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**Intestinal microbiota: The explosive mixture at the origin of inflammatory bowel disease?**

Bringiotti R *et al.* Microbiota and inflammatory bowel diseases

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**Abstract**

The inflammatory bowel diseases (IBD), namely Crohn’s disease and Ulcerative colitis, are lifelong chronic disorders arising from interactions among genetic, immunological and environmental factors. Although the origin of IBD is closely linked to immune response alterations and this point governs most medical decision making, recent findings suggest that gut microbiota may be involved in the IBD pathogenesis. Epidemiologic evidence and several studies have shown that a dysregulation of gut microbiota (*i.e.,* dysbiosis) may trigger the onset of intestinal disorders such as IBD. Animal and human investigations focused on the microbiota-IBD relationship have suggested an altered balance of the intestinal microbial population in the active phase of IBD. Rigorous microbiota typing could, therefore, soon become part of a complete phenotypic analysis of IBD patients. Moreover, individual susceptibility and environmental triggers such as nutrition, medications, age or smoking could modify bacterial strains in the bowel habitat. Pharmacological manipulation of bowel microbiota is somewhat controversial. The employment of antibiotics, probiotics, prebiotics and synbiotics has been widely addressed in the literature worldwide, with the aim of obtaining positive results in few IBD patients settings, and determining the right timing and modality of this intervention. In the latest, novel treatments for IBD, such as Fecal Microbiota Transplantation, when accepted by patients, show promising results. Controlled studies are being designed. In the near future, new therapeutic strategies can be expected, with non-pathogenic or modified food organisms that can be genetically planned to exert anti-inflammatory properties.

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**Key words:** Intestinal microbiota; Inflammatory bowel diseases; Probiotics; Prebiotics; Symbiotics

**Core tip:** This paper focuses on the scientific scenario about a potential function of gut microbiota in the inflammatory bowel diseases (IBD) origin. Epidemiologic findings suggest that heterogeneity and disruption of gut microbiota can be significant in modulating and addressing the immune reactions underlying the IBD pathogenesis. Traditional or innovative manipulation strategies of gut microbiota may be possible future treatment options for the management of these disorders.

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**INTRODUCTION**

The inflammatory bowel diseases (IBD) are lifelong chronic disorders arising from interactions among genetic, immunological and environmental factors[1].

Technological advances have allowed novel predictive factors to be assessed, that can identify the disease in an early stage and determine an accurate diagnosis even long before the onset of clinical manifestations[2]. Recent findings suggest that, in addition to genetic and environmental factors, interactions with the gut microbiota may play a relevant role in a “Perfect Storm” driving the pathogenesis of IBD[3].

**MICROBIOTA AND IBD**

The human intestinal tract includes several and multifaceted microbial populations with an essential function for general health. Human gut contains, in the assortment of 1000 bacterial species, 100-fold more genes than human genome. The new high throughput sequencing technologies, as also the presence of 16S rRNA genes in the gut bacterial composition, as well as recent non genomic techniques, have well-stated the function of gut microbiota in some human diseases[4,5].

Although the microbiota of the colon is apparently similar in different people, there are marked variations between individuals in different bacterial populations within the single species. It has been, moreover, demonstrated that an increase in biodiversity requires a different metabolic homeostasis and structural stability, while deteriorating species configuration, due to elderly, illness or antibiotics, reduce the capacity of the intestinal environment to fight infecting pathogens[6,7].

In fact, epidemiological evidence and experimental studies have suggested that the falling-out of the gut microbiota (*i.e.*, dysbiosis) can be relevant for intestinal conditions such as chronic IBD[8].

Clinical evidence confirms the role of microbiota in IBD and an abnormal microbial composition in IBD has been amply demonstrated. The most common site of IBD is the colon, where the highest intestinal bacterial concentrations are found. Additionally, fecal stream diversion can prevent and treat Crohn’s disease and pouchitis. Finally, many studies have shown that antibiotics and probiotics improve the histological, endoscopic and clinical picture[9]. Despite this evidence-based platform, there are still some unexplained hit points such as the IBD response to immunosuppressive therapy or the protective role of poor hygienic conditions, which do not appear likely to be related to the microbiota state[10].

***Animals studies***

It is known that non-pathogenic microbiota controls bowel immunity, but interactions in the gut with host-microbes can be bidirectional. The mucosal immune system can be affected by the pro-inflammatory potential of an abnormal growth of microbiota elements and ultimately determine or influence an inflammatory reaction and induce a possibility of illness development. Several animal studies have shown that this interaction is possible and can induce colitis.

Germ-free interleukin 10-deficient (IL-10-/-) mice, that fail to acquire spontaneous colitis and immune activation, support this hypothesis[11]. Indeed, some studies show that regardless of the background strain of these animals, the onset and degree of spontaneous colitis depends on the setting of the enteric gut microbiota[11,12]. Penetrance of colitis increases to nearly 100% when immune system response is characterized by a T-helper 1 (Th1) IFN-gamma reaction [12].

Therefore, in this prototype of colitis, it has been demonstrated that the disease may show different characteristics and distribution based on the intestinal bacteria presence. Furthermore, IL-10-/- germ-free - mice bacterial colonization of non-pathogenic bacteria such as *Escherichia coli* or *Bilophila wadsworthia* provokes different types of colitis[13]. In particular, *Bilophila wadsworthia* produces a low grade colitis involving the distal colon, associated to an exclusively Th1-mediated immune response. In contrast, *Escherichia coli* conducts to an early (3 wk) development of mild-moderate inflammation that is more severe in the cecum. In the same study, *Bacteroides vulgatus*, but not *Escherichia coli,* provokes mucosal inflammation of the colon in HLA-B27 transgenic mice without bone marrow involvement in transplanted CD3 transgenic mice[13].

Finally, novel experimental evidences demonstrated that *Klebsiella* may provoke moderate pancolitis while *Bifidobacterium animali*s could cause a mild degree of inflammation in the distal colon and duodenum[14,15].

***Human studies***

A few studies in humans have suggested that IBD patients seem to have an altered balance of intestinal microbiota in the active phase. Bacterial 16S rRNA gene examination did not show relevant differences in bacterial constitution in the intestinal mucosa of CD and UC patients. Moreover, in ulcerative colitis (UC) patients a more decreased bacterial load was observed even if it was not significant when compared to CD ones[16-18].

Therefore, another interesting finding, *i.e.*, a thinner and less suphated mucus in patients affected by UC has been demonstrated and may account for an increased number of bacteria colonizing the mucosa[19,20]. Indeed, a poor mucus layer with a microbiota overgrowth could enhance the presentation of bacterial antigens to the immune system of gut mucosa. In UC patients the colonic surface and inflamed areas are colonized by a broad variety of bacteria. For example, in UC specimens *Clostridium histolyticum* and *lituseburense* accounted for the 21% of the microbiota composition. *Enterobacteriaceae* such as *Escherichia* and *Klebsiella* have also been considered to be implicated in the pathogenetic mechanism of UC. Indeed, their aptitude to adhere to enterocytes, penetrate mucosal layer thus delivering enterotoxins, might account for this hypothesis[21,22].

***Genetics in IBD pathogenesis***

The interaction between genetic factors and a deregulated response of immune system to bacterial antigens are still strongly supported hypotheses in the pathogenesis of IBD. Indeed, the Genome Wide Association Studies (GWAS) showed that several genes are associated with IBD susceptibility[23]. These genes, that are genetic risk factors for CD and UC, encode for proteins that may discern the microbiota (NOD2/CARD15) or may control host responses (IL-12-IL23R pathway or autophagy)[24,25] and constitute a barrier function notably for UC[26].

One of these proteins, the “NOD2”, may be crucial in order to distinguish between non-pathogenic and pathogenic organisms; indeed, it starts the signal transduction thus promoting NFĸB translocation into the nucleus, where the expression of specific genes determinates the response of primary and adaptive immune mechanisms[27-29].

The multi-functionality genetic linkage of NOD2/CARD15 is demonstrated by the protein ability to identify bacterial muramyl-dipeptide and by the capacity to impact on the homeostasis of non-pathogenic bacteria, regulatory T cells (Tregs), and viral identification by immune system[24].

Although the condition of NOD2 homozygosity may carry a 20-fold propensity to CD, notably for ileal location, less than 20% of patients affected by CD are homozygous for NOD2 polymorphisms[30,31]. So, while these studies and GWAS have provided important details about the IBD pathogenesis, investigations on genetic variant distribution in different populations are poor to explain the large discrepancies in IBD prevalence between different geographic areas as well as the increasing incidence of IBD in Western countries over the past five decades[2].

These evidences strongly support that IBD are polygenetic disorders and their heterogeneity is due to the complexity of their genetic background as well as to different lifestyles and environmental exposure, including a variable microbiota composition.

***Environmental triggers***

It is known that nutrition, medications (NSAIDs) and smoking affect the configuration of the gut microbiota and it is known that changes in this multifaceted structure have been identified as contributing factors in the origin of some disorders including IBD.

Smoking is a relevant risk factor in CD pathogenesis[[32-36]](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597605/). Indeed, it may alter intestinal microbiota as well as its interruption may further modify intestinal microbial arrangement. Indeed, simultaneous increased *Firmicutes* and *Actinobacteria* and decreased *Proteobacteria* and *Bacteroidetes* characterize smoking cessation; by contrast, the composition of the flora in continuous smokers and non-smokers remains stable[[37]](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597605/).

As regards the altered gut microbiota composition, many studies have reported a modification in migrants populations, from developing to developed countries [[38]](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597605/). In these subjects, diet, family size, antibiotic assumption, urbanization, declining parasitism, reduction of exposure to infantile infections such as hepatitis A and *Helicobacter pylori,* are associated with changed microbiota.

Newborns show a sterile or, at least, characterized by a very low microbial load intestine[39]. Bacterial strains colonize infant bowel after delivery according to some factors, as way of delivery, breast or artificial feeding, antibiotic administration[40]. There is an early colonization of *Lactobacillus* and *Prevotella* after vaginal delivery and a colonization by a higher rate of *Firmicutes* in neonates delivered by cesarean section, that predisposes to a greater susceptibility to some pathogens and a higher risk of atopic disease[41,42].. Therefore, growth from newborn to early childhood and finally adulthood is associated with changes in gut microbiota, featuring a reduction of *Lactobacillus* and *Bifidobacteria* and increase of *Firmicutes, Clostridia* and *Bacteroides* species, that may lead to a high risk of allergic and immunological diseases[43]. This raises the hypothesis that a decreased biodiversity within non-pathogenic microbiota, with an altered immunity maturation, could negatively influence the immune recognition and activation, and thereby determinate a risk for developing an IBD in adulthood[38].

As regards the impact of a high-fat dietary intake on the non-pathogenic microbiota, it has been demonstrated that it can radically remodel the intestinal microbiota[44,45]. Moreover, there is evidence that non-absorbed carbohydrates (inulin and fructooligosaccharides) promote the growth of beneficial species, supplying a substrate for the production of short-chain fatty acids (SCFAs)[46].

Recently, novel studies have focused on the role of NSAIDs in inducing and maintaining mucosal damage, thus contributing to the genesis of IBD. In particular, several evidences demonstrated that NSAIDs are able to cause an injury by means of microbiota modulation[47]. NSAIDs, indeed, can promote the overexpression of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and Interferon gamma (IFNγ) through the mediation of the microbiota[48], and further allow bacterial translocation through the intestinal barrier. This hypothesis is confirmed by the evidence that the levels of such proinflammatory cytokines are significantly increased in IBD patients.

***Microbiota and IBD: Comments on the literature data***

There can be no doubt, in view of all the experimental data, that microbiota can be considered a key actor in the origin of IBD and not only a by-stander. Studies performed on animal models provide strong evidence for a primary role played by microbiota in IBD but human studies do not fully support this pathogenic hypothesis owing to the lack of sufficient scientific proof. For instance, it is well-known that in CD the entire alimentary tract from the oral cavity to the anus may be involved, but no data from human studies are available about this topic. Conversely, animal studies have demonstrated that the microbiota composition may influence the onset of IBD in a selected part of the digestive system. El Aidy *et al*[49] investigated the responses of the jejunal mucosa to bacterial colonization in germ-free mice, showing a consequent shift to anaerobic metabolism, a condition that may strongly influence the mucosal oxygenation in IBD. Moreover, in an experimental model of small bowel CD, a single strain of *E. coli* (LF82) has been demonstrated to stimulate the production of proinflammatory cytokines, an effect that was counteracted by lactoferrin, another microbial product[50].

There has been much discussion as to whether infectious factors could be a trigger for IBD. No evidence is available from human studies, but animal models offer interesting insights. Couturier-Maillard *et al*[51] demonstrated that microbiota transplantation from healthy wild type mice may reduce the IBD risk in Nod2-deficient mice and lead to long-term alterations in the gut microbiota. On the other hand, disease risk was promoted in wild-type mice that were recolonized with dysbiotic fecal microbiota from Nod2-deficient mice. In conclusion, animal models must be seen as just a starting point for microbiota investigation in man, and the main lesson that we can deduce is that an imbalance of bacterial species is one of the main reasons that can explain the “different types of colitis” induced by the effect of different bacteria.

**PHARMACOLOGICAL MANIPULATION OF MICROBIOTA IN IBD:**

***Antibiotics***

Antibiotics are established to have an important role in the management of septic complications of IBD, *e.g.*, the intra-abdominal and perianal abscesses and fistulae of Crohn’s disease, superinfections, and post-surgical wound infective complications. Nonetheless, the treatment with antibiotics for active luminal CD and UC is not widely accepted as a first-line choice. Although the use of antibiotics against pathogenic bacteria is proven and based on the relying evidences of experimental enterocolitis and IBD, there are some clinical trials that do not sufficiently support the efficacy of these drugs in patients affected by IBD[52].

The most representative published studies are summarized in Table 1[53-68]. Metronidazole, ciprofloxacin, or the contemporary use of these agents are useful in Crohn’s colitis, ileocolitis and pouchitis, but not in isolated ileal location. They are recommended for pouchitis in the European Crohn’s and Colitis Organisation (ECCO) statements, which also indicate that ciprofloxacin seems to have less side effects (statements 8C, 8D)[69].

***Probiotics***

Probiotics are viable microorganisms that have been cultured from foods, in particular milk. Various species and bacterial strains that have been used in IBD clinical trials, are believed to have a potential beneficial role. The most evaluated probiotics are *Escherichia coli Nissle*[70], *VSL#3* mixture (four strains of *lactobacilli*, three strains of *bifidobacteria*, and one strain of *Streptococcus salivarius Thermophilus* )[68, 71-73], *BIO-THREE* mixture (*Streptococcus faecalis, Clostridium butyricum,* and *Bacillus mesentericus*)[74], a mixture of *Lactobacillus rhamnosus* and *Lactobacillus reuteri*[75], *Lactobacillus rhamnosus GG*[76], Yakult strains of *Bifidobacterium brevis, Bifidobacterium bifidum and lactobacillus acidophilus*[77]. Recently, advanced genetic engineering has produced modified species that are able to produce immunosuppressive molecules such as interleukin-10 (IL-10)[78].

These studies have shown that probiotics supplementation can re-establish bacterial homeostasis in the intestine and downregulate gut inflammation that characterizes IBD patients, thus modulating the inflammatory/anti-inflammatory balance. A reduction in the number of microbiome elements was also found. Indeed, the administration of probiotics can normalize altered intestinal microbiota in IBD patients, and increase protective species by reducing pathogen load, positively affecting intestinal permeability, balancing local immune response, producing beneficial substances, disintegrating pathogenic antigens in intestinal lumen[79].

In animal model experiments (Table 2) *Lactobacilli* and *Bifidobacteria* reduced the severity of experimental colitis in IL-10 knockout mice[80, 81]..

In another study *Lactobacillus plantarum* prevented colitis onset in HLA B27 transgenic rats. This and other reports confirm the protective effects of several probiotics in selected hosts and special inflammatory conditions. Therefore, in experimental colitis induced in B27 transgenic rats, achieving remission with broad-spectrum antibiotics, probiotics prevented recurrence of colitis. However, the only probiotic treatment was unable to determinate the remission of induced disease[82].

Probiotics beneficial effect was demonstrated in rats with induced colitis by instillation of 4% acetic acid, thus causing altered intestinal permeability. In particular, after four days of acetic acid treatment the activity of myeloperoxidase (MPO) had a three-fold increase, paralleling with a six-fold increase of mucosal permeability in the colonic samples. The use of *Lactobacillus reuteri R2LC,* after acetic acid administration, reduced the morphological score, MPO activity, mucosal permeability, and blocked the onset of colitis[83].

In human studies, a 9-mo daily use of a probiotic formula, *i.e.*, *VSL#3,* was effective to prevent the relapse of chronic pouchitis after remission induced by antibiotics[68]. Another investigation replicated the same results, and, in addition, showed a decreased frequency of pouchitis when *VSL#3* was given starting from the achievement of pouch closure[84].

In cases of mild-to-moderate active UC, treated with probiotics, the improvement in clinical severity, the reduction of relapses, and the induction of remission were proven. Moreover, these findings paralleled with high histological scores and increased levels of faecal butyrate and other SCFAs[73-77].

Indeed, basic science studies in UC patients underlined that the prevention of flare-ups by probiotics was associated with inactivation of NF-κB, down-regulation of TNF-α and IL-1β, with a simultaneous increase of anti-inflammatory cytokines, such as IL-10[85]. Few data are available about the mechanism by which probiotics could modify the composition of the resident microbiota, even though it has been hypothesized that they might increase the load of *lactobacilli* and/or *bifidobacteria*[74,85].

On the other hand, clinical trials with the use of probiotics in CD, are less concordant than in UC. Malchow et al found that *Escherichia coli Nissle* was more effective than placebo in preventing relapse of CD in the remission phase induced by conventional therapy[86], but supplementation of probiotics was found to be ineffective in prolonging remission after the administration of *Lactobacillus johnsonii LA1* following surgical resection[87, 88]. Similarly, a study of Prantera et al, did not demonstrate any benefit by *Lactobacillus GG* 1 year-assumption in the prevention of post-surgical clinical or endoscopic relapses in the neo-terminal ileum[80].

As reported above, Butterworth *et al*[89] evaluated twelve potentially relevant studies of the efficacy of probiotics in CD, even if eleven did not fulfill inclusion criteria. In the only study satisfying stated criteria, patients with moderate active CD received *Lactobacillus rhamnosus* GG for 6 months without obtaining the expected results.

***Prebiotics***

Prebiotics are dietary supplementations, usually non digestible glycides, which are energetic substrates for protective intestinal organisms. Lactosucrose, fructo-oligosaccharides, inulin, bran, psyllium, and germinated barley extracts promote *Lactobacilli and Bifidobacteria* growth, thus inducing SCFA production, in particular butyrate[90-92]. Therefore, these substances are able to re-establish the optimal beneficial/pathogen bacteria ratio in IBD patients. These physiological dietary supplements raise protective lactic acid bacilli load, with a consequent inhibition of harmful species by decreasing the luminal pH, reducing epithelial adhesion, and producing bactericidal molecules.

Animal studies elicited a protective effect in rat colitis models (Table 3)[93,94]. Several small controlled studies but only few randomized controlled trials (RTC) in IBD patients have been performed, less than the studies with probiotics.

Interestingly, Welter et al carried out a clinical trial in twenty patients with an ileal pouch-anal anastomosis who assumed 24 g of inulin or placebo daily for 3 wk. pH, short chain fatty acids, microflora, and bile acids were assayed in the stools, while the inflammatory status was evaluated by clinical, endoscopic and histological parameters. It was proven that the treatment enhanced butyrate levels, reduced pH, diminished the number of *Bacteroides fragili*s as well as fecal concentrations of secondary bile acids. These findings were accompanied by reduction of inflammation in the ileal reservoir mucosa[95].

In another open label study, ten patients with active ileocolonic CD were enrolled to receive a daily three week 15 g dose of Fructo-oligosaccharides (FOS). Harvey Bradshaw index was chosen to assess the disease activity and fluorescence in situ hybridization was used to calculate *bifidobacteria* in stools; flow cytometry of dissociated rectal biopsies evaluated mucosal dendritic cell, IL-10 and TLR expression. The results of this study were promising: the use of FOS determinated a significant reduction in the Harvey Bradshaw index, and a significant increase in faecal *bifidobacteria* concentrations. The percentage of IL-10 positive dendritic cells was amplified from 30% to 53%. Moreover, an increase of the percentage of dendritic cells expressing TLR2 and TLR4 was found (from 1.7% to 36.8% and from 3.6% to 75.4%, respectively) [96].

***Symbiotics***

Probiotic therapy can potentially be improved by simultaneous administering of prebiotics (non-digestible and non-absorbable carbohydrates) that enhance probiotic proliferation in the gut. This mixture is referred as a symbiotic. The main benefit of symbiotic formulation is that prebiotic constituent could positively modulate the increase of local microbiota, which is further regulated by probiotic component of synbiotic formulation. In animal models, Schultz et al evaluated the effect of a symbioticpreparation composed by a probiotic combination of *lactobacilli, bifidobacteria* and inulin (SIM) in HLA-B27-beta(2)-microglobulin transgenic (TG) rats affected by severe colitis. After 4 mo of SIM treatment, the colonic disease achieved histological improvement and, furthermore, there was an alteration in the microflora profile, featuring an increased variety, and specifically stimulated growth of *Bifidobacterium animalis* as compared to untreated rats[97].

Few well conducted studies have supported the usefulness of symbiotic supplementation. Furrie *et al*[98], in a double-blinded RTC, developed a symbiotic called Synergy 1, made up of a combination of a probiotic (*Bifidobacterium longum*) and a prebiotic composed by an inulin-oligofructose providing metabolic substrate for the *Bifidobacterium* strain, obtaining promising results in UC patients.

***Faecal* *transplantation***

A novel promising treatment for the IBD is faecal microbiota transplantation (FMT). FMT consists of taking gastrointestinal microbiota from a healthy donor, which is then instilled via enema through a liquid stool suspension. FMT has recently gained ground as a therapy for refractory and/or recurrent *Clostridium difficile* infection[99-102].

In a recent systematic review conducted by Anderson *et al*[103], following Cochraine and PRISMA recommendations, 5320 articles on FMT in patients with IBD were identified. 17 articles were selected, including reports on FMT given for single cases to treat IBD and others for management of infectious diarrhoea in IBD. The 17 trials enclosed 41 subjects followed up for 2 wk-13 years. FMT was able to determinate a reduction of symptoms in most of IBD patients, the interruption of IBD medications and disease remission. In those patients who experienced a contemporary *Clostridium difficile* infection, a complete eradication of the bacterium was achieved. Even though this procedure may face difficult acceptance by patients, the review describes promising results.

Despite there are no sufficient data on FMT in IBD, this procedure is potentially an effective and safe treatment; it may be suggested in subjects who failed conventional treatments. It is necessary to perform new well-designed and randomized trials to enrich the data about FMT in IBD to: (1) evaluate safety and success rate; and (2) to standardize protocols. Without these considerations, FMT could not become a standard part of clinical therapy[103].

**CONCLUSION**

Patients affected by IBD, either UC or CD, suffer from a heterogeneic entity whose pathogenic etiology must be explored in the context of a “multihit” phenomenon that precipitates the disease through a multi factorial platform resulting from interactions among genetic, immunological and environmental triggers. Although the microbiota may probably play a crucial role in the origin of IBD, up-to date therapeutic strategies have a primary purpose of suppressing the host response, and so a significant fraction of patients fail to accomplish sustained remission.

While novel techniques in molecular biology and engineering have enabled further discoveries about the gut microbiota, the relationship between intestinal microbiota and IBD has not been completely yet clarified. A better comprehension of the role that some bacterial species play in the IBD pathogenesis is essential in order to develop appropriate management strategies.

The possibility of modulating our gut community by interventions on microbial “intelligence” and the right timing of this operation have important implications on efforts to improve gastro-intestinal health. Nevertheless, microbiology should support, but not replace, the genetics of IBD, and meticulous typing of the intestinal microflora should shortly take a decisive place for the complete characterization in order to explore the relationship between genes and environment in healthy and disease. Finally, the future needs to be directed towards two areas: (1) improvements of strain selection with the goal to realize new screening procedures for a better understanding of the mechanisms of action, and ensure an adequate efficacy; (2) a new therapeutic strategy with non pathogenic organisms of alimentary origin that can be genetically modified with the aim of producing anti-inflammatory substances.

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**Table 1 Antibiotic therapy in inflammatory bowel diseases**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Ref. | Year | | Antibiotics | Duration | Result |
| **Crohn’s disease—primary therapy** | |  | | | | |
| Ursing[53] | 1982 | | Metronidazole 800 mg/d | 16 wk | No difference from sulfasalazine |
| Sutherlan [54] | 1991 | | Metronidazole 10 or 20 mg/kg | 16 wk | Superior to placebo (↓ CDAI), no difference in remission |
| Colombel[55] | 1999 | | Ciprofloxacin 500 mg 2 × day | 6 wk | No difference from mesalamine |
| Arnold[56] | 2002 | | Ciprofloxacin 500 mg 2 × day | 6 mo | Superior to placebo (CDAI) |
| Prantera[57] | 1996 | | Ciprofloxacin 500 mg 2 × day + metronidazole 250 mg 4 × day | 12 wk | No difference from prednisolone |
| Greenbloom[58] | 1998 | | Ciprofloxacin 500 mg 2 × day + metronidazole 250 mg 3 × day | 10 wk | Uncontrolled, 68% remission |
| Leiper[59] | 2000 | | Clarithromycin 250 mg 2 × day | 4 wk | Uncontrolled, 64% response, 48% remission |
| Steinhart[60] | 2002 | | Ciprofloxacin 500 mg 2 × day + metronidazole 250 mg 3 × day | 8 wk | No improvement over budesonide alone (33% *vs* 38% remission) |
| **Crohn’s disease-prevention of postsurgical relapse** | |  | | | | |
| Rutgeerts[61] | 1995 | | Metronidazole 20 mg/kg | 12 wk | ↓ clinical relapse 1 yr *vs* placebo |
| Rutgeerts[62] | 2005 | | Ornidazole 1 g/d | 52 wk | ↓ severe endoscopic relapse *vs* placebo |
| **Ulcerative colitis-primary therapy** | |  | | | | |
| Turunen [63] | 1999 | | Cipro 500 mg 2 × day | 6 mo | Superior to placebo |
| Mantzaris [64] | 1997 | | Cipro 500 mg 2 × day | 6 mo | No benefit *vs* placebo |
| Casellas [65] | 1998 | | Amoxicillin 1 g/ Clavulanic acid 250 mg | 5 days | ↓ mucosal IL-8 and eicosanoids *vs* placebo |
| Turner [66] | 2014 | | metronidazole, amoxicillin, doxycycline (Paediatrics) |  | Remission (46.6%) |
| **Pouchitis** | |  | | | | |
| Shen [67] | 2001 | | Metronidazole 20 mg/kg or Cipro 500 mg 2 × day | 6 mo | Both effective, Cipro > metronidazole |
| Gionchetti [68] | 2000 | | Cipro 500 mg 2 × day and Rifaximin 1 g 2 × day | 5 days | 89% response, 33% remission, uncontrolled |

**Table 2 Probiotic therapy in inflammatory bowel diseases**

|  |  |  |
| --- | --- | --- |
| **Model** | **Probiotic** | **Effect** |
| Trinitrobenzene sulphonic acid or dinitrobenezene sulphonic acid | *Bi. infantis* | No effect |
|  | *L. acidophilus*, *L. casei* and *Bi. animalis* | Reduced inflammation |
|  | VSL#3 | No effect |
|  | *Lactobacillus GG* | No effect |
|  | *L. plantarum* 299 | No effect |
|  | VSL#3 (DNA, subcutaneously) | Reduced inflammation |
| Iodoacetamide | VSL#3 | Reduced inflammation |
|  | *Lactobacillus GG* | Reduced inflammation |
| Acetic acid | *L. rhamnosus GG* | No effect |
|  | *L. reuteri R2LC* | Reduced inflammation |
|  | *L. reuteri R2LC* | Reduced inflammation |
| Dextran sodium sulphate | VSL#3 (irradiated and DNA\*) | Reduced inflammation |
| IL-10 knockout mice | *L. salivarius* 118 (subcutaneously) | Reduced inflammation |
|  | *L. salivarius* | Reduced inflammation |
|  | *Bi. infantis* | Reduced inflammation |
|  | *L. plantarum* 299*V* | Reduced inflammation |
|  | VSL#3 | Reduced inflammation |
|  | *L. salivarius* | Reduced inflammation |
|  | *L. reuteri* | Reduced inflammation |
|  | VSL#3 (DNA, subcutaneously) | Reduced inflammation |
| *E. coli*-induced colitis in IL-2 knockout mice | *B. vulgatus* | Reduced inflammation |
| *B. vulgatus*-induced colitis | *Lactobacillus GG* | Prevented recurrent colitis |
|  | *L. plantarum* 299*V* | No prevention of recurrent colitis |

**Table 3 Inflammatory bowel diseases prebiotic therapy**

|  |  |  |
| --- | --- | --- |
| **Model** | **Prebiotic** | **Effect** |
| Trinitrobenzene sulphonic acid | Fructo-oligosaccharide | Reduced inflammation |
|  | Galacto-oligosaccharide | No effect on inflammation |
| Dextran sodium sulphate | Fructo-oligosaccharide | No effect on inflammation |
|  | Resistant starch | Reduced inflammation |
|  | Germinated barley foodstuff | Reduced inflammation |
|  | Germinated barley foodstuff | Reduced inflammation |
|  | Inulin | Reduced inflammation |
|  | Germinated barley foodstuff | Reduced inflammation |
| IL-10 knockout mice | Lactulose | Reduced inflammation |