, therapy vs control	PMID
							response (71% vs 36%, P=0.06)	
Wildt, 2011	remission	20/12	5-ASA, salazopyrine	Probio-Tec (*Lactobacillus acidophilus* La-5, *Bifidobacterium animalis* subsp. *lactis* BB-12)	oral	52 w	NS (relapse rate: 75% vs 92%)	21453880
D'Inca, 2011	active	8/11/7	5-ASA	Oral *Lactobacillus casei* DG + oral 5-ASA vs rectal *Lactobacillus casei* DG + oral 5-ASA vs oral 5-ASA	oral vs rectal	8 w	TLR4, IL1b,microbiota: only rectal is effective. rectally administered *L. casei* DG, it modified colonic microbiota by increasing Lactobacillus spp. and reducing Enterobacteriaceae.	20737210
Oliva, 2012	active, child	16/15	5-ASA	*Lactobacillus reuteri* ATCC55730	rectal	8 w	Improve clinical and endoscopic Mayo scores, histological scores and cytokine profiles	22150569
Groeger, 2013	active	13/9		*Bifidobacterium infantis* 35624	oral	6-8 w	Reduced CRP, TNF-a, IL-6	23842110
Petersen, 2014	active	25/25/25/25	5-ASA, AZA, 6-MP, steroid	+/− pre-cipro (1w) +/− *E.coli* Nissle1917 (7w)	oral	7 w	NS	24972748
Yoshimatsu, 2015	remission	9/9	5-ASA, salazopyrin	Bio-three (*Streptococcus faecalis* T-110, *Clostridium butyricum* TO-A, *Bificobacterium mesentericus* TO-A)	oral	12 m	Relapse: 0% vs 17%(3m), 9% vs 26%(6m), 22% vs 35%(9m) Remission: 70% vs 57% (12m) P=0.248	26019464
Tamaki, 2016	active	28/28	5-ASA, AZA, steroid	*Bificobacterium longum* BB536	oral	8 w	Improve clinical and endoscopic scores	26418574
Palumbo, 2016	active	30/30	5-ASA	*Lactobacillus salivarius, Lactobacillus acidophilus, Bifidobacterium bifidus* BGN4	oral	24 m	Improve clinical and endoscopic scores	27623957
Matsuoka, 2018	remission	98/97	5-ASA	bifidobacteria-fermented milk	oral	48 w	NS	29450747
Bharat, 2018	active	11/15/15/17		SER-287 (cocktail of Firmicutes spores) placebo/ placebo daily vs vanco/SER287 daily vs placebo/ SER287 weekly vs vanco/ SER-287 weekly	oral	8 w	Improve remission rate (placebo/placebo daily: 0%, vanco/ SER287 daily: 40%, placebo/SER287 weekly: 13.3%, vanco/SER-287 weekly: 17.7%)	Abst (b)
Pouchitis								
Gionchetti, 2000	remission	20/20		VSL#3	oral	9 m	Improve relapse rate (15% vs 100%)	10930365

Author, year	Disease activity	Case /Control	Base Therapy	Agent (s)	Route	Therapy duration	Outcomes, therapy vs control	PMID
Gionchetti, 2003	inactive	20/20		VSL#3	oral	12 m	Improve onset rate (10% vs 40%) and IBDQ	12730861
Kuisma, 2003	active	10/10		*Lactobacillus rhamnosus* GG	oral	3 m	NS	12622759
Mimura, 2004	inactive	20/16		VSL#3	oral	12 m	Improve relapse rate (15% vs 94%) and IBDQ	14684584
Tomasz, 2014	active	22/21		*Lactobacillus acidophilus, Lactobacillus delbrueckii supsp. bulgaricus, Bificobacterium bifidus*	oral	9m	Improve clinical and endoscopic scores and calprotectin	24579075
Yasueda, 2016	inactive	9/8		*Clostridium butyricum* MIYAIRI	oral	24 m	Improve relapse rate (11% vs 50%) and CRP	26510664
Bengtsson, 2016	poor pouch function	16/16		*Lactobacillus plantarum* 299 + *Bifidobacterium infantis* Cure21	oral	21 d	NS	27150635
Crohn's disease								
Plein, 1993	inactive	10/7		*Saccharomyces boulardii*	oral	10 w	Improve CDAI (<150: 90% vs 14%)	8465554
Malchow, 1997	inactive	16/12	Steroid	*Escherichia coli* Nissle1917	oral	3 m	NS	9451682
Malchow, 1997	active, inactive	12/11	Steroid	*Escherichia coli* Nissle1917	oral	12 m	NS (relapse rate: 33% vs 64%)	9451682
Guslandi, 2000	remission	16/16	5-ASA	*Saccharomyces boulardii*	oral	6 m	Improve relapse rate (6% vs 38%)	10961730
Campieri, 2000	remission	20/20		pre-rifaximin + VSL#3 vs 5-ASA	oral	12 m	Improve endoscopic score (80% vs 60%)	Abst (c)
Prantera, 2002	remission	23/22		*Lactobacillus casei* subsp. *rhamnosus*	oral	12 m	NS	12171964
Schultz, 2004	active	5/6	Steroid, antibiotics	*Lactobacillus* GG	oral	6 m	NS	15113451
Bousvaros, 2005	remission	39/36	5-ASA, AZA, 6-MP, steroid	*Lactobacillus* GG	oral	2 y	NS	16116318
Marteau, 2006	inactive	48/50	Steroid	*Lactobacillus johnsonii* LA1	oral	6 m	NS	16377775
Van Gossum, 2007	inactive	34/36		*Lactobacillus johnsonii* LA1	oral	3 m	NS	17206696
Garcia Vilela, 2008	inactive	12/13	5-ASA, AZA, steroid, thalidomide. metronidazole	*Saccharomyces boulardii*	oral	3 m	Improve intestinal permeability	18584523
Bourreille, 2013	inactive	59/66	AZA, 6-MP, steroid, MTX, anti-TNF-α	*Saccharomyces boulardii*	oral	1 y	NS	23466709
Fedorak, 2015	inactive after surgery	59/60		VSL#3	oral	1 y	Improve mucosal inflammatory cytokine levels	25460016

Author, year	Disease activity	Case /Control	Base Therapy	Agent (s)	Route	Therapy duration	Outcomes, therapy vs control	PMID
							Reccurence of lesions (10% vs 27%, P=0.09)	

IBD: inflammatory bowel disease, PMID: PubMed identifier, NS: no statistically significant difference in disease activity, 5-ASA: 5-aminosalicylic acid, sulfa: salazosulfapyridine, AZA; azathioprine, 6-MP: 6-Mercaptopurine, MTX: methotrexate, DC: dendritic cell, TLR: toll-like receptor, IBDQ: inflammatory bowel disease questionnaire, CDAI: Crohn's disease activity index,VSL#3: *Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, *Streptococcus salivarius* subsp. *thermophilus,* bifidobacteria-fermented milk containing *Bifidobacterium breve* Yakult, *Bifidobacterium bifidum* Yakult, *Lactobacillus acidophillus* YIT0168, ↑:increase, ↓:decrease. Abst (a): Gastroenterology 2006, 130, A44, Abst (b): Gastroenterology 2018, 154, S85, Abst (c): Gastroenterology 2000, 118, A781.

Table 4

Prebiotics and synbiotics for IBD (Randomized trials)

Author, year	Disease activity	Case /Control	Base Therapy	Agent (s)	Therapy duration	Outcomes, therapy vs control	PMID
Prebiotics							
Ulcerative colitis							
Hallert, 1991	inactive	16/13		Psyllium	4 m	Improve symptoms	1654592
Ejderhamn, 1992	inactive, child	10/10	Sulfa	Wheat bran vs psyllium	6 m	Reduce total bile acid and modified composition	1360699
Fernandez-Banares, 1999	inactive	35/37/30		Psyllium vs 5-ASA vs combined	12 m	Equivalent relapse rate (40%, 35%, 30%) Increase butyrate	10022641
Hallert, 2003	inactive	22/10		Wheat bran	3 m	Increase butyrate	12769445
Hanai, 2004	inactive	22/37		GBF	12 m	Improve remission period and tapering steroid	15067363
Hafer, 2007	active	7/7	5-ASA, steroid, immunosuppressant or antibiotics	Lactulose	4 m	NS on clinical, endoscopic scores Improve QOL	17784949
Casellas, 2007	active	10/9	5-ASA	Oligofructose-enriched inulin	2 w	Improve fecal calprotectin, symptoms	17439507
Fujimori, 2009	inactive, mild	40/40/40	5-ASA, steroid	Psyllium vs *Bifidobacterium longum* vs synbiotics	4 w	NS on clinical, endoscopic scores Improve QOL	19201576
Faghfoori, 2011	inactive	21/20	Standard drugs	GBF	2 m	Improve inflammatory cytokines	21367884
Faghfoori, 2014	inactive	23/23	Standard drugs	GBF	2 m	Improve CRP, symptoms	25097845
James, 2015	inactive	7/7	5-ASA, steroid, thiopurine	Inulin-type fructans etc.	17 d	Tend to normalise gut transit, but does not increase the proportion of carbohydrate fermented, nor increase short-chain fatty acids	25037189
Pouchitis							
Alles, 1997	inactive	Crossover 15	Steroid	Fructo-oligosaccharide (FOS) or resistant starch	7 d	Resistant starch increases butyrate FOS reduced isobutyrate and isovalerate excretion	9356550
Meijer, 2000	active	Crossover 20		Inulin	3 w	NS (increase butyrate, not significant, correlated with disease activity	11052521
Welters, 2002	active	Crossover 20		Inulin	3 w	Improve endoscopic and histological scores	12004211
Crohn's disease							
Heaton, 1979 (retro)	active	22/32	Steroid, AZA, or sulfa	Fiber-rich, unrefined-carbohydrate diet	4.3 y	Improve hospital admission (fewer and shoter: 111 d vs 533 d), surgical rate (5% vs 16%)	519185

Author, year	Disease activity	Case /Control	Base Therapy	Agent (s)	Therapy duration	Outcomes, therapy vs control	PMID
Jones, 1985	inactive	10/10		Fiber-rich, unrefined-carbohydrate diet	6 m	Improve relapse rate (0% vs 70%) and ESR	2862371
Levenstein, 1985	inactive, active	28/30		Normal diet vs fiber-restricted diet	29 m	Fiber-restriction does not improve outcome (symptoms, need for surgery or hospitalization)	2996991
Hafer, 2007	active	8/9	5-ASA, steroid, immunosuppressant or antibiotics	Lacturose	4 m	NS	17784949
Benjamin, 2011	active	54/49		Fructo-oligosaccharide	4 w	NS (clinical response: 22% vs 39%) Reduce IL-6$^+$ DC, increase IL-10$^+$ DC	21262918
Brotherton, 2011	inactive	4/3		Wheat bran	4 w	Improve QOL	24871666
Joossens, 2012	inactive, active	34/33		Oligofructose-enriched inulin	4 w	Improve disease activity	21749983
De Preter, 2013	inactive, active	25/20		Oligofructose-enriched inulin	4 w	Improve clinical diseaese activity Increase acetaldehyde and butyrate	23303175
Synbiotics (Probiotics + Prebiotics)							
Ulcerative colitis							
Furrie, 2005	active	8/8		*Bifidobacterium longum* + fructo-oligosaccharide/ inulin	4 w	Improve endoscopic score (P=0.06) and b-defencin (P<0.05), TNF-α (P=0.018), IL-1 (P=0.023)	15647189
Fujimori, 2009	inactive, mild	40/40/40	5-ASA, steroid	Psyllium/ *Bifidobacterium longum* /synbiotics	4 w	Improve QOL and CRP	19201576
Ishikawa, 2011	inactive, active	21/20		*Bifidobacterium breve* Yakult + galacto-oligosaccharide	2 w	Improve endoscopic score	21525768
Crohn's disease							
Chermesh, 2007	inactive	20/10		*Pediacoccus pentoseceus, Lactobacillus raffinolactis, L. paracasei* subsp. *paracasei* 19, L. plantarum 2362 and beta-glucans, inulin, pectin, resistant starch	24 m	NS	17211699
Steed, 2010	active	13/11		*Bifidobacterium longum* + fructo-oligosaccharide/ inulin	6 m	Improve remission rate (62% vs 45%), clinial and histological scores and inflammatory cytokines	20735782

IBD: inflammatory bowel disease, PMID: PubMed identifier, NS: no statistically significant difference in disease activity, AZA; azathioprine, sulfa: salazosulfapyridine, 5-ASA: 5-aminosalicylic acid, DC: dendritic cell, QOL: quality of life, ESR: erythrocyte sedimentation rate, GBF: germinated barley foodstuff, CRP: C-reactive protein, CDAI: Crohn's disease activity index.

Table 5

FMT for IBD (RCTs and case serieses)

Author, year	Design	Disease activity	Case /Ctrl	FMT route and others	Outcomes, thrapy vs control	PMID
Ulcerative colitis						
Borody, 2003	Cases	active	6/0	Enema, pre-antibiotics	Clinical response: 100% at 4 m	12811208
Kunde, 2013	Cases	active	10/0 child	Enema	Clinical response: 78% at 1 w Clinical remission: 33% at 1 w	23542823
Moayyedi, 2015	RCT	active	36/34	Enema, multiple	Improve remission rate (24% vs 5%) at 7 w	25857665
Rossen, 2015	RCT	active	23/25	Nasoduodenal, multiple	NS (41% vs 25%, in per-protocol population) at 12 w	25836986
Damman, 2015	Cases	active	7/0	Colonoscopy	Clinical remission: 14% from 1 m until 3 m	26288277
Suskind, 2015	Cases	active	4/0 child	Nasogastric	NS	25647155
Wei, 2015	Cases	active	11/0	Colonoscopy or nasojejunal	Improve Mayo score and IBDQ score at 4 w	26146498
Wei, 2016	Cases	active	10/10	FMT vs FMT +pectin (FMTP)	Mayo scores were significantly lower in the FMTP group than in the FMT at 4 w and 12 w	27809778
Vermeire, 2016	Cases	active	8/0	Colonoscopy or nasojejunal	Endoscopic remission: 25% at 8 w	26519463
Goyal, 2016	Cases	active	7/0	Colonoscopy or nasojejunal	Clinical response: 16% at 180 d	Abst (a)
Paramsothy, 2017	RCT	active	42/43	Single colonoscopy and multiple enema, pooled FMT	Improve remission rate (27% vs 8%) at 8 w	28214091
Jacob, 2017	Cases	active	20/0	Colonoscopy	Clinical response: 35% Clinical remission: 15% Mucosal healing 10% at 4 w	28445246
Uygun, 2017	Cases	active	30/0	Colonoscopy	Clinical response: 70% Clinical&Endoscopic remission: 43% at 12 w	28422836
Ishikawa, 2017	Cases	active	17/19	Colonoscopy, pre-AFM antibiotics + FMT vs AFM alone	Pre-AFM contributed to Bacteroidetes recovery associated with UC activity at 4 w	27893543
Nishida, 2017	Cases	active	41/0	Colonoscopy	Clinical response: 27% at 8 w	27730312
Goyal, 2018	Cases	active	14/0 child	Single upper and lower endoscopy	Clinical response: 50% Clinical remission: 0% at 6 m	29361092
Costello, 2019	RCT	active	38/35	Enema and colonoscopy, anaerobically prepared pooled FMT	Improve remission rate (32% vs 9%) at w8 42% of responder keep remission at 12 m	30644982
Pouchitis						
Landy, 2015	Cases	active	8/0	Nasogastric	Clinical response: 25% Clinical remission: 0%	26264409
El-Nachef, 2016	Cases	active	7/0	Pouchoscopy	Improve symptoms (71%)	Abst (b)
Stallmach, 2016	Cases	active	5/0	multiple	Clinical response: 100% Clinical remission: 4/5	27018122
Herfarth, 2019	RCT -> open	active	6/0	Single colonoscopy and daily oral	Clinical remission: 17% at 2 w	31172007

Author, year	Design	Disease activity	Case /Ctrl	FMT route and others	Outcomes, thrapy vs control	PMID
Selvig, 2019	Cases	active	19/0	Single colonoscopy	NS on clinical activity Improve bowel movement frequency and abd pain, microbial diversity at 4 w	31302808
Crohn's disease						
Suskind, 2015	Cases	active	9/0 child	Nasogastric	Remission: 78% at 2 w	25647155
Cui, 2015	Cases	active	child 30/0	Gastroscope+mid-gut tube	Response (87%), remission (77%)	25168749
Wei, 2015	Cases	active	3/0	Conoloscopy or nasogastric	NS (clinical activity) Improve IBDQ score at 4 w	26146498
Vanghn, 2016	Cases	active	19/0	Colonoscopy	Clinical response (58%) Increase in colonic regulatory T cells at 12 w	27542133
Vermeire, 2016	Cases	active	6/0	Colonoscopy or nasojejunal	NS	26519463
Goyal, 2016	Cases	active	4/0 child	Nasojejunal and colonoscopy	Response: 75% at 180 d	Abst (a)
He, 2017	Cases	active	25/0	Colonoscopy + tube	Response: 68%, Remission: 52% reduce inflammatory mass	28684845
Goyal, 2018	Cases	active	7/0 child	Single upper and lower endoscopy	Response: 71%, remission: 29% at 6m	29361092
Li, 2019	Cases	active	165/0	Mid-gut/nasal-jejunal transendoscopic enteral tubing	Analysis of timing for sencond FMT Second<4 m is better	30357440

IBD: inflammatory bowel disease, FMT, fecal microbiota transplantation, RCT: randomized controlled trial, PMID: PubMed identifier, NS: no statistically significant difference in disease activity, IBDQ: inflammatory bowel disease questionnaire, AFM: amoxicillin, fosfomycin, metronidazole. Abst (a): JPGN 2016, 63, S212, Abst (b): Gastroenterology 2016, 150, S544.

Table 6

Ongoing microbial-based and microbial-targeted clinical trials in IBD (Randomized trials)

NCT number	Country	Start year	Agent (s)	Target disease (s)	Others
Antibiotics					
NCT00061282	US	2002	Clotrimazole	Pouchitis	
NCT00603616	US	2008	Rifaximin	CD (active)	Induction of remission
NCT01951326	US	2013	Anti-*Mycobacterium*	CD (active)	Induction of remission
NCT02033408	Canada, Italy, Finland, Israel, Poland, Spain	2014	Antibiotics and FMT	UC, CD	
NCT01783106	UK	2014	Ciprofloxacin, Doxycycline, Hydroxychloroquine, Budesonide	CD	
NCT02620007	France	2015	Ciprofloxacin Rifaximin	CD (active)	Induction of remission AIEC targeted
NCT03537157	Italy	2017	Rifaximin	CD (post-ope)	
NCT03476317 NCT02765256	US	2018	Vancomycin, Neomycin, Ciprofloxacin Polyethylene Glycol, Fluconazole	CD (refractory)	
NCT03221166	Italy	2018	Thalidomide, Infliximab	CD (new onset)	
NCT04082559	Israel	2019	Personalized antibiotics (Ciprofoxacin, Doxycycline) + diet (SCD, MSD)	Pouchitis, CD	
NCT03794765	India	2019	Adjuvant ceftriaxone, metronidazole	UC (active)	
NCT03986996	Israel	2019	Amoxicillin+Tetracycline +Metronidazole vs Amoxicillin +Tetracycline	UC	Induction of remission
LBP (probiotics)					
NCT03266484	US	2017	Mixture (8 different bacterial strains)	CD, UC (inactive)	
NCT03415711	Italy	2017	VSL#3	UC (active)	Induction of clinical and endoscopic remission
NCT04102852	Italy	2019	*Lactobacillus rhamnosus* GG	UC (active)	Induction of clinical remission
Prebiotics					
NCT02825914	Denmark	2016	Casein glycomacropepptide	UC	
NCT03500653	Israel	2018	Curcumin	IBD	
NCT03653481	US	2018	Oligofructoseenriched Inulin	IBD	
NCT03847467	US	2019	Fucosyllactose	CD, UC (child, adult)	Patients receiving stable maintenance anti-TNF therapy
NCT03998488	US	2019	FMT + Psyllium	UC (active)	
NCT02277223	Israel	2019	Curcumin	UC (pediatric)	
NCT02683759	India	2019	Curcumin	UC	
Diet					

NCT number	Country	Start year	Agent (s)	Target disease (s)	Others
NCT04046913	UK	2013	Low additive diet	CD	
NCT02472457	US	2015	Crohn's Disease Exclusion Diet	CD	
NCT02796339	Greece	2016	Mastiha (Pistacia lentiscus)	IBD	
NCT02734589	France, Israel, Italy	2017	Novel diet for the donor + FMT	UC	
NCT03000101	Italy	2017	Pomegranate	CD, UC	Protocol in PMID 31171016
NCT03012542	US	2017	carbohydrates- or fiber- controled diet	CD	
NCT03053713	Canada	2017	MSD	UC	
NCT03058679	US	2017	MSD, SCD	CD	
NCT03301311	US	2018	SCD, modified SCD	CD, UC (inactive)	
NCT02843100	Canada, Ireland, Israel, Spain	2018	Modified Exclusive Enteral Nutrition, Crohn's Disease Exclusion Diet, Partial Enteral Nutrition, Standard Exclusive Enteral Nutrition	CD	
NCT04143633	Mexico	2018	Low FOMAP diet	UC	
NCT02201758	Canada	2018	Flaxseed lignanenriched complex	UC	
NCT04147585	US	2019	Intermittent reduced calorie diet	CD	
NCT03615690	US	2019	Fasting mimicking diet	UC	
NCT04082559	Israel	2019	Personalized antibiotics (Ciprofoxacin, Doxycycline) + diet (SCD, MSD)	Pouchitis	
NCT03850600	US	2019	Diet intervention (no details)	CD (pregnancy)	
NCT04014517	Italy	2019	Nestle IMPACT	CD	Prevention of reccurence after surgery
NCT03980405	Israel	2019	Ulcerative collitis diet	UC	Adjuvant to 5-ASA
NCT04018040	Australia	2019	Lacto-ovo vegetarian diet	UC	
Synbiotics					
NCT02865707	Canada	2016	Synergy-1	UC	Prevention of relapse
FMT					
NCT01790061	China	2012	Standardized FMT vs traditional FMT	UC	
NCT02636517	US	2015	FMT	CD, UC	
NCT02390726	US	2015	FMT	UC (active)	
NCT03561532	Finland	2016	FMT	UC	
NCT02291523	US	2016	FMT	UC (pediatric)	
NCT02606032	Canada	2016	4 arms of pre-antibiotics + FMT	UC (active)	
NCT03078803	Canada	2017	FMT via colonoscope or oral FMT	CD	
NCT03110289	Belgium	2017	FMT superdonor vs FMT autologous	UC	Superdonor is based on abundance of taxa of the investigators' interest
NCT03273465	Israel	2017	FMT	UC (active)	

NCT number	Country	Start year	Agent (s)	Target disease (s)	Others
NCT03104036	Czechia	2017	FMT vs 5-ASA enema	UC (active)	
NCT03006809	US	2017	+/−Pre-Ax + low/high FMT	UC (active)	
NCT03378167	Canada	2018	FMT oral	CD (pediatric)	
NCT03582969	Israel	2018	FMT	UC (pediatric)	
NCT03378921	Finland	2018	FMT	UC, Pouchitis	
NCT03716388	India	2018	FMT vs FMT+5-ASA vs 5-ASA	UC (active)	
NCT04100291	Denmark	2019	FMT	UC, Pouchitis	
NCT03843385	Germany	2019	FMT-filtrated vs FMT vs Plaebo	UC	
NCT03829475	US	2019	FMT	+/− Bezlotoxumab	IBD
NCT03998488	US	2019	FMT+Psyllium	UC (active)	
NCT03483246	France	2019	FMT	UC	
NCT03747718	US	2019	FMT single vs maintainance	CD	
NCT04034758	China	2019	Heterologous FMT	UC (active, adult, older adult)	
NCT03804931	China	2019	5-ASA/steroid +/− FMT	UC	
NCT03948919	US	2019	Low sulfur FMT	UC (active)	
NCT03917095	China	2019	Colonic transendoscopic enteral tubing	UC (active)	
Bacteriophage					
NCT03808103	US	2019	EcoActive	CD	

Information from ClinicalTrials.gov., IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis, FMT: fecal microbiota transplant, 5-ASA: 5-aminosalicylic acid, PMID: PubMed identifier, SCD: specific carbohydrate diet, MSD: mediterranean style diet, FOMAP:low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol , AIEC: adherent-invasive Escherichia coli