# Probiotics, Prebiotics, and Antibiotics in IBD

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Paolo Gionchetti, Carlo Calabrese, Andrea Calafiore, and Fernando Rizzello

## Introduction

The rationale for using probiotics, prebiotics, and antibiotics in IBD is based on convincing evidence that implicates intestinal bacteria in the pathogenesis of the disease. The distal ileum and the colon are the areas with the highest bacterial concentrations and represent the sites of inflammation in IBD. Similarly, pouchitis, the nonspecific inflammation of the ileal reservoir after ileo-anal anastomosis, appears to be associated with bacterial overgrowth and dysbiosis. Enteric bacteria and their products have been found within the inflamed mucosa of patients with Crohn's disease (CD) [1]. The composition of the enteric flora is altered in patients with IBD. Increased numbers of aggressive bacteria, such as Bacteroides, adherent/invasive Escherichia coli, and enterococci, and decreased numbers of protective lactobacilli and bifidobacteria have been observed [2]. Manichanh et al. reported a restriction of biodiversity in the fecal microbiota of CD patients [3]. The phylum Firmicutes and particularly the species *F. prausnitzii* are underrepresented in active CD and UC compared with healthy subjects [4], and reduction of *F. prausnitzii* is associated with higher risk of postoperative recurrence of ileal CD [5]. There is evidence of a loss of immunological tolerance to commensal bacteria in patients with IBD [6]. Patients with CD consistently respond to diversion of fecal stream, with immediate recurrence of inflammation after restoration of intestinal continuity or infusion of luminal content into the bypassed ileum [7, 8]. Furthermore, pouchitis does not occur prior to closure of the ileostomy [9].

P. Gionchetti, M.D. (✉) • C. Calabrese • A. Calafiore • F. Rizzello
Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Policlinico S. Orsola, Via Massarenti 9, 40138 Bologna, Italy
e-mail: paolo.gionchetti@unibo.it

The most compelling evidence that intestinal bacteria play a role in IBD is derived from animal models. Despite great diversity in genetic defects and immunopathology, a consistent feature of many transgenic and knockout mutant murine models of colitis is that the presence of normal enteric flora is required for full expression of inflammation [10].

All of these observations suggest that IBD may be prevented or treated by the manipulation of intestinal microflora, and increasing evidence supports a therapeutic role for probiotics, prebiotics, and antibiotics in IBD [11].

## Probiotics

The potential benefit of probiotics in health maintenance and disease prevention has long been acknowledged. At the turn of the last century, the Russian Nobel Prize winner Elie Metchnikoff suggested that high concentrations of lactobacilli in the intestinal flora were important for health and longevity in humans [12]. Probiotics are defined as "living organisms, which upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition" [13].

The bacteria most commonly associated with probiotic activity are lactobacilli, bifidobacteria, and streptococci, but other, nonpathogenic bacteria (e.g., some strains of *E. coli*) and nonbacterial organisms (e.g., the yeast *Saccharomyces boulardii*) have been used (Table 46.1). It is believed that in order to be clinically useful for probiotics it is important to be: resistant to acid and bile, metabolically active within the luminal flora, where they should survive but not persist in the long term, antagonistic against pathogenic bacteria, safe for human use, and viable following manufacturing processes [14].

Several mechanisms have been proposed to account for the action of probiotics (Table 46.2). These may include modulation of microbiota, enhancement of barrier function,



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**Table 46.1** Organisms associated with probiotic activity

| |
|---|
| *Bacteria* |
| • Lactobacilli |
| • Bifidobacteria |
| • Streptococci |
| • Enterococci |
| • Nonpathogenic *Escherichia coli* |
| Nonbacterial organisms |
| • The yeast *Saccharomyces boulardii* |

**Table 46.2** Mechanisms of action of probiotics

| Action | Mechanism |
|---|---|
| Inhibit pathogenic enteric bacteria | • Decrease luminal pH<br>• Secrete bacteriocidal proteins<br>• Colonization resistance<br>• Block epithelial binding |
| Improve epithelial and mucosal barrier function | • Produce short-chain fatty acids<br>• Enhance mucus production<br>• Increase barrier integrity |
| Alter immunoregulation | • Increase IL-10 and TGF-β and decrease TNF-α<br>• Increase immunoglobulin A production |

*IL-10* interleukin-10, *TGF-β* transforming growth factor-β, *TNF* tumor necrosis factor-α

and immunomodulation through direct effects of probiotic bacteria on different immune and epithelial cell types [15].

## Studies in Animal Models

Encouraging results have been obtained with probiotic therapy in experimental colitis. Administration of *Lactobacillus reuteri* has been shown to significantly reduce inflammation in acetic acid- and methotrexate-induced colitis in rats [16, 17]. More recently, a mixture of species of lactobacilli was shown to prevent the development of spontaneous colitis in interleukin-10 (IL-10)-deficient mice [18], and continuous feeding with *Lactobacillus plantarum* was shown to attenuate established colitis in the same knockout model [19]. A strain of Lactobacillus, *Lactobacillus salivarius* subsp. salivarius UCC18, has been reported to reduce the rate of progression from inflammation through dysplasia and colon cancer in IL-10-deficient mice [20]. Furthermore, certain strains of Bifidobacterium infantis and L. salivarius have been shown to attenuate inflammation by reducing T helper type 1 cytokine production in the IL-10 knockout model [21]. Shibolet and colleagues demonstrated that VSL#3 (VSL Pharmaceuticals, Inc., Ft. Laudersdale, FL, USA), a cocktail of probiotic bacteria, significantly attenuates inflammation by decreasing myeloperoxidase and nitric oxide synthase activity in iodoacetamide-induced colitis in rats [22]. Using the same probiotic mixture, Madsen and colleagues reported a significant improvement in inflammation, a reduction in mucosal levels of proinflammatory cytokines, and normalization of colonic barrier integrity in IL-10 knockout mice [23]. More recently Pagnini et al. have shown that VSL#3 was able to promote gut health through stimulation of the innate immune system in a model of chronic CD-like ileitis [24].

## Ulcerative Colitis

Tables 46.3 and 46.4 summarize results of clinical trials carried-out with probiotics in UC. Three double-blind, controlled trials have evaluated the efficacy of the probiotic preparation Escherichia coli Nissle 1917 (ECN) in the prevention of relapses of ulcerative colitis (UC). In the first study 120 patients with UC were treated for 12 weeks with either $5 \times 10^{10}$ colony forming units (cfu) of ECN or 1.5 g/day mesalazine. After 12 weeks 16 % of the patients in ECN group and 11.3 % in the mesalazine group relapsed. The statistical power of this study was low and duration of treatment too short, and therefore the equivalence was not demonstrated [25]. In the second study 116 patients were treated with ECN or mesalazine at lower dose (1.2 g/day) for 1 year. Surprisingly high relapse rate occurred in both the ECN and mesalazine group (67 % versus 73 %) [26]. In the third study 327 patients were treated with either ECN or mesalazine (1.5 g/day) for 1 year. The relapse rate was respectively of 36 % and 34 % in the probiotic group and mesalazine, showing equivalence of the two treatments in an appropriate way [27].

More recently the same preparation has been used as enemas in patients with mild to moderate distal UC in a double-blind study. Ninety patients were randomly assigned to receive 40, 20, or 10 ml containing ECN or placebo for 8 weeks. In the PP analysis ECN rectal application was significantly superior to placebo and well tolerated, in contrast to ITT analysis [28].

In another small randomized controlled trial, Ishikawa et al. evaluated the efficacy of a Bifidobacterium fermented milk as a dietary adjunct in maintaining remission of UC. Twenty-one patients were included in the study; in the group treated with Bifidobacterium fermented milk 3 of (27 %) patients had a relapse of UC compared with 10 of 11 (90 %) of patients in the control group [29]. Similarly, in a 4-week, open-label study, 25 patients with mild to moderate clinical flare-up were treated with the yeast *S. boulardii* at the dose of 250 mg three times/day for 4 weeks; 17 patients (68 %) attained clinical remission [30].

**Table 46.3** Probiotics in UC: induction of remission

| Study | *N* | Duration | Probiotic | Control | Remission Probiotic/Cont | *P* |
|---|---|---|---|---|---|---|
| Rembacken 1999 | 116 | 4 months | Prednisone/ Gentamicin + *E. coli* Nissle | Prednisone/ Gentamicin + 5ASA | 68 %; 75 % | Equal to 5ASA? Pred effect |
| Guslandi 2003 | 25 | 1 month | *S. boulardii* | Open label | 68 % | |
| Bibiloni 2005 | 34 | 6 week | VSL#3 | Open label | 63 % | |
| Sood 2009 | 147 | 12 week | VSL#3 | Placebo | 32.5 %; 10 % | <0.001 |
| Tursi 2010 | 144 | 8 week | VSL#3 | Placebo | Improvement in UCDAI 60.5 %, | <0.017 |
| Miele 2009 | 29 | 1 month | VSL#3 | Placebo | 92 % 36.4 % | <0.001 |
| Huynh et al. 2009 | 13 | 8 week | VSL#3 | Open label | 56 % | |

**Table 46.4** Probiotics in UC: maintenance of remission

| Study | *N* | Duration | Probiotic | Control | Remission Probiotic; Cont | *P* |
|---|---|---|---|---|---|---|
| Rembacken 1999 | 116 | 12 months | *E. coli* Nissle | 5ASA | 26 %; 25 % | Relapse rates near placebo |
| Kruis 1997 | 120 | 3 months | *E. coli* Nissle | 5ASA | 84 %; 89 % | Equivalence to 5ASA |
| Kruis 2004 | 327 | 12 months | *E. coli* Nissle | 5ASA | 64 %; 66 % | Equivalence to 5ASA |
| Venturi 1999 | 20 | 12 months | VSL#3 | Open label | 75 % | |
| Ishikawa 2003 | 21 | 12 months | Bifidobacterium fermented milk | Placebo | 73 %; 10 % | 0.018 |
| Miele 2009 Pediatric patients | 29 | 12 months | VSL#3 | Mesalamine | 79.6 %;26.7 % | 0.014 |

Also VSL#3 has been investigated in the treatment of UC. This product contains cells of four strains of lactobacilli (*L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii* subsp. bulgaricus), three strains of bifidobacteria (*B. longum*, *B. breve*, *B. infantis*), and one strain of *Streptococcus salivarius* subsp. thermophilus. Each packet of VSL#3 contains 450 billion viable lyophilized bacteria. A pilot study was performed using VSL#3 as a maintenance treatment in UC patients in remission who were either allergic or intolerant to sulfasalazine and mesalazine. Patients ($n=20$) received, $1.8\times10^{12}$ CFU VSL#3 for 12 months and were assessed clinically and endoscopically at baseline, at 6 and 12 months, or if relapse occurred.

Fecal concentrations of lactobacilli, bifidobacteria, and *S. thermophilus* were significantly increased by VSL#3. In total, 15 of the 20 patients (75 %) remained in remission during the study [31]. In an open-label study, high-dose VSL#3 ($3.6\times10^{12}$ CFU) induced remission, after 6 weeks, in 63 % of patients with active mild-to-moderate disease, who failed to respond to mesalazine or corticosteroids, and was associated with a positive response in a further 23 % [32]. In a multicenter, double-blind, placebo-controlled trial 147 patients with mild to moderate UC were randomized to receive either $3.6\times10^{12}$ CFU VSL#3 or placebo for 12 weeks. At 6 weeks the rate of patients with >50 % reduction in UCDAI (primary end-point) were respectively 32.5 and 10 % for VSL#3 and placebo ($p=0.001$). At 12 weeks the rate of remission was 42.9 % for VSL#3 and 15.7 % for placebo ($p<0.001$). The VSL# group had significantly greater decreases in UCDAI scores and individual symptoms at weeks 6 and 12 weeks compared with placebo group [33].

More recently, in a multicenter, double-blind, randomized, placebo-controlled study, a total of 144 patients with relapsing UC, while on treatment with salicylates or immunosuppressants, were treated with either VSL#3 (71 patients) at the dose of $3.6\times10^{12}$ CFU/day or placebo (73 patients) for 8 weeks. The decrease of UC activity index (UCDAI) scores of 50 % or more and improvement in rectal bleeding were significantly higher in the VSL#3 treated group, while endoscopic improvement and remission rate did not reach statistical significance. Only few patients reported mild side-effects with placebo and VSL#3 [34].

In two small recent studies, VSL#3 has been reported to achieve remission/response in children with mild to moderate UC. In the first double-blind, placebo-controlled study, 29 patients with newly diagnosed UC were randomized to receive either VSL#3 (weight-based dose, range $0.45\times10^{12}$ CFU -$1.8\times10^{12}$ CFU) or placebo both in induction and

maintenance of remission in adjunct to standard therapy. Remission was achieved in 13 (92.8 %) treated with VSL#3 and in 4 (36.4 %) treated with placebo ($p < 0.001$). VSL#3 was also significantly superior in maintenance of remission [35]. In the second, open-label trial, 18 patients with mild to moderate active UC were treated with VSL#3 in two divided doses (the dose was based on the age of children) for 8 weeks; 10 (56 %) children achieved remission after 8 weeks, and post-VSL#3 treatment demonstrated a bacterial taxonomy change in rectal biopsy. VSL#3 was well tolerated [36].

## Pouchitis

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for most patients with ulcerative colitis (UC) requiring colectomy Pouchitis is a nonspecific inflammation of the ileal reservoir and the most common complication of IPAA in patients with UC [37]. Its frequency is related to the duration of follow up, occurring in up to 50 % of patients 10 years after IPAA in large series from major referral centers [38–44]. It is most frequently seen within the first year after ileostomy closure.

Symptoms related to pouchitis include increased stool frequency and liquidity, abdominal cramping, urgency, tenesmus and pelvic discomfort [45]. Rectal bleeding, fever, or extraintestinal manifestations may occur. Fecal incontinence may occur in the absence of pouchitis after IPAA, but is more common in patients with pouchitis. Symptoms of pouch dysfunction in patients with IPAA may be caused by conditions other than pouchitis, including Crohn's disease of the pouch, cuffitis, and an irritable pouch. This is why the diagnosis depends on endoscopic and histological findings in conjunction with symptoms.

On the basis of symptoms and endoscopy, pouchitis can be divided into remission (normal pouch frequency) or active pouchitis (increased frequency with endoscopic appearances and histology consistent with pouchitis) [46, 47]. Active pouchitis may then be divided into acute or chronic, depending on the symptom duration. The threshold for chronicity is a symptom duration of >4 weeks. Up to 10 % of patients develop chronic pouchitis requiring long-term treatment, and a small subgroup has pouchitis refractory to medical treatment [5]. The Pouchitis Disease Activity Index (PDAI) has been developed to standardize diagnostic criteria and assess the severity of pouchitis [48]. The PDAI is a composite score that evaluates symptoms, endoscopy and histology. Each component of the score has a maximum of 6 points. Patients with a total PDAI score ≥7 are classified as having pouchitis although a patient should exhibit both clinical symptoms and endoscopic or histological evidence of pouchitis.

Pouchitis recurs in more than 50 % patients; patients with recurrent pouchitis can broadly be grouped into three categories: infrequent episodes (<1/year), a relapsing course (1–3 episodes/year) or a continuous course. Pouchitis may further be termed treatment responsive or refractory, based on response to antibiotic monotherapy [37, 45].

In the majority of cases the etiology and pathogenesis of pouchitis remains unclear, and patients are labelled as having idiopathic pouchitis. Risk factors, genetic associations, and serological markers of pouchitis suggest that a close interaction between the host immune response and the pouch microbiota plays a relevant role in the etiology of this idiopathic inflammatory condition [49]. Although we do not know the cause of pouchitis, we do believe that the intestinal microbial community plays an important role in maintaining pouch health or driving pouch inflammation [50]. In support of this assumption, it is observed that pouchitis only occurs after restoration of the fecal stream through the pouch [51, 52]. In addition a dysbiosis in pouchitis has been documented [53], and several genes associated with the innate immune response and microbial sensing and recognition have been associated with an increased risk for pouchitis including the NOD2/CARD15 gene [54, 55], Il-1 receptor antagonist gene [56], and Toll-like receptor genes [57].

Table 46.5 summarizes the results of trials carried-out with probiotics in pouchitis. A double-blind study to compare the efficacy of VSL#3 with placebo in the maintenance treatment of chronic pouchitis was carried-out. Patients ($n = 40$) who were in clinical and endoscopic remission after 1 month of combined antibiotic treatment (2 g/day of rifaximin plus 1 g/day of ciprofloxacin) were randomized to receive either VSL#3 ($1.8 \times 10^{12}$ CFU) or placebo for 9 months. Patients were assessed clinically every month, and assessed endoscopically and histologically at entry and every 2 months thereafter. Stool culture was performed before and after antibiotic treatment, and monthly during maintenance treatment. Relapse was defined as an increase of at least 2 points in the clinical section of the Pouchitis Disease Activity Index (PDAI) and was confirmed endoscopically and histologically. All 20 patients treated with placebo relapsed during the follow-up period. In contrast, 17 of the 20 (85 %) patients treated with VSL#3 were still in remission after 9 months. Interestingly, all these 17 patients relapsed within 4 months of suspension of the active treatment. Fecal concentrations of lactobacilli, bifidobacteria, and *S. thermophilus* were significantly increased within 1 month of treatment initiation and remained stable throughout the study only in the group treated with VSL#3 [58]. A subsequent double-blind, placebo-controlled study on the effectiveness of VSL#3 (at a daily dose of $1.8 \times 10^{12}$ CFU) in the maintenance of antibiotic-induced remission in patients with refractory or recurrent pouchitis reported similar results [59]. After 1 year of

**Table 46.5** Probiotics in pouchitis

| Study | *N* | Duration | Probiotic | Control | Remission Probiotic; Cont | *P* |
|---|---|---|---|---|---|---|
| *Gionchetti 2002* [Maintenance: antibiotic–remission] | 40 | 9 months | VSL#3 | Placebo | 85 %; 0 % | <0.001 |
| *Mimura 2004* [Maintenance: antibiotic–remission] | 36 | 12 months | VSL#3 | Placebo | 85 %; 6 % | <0.001 |
| *Gionchetti 2003* [Prevention of onset] | 40 | 12 months | VSL#3 | Placebo | 90 %; 60 % | <0.05 |
| *Shen 2005* [Maintenance antibiotic-dependent] | 31 | 8 months | VSL#3 | Open label | 19.4 % | ns |
| *Kuisma 2003* [Acute pouchitis] | 20 | 3 months | *Lactobacillus GG* | Placebo | 0 %; 0 % | ns |
| *Gionchetti 2007* [Acute pouchitis] | 29 | 4 weeks | VSL#3 | Open label | 69 % | P<0.01 |

treatment, 85 % of those in the VSL#3 group were in remission versus only 6 % of those in the placebo group. As regards the mechanism of action of VSL#3 in these patients, continuous administration of VSL#3 decreases matrix metalloproteinase activity, significantly increases tissue levels of IL-10, and significantly decreases tissue levels of the proinflammatory cytokines IL-1, tumor necrosis factor-α, and interferon γ [60].

In contrast, however, a more recent 8-month open-label clinical study reported that less than 20 % of patients treated with were able to maintain remission in clinical practice [61].

The reason for the difference in these results is not clear but differences in the design and protocol of the two studies may have contributed. Particularly, studies by Gionchetti and colleagues and Mimura and colleagues excluded patients who did not achieve complete or near-complete endoscopic remission whereas Shen et al. did not repeat the pouchoscopy after clinical remission. It is known that some patients do not achieve endoscopic remission despite clinical remission following antibiotic treatment, and it is possible that this subset of patients have a more difficult to treat disease which may not respond to probiotics. Gionchetti's and Mimura's groups used a combination of ciprofloxacin and rifaximin or metronidazole for 4 weeks whereas Shen and colleagues used a 2-week course of ciprofloxacin only to induce remission. It is possible that probiotic therapy is more effective following a combination of two different antibiotic agents for a prolonged period. Gionchetti and colleagues' and Mimura and colleagues' studies recruited patients with refractory pouchitis, defined as three or more episodes of pouchitis per year, whereas Shen and colleagues only recruited patients with chronic antibiotic-dependent pouchitis, defined as four or more episodes of pouchitis per year. Therefore, many of the patients included in the studies of Gionchetti's and Mimura's groups had less-aggressive disease in which maintenance of remission may have been easier to achieve. Finally patients had to purchase VSL#3 which was obtained from the company's website; VSL#3 is not covered by insurance and therefore patient's adherence to therapy was a problem; moreover, because VSL#3 was self-administered by patients, medicine counts and prescription records were impossible. Further, fecal bacteriology, as in the previous study, was not done and this further raises the issue of adherence to therapy.

In a 3-month double-blind, placebo-controlled trial *Lactobacillus rhamnosus* strain GG (two gelatin capsules/day of $0.5–1 \times 10^{10}$ CFU/capsule) in patients with a previous history of pouchitis showed that this probiotic was not effective in preventing relapses [62].

Recently, probiotic treatment with Ecologic 825 was able to restore mucosal barrier during maintenance therapy after clinical remission was achieved with combined antibiotic treatment [63].

The efficacy of VSL#3 in the prevention of pouchitis onset was evaluated in a double-blind, placebo-controlled trial [64]. Within 1 week after ileostomy closure, 40 patients were randomized to receive either VSL#3 ($0.9 \times 10^{12}$ CFU) or placebo for 12 months. Patients were assessed clinically, endoscopically, and histologically at 1, 3, 6, 9, and 12 months according to PDAI score. During the first year after ileostomy closure, patients treated with VSL#3 had a significantly lower incidence of acute pouchitis compared with those treated with placebo (10 % vs. 40 %; $p<0.05$). Moreover, IBD questionnaire score was significantly improved only in the group treated with VSL#3 and among those who did not develop pouchitis, the median stool frequency was significantly lower in the VSL#3 group. More recently, an open-label study evaluated the efficacy of high-dose of VSL#3

($3.6 \times 10^{12}$ CFU/day) in the treatment of mild pouchitis, defined as a score between 7 and 12 in the PDAI. Sixteen of 29 patients (69 %) were in remission after 4 weeks [65].

The treatment and prevention of pouchitis has been systematically reviewed in 2010 by a Cochrane analysis [66] In the Cochrane systematic review VSL#3 was more effective than placebo in maintaining remission of chronic pouchitis in patients who achieved remission with antibiotics and VSL#3 was more effective than placebo for the prevention of pouchitis . European Crohn's Colitis (ECCO) guidelines state that VSL#3 is effective in maintaining antibiotic-induced remission and in preventing pouchitis onset [67].

## Crohn's Disease

Tables 46.6 and 46.7 summarize the results of clinical trials carried-out in CD. In a small pilot study, E. coli Nissle 1917 was compared with placebo in the maintenance of steroid-induced remission of colonic CD [68]. Twelve patients were treated with *E. coli* Nissle 1917 and 11 were treated with placebo. At the end of the 12-week treatment period, relapse rates were 33 % in the *E. coli* group and 63 % in the placebo group; unfortunately, due the very small number of patients treated, this difference did not reach statistical significance. In a small, comparative, 6-month, open-label study, 32 patients with CD in clinical remission were randomized to receive either combination therapy with the yeast *S. boulardii* (1 g/day) plus mesalamine (2 g/day) or mesalamine (3 g/day). Relapse rates were 37.5 % and 6.25 % respectively in the mesalamine monotherapy group and in the combination group [69]. In a 1-year, double-blind, placebo-controlled trial, Lactobacillus. GG was not effective in the prevention of postoperative recurrence [70]. Similarly in a double-blind trial Lactobacillus GG was shown not be superior than placebo in prolonging remission in children with CD when given as an adjunct to standard therapy [71].

Two randomized double-blind, placebo-controlled study showed *Lactobacillus johnsonii* LA1 ($4 \times 10^9$ cfu/day) was not superior to placebo to prevent endoscopic recurrence of CD [72, 73].

More recently, in a randomized, placebo-controlled trial, the effects of *Saccharomyces boulardii* in patients with CD who underwent remission after therapy with steroids or salicylates were evaluated. Patients were assigned to placebo or *Saccharomyces boulardii* (1 g/day) for 52 weeks. Relapse rate was not significantly different between the two groups (53.2 % in placebo vs 47.5 % in *Saccharomyces boulardii*), as was the time to relapse [74].

We performed a single-blind study to compare a sequential antibiotic–probiotic treatment with mesalazine in the prevention of postoperative recurrence of CD. Within 1 week after curative surgery, 40 patients were randomized to receive either high-dose rifaximin (a nonabsorbable wide-spectrum antibiotic) for 3 months followed by VSL#3 ($1.8 \times 10^{12}$ CFU/

**Table 46.6** Probiotics in CD: maintenance of remission

| Study | *N* | Duration | Probiotic | Control | Remission Probiotic; Cont | *P* |
|---|---|---|---|---|---|---|
| Malchow 1997 | 28 | 12 months | *E. coli* Nissle 1917 | Placebo | 70 %; 30 % | ns |
| Guslandi 2000 | 32 | 6 months | *S. boulardii* | 5ASA | 62.5 %;93.75 % | 0.04 |
| Bousvaros 2005 | 75 | 24 months | *L. rhamnosus* GG + standard therapy | Placebo + standard therapy | 71 %; 83 % | ns |
| Willert 2010 | 38 | 12 months | VSL#3+ standard therapy | Placebo + standard therapy | 43 %; 11 % | ns |

**Table 46.7** Probiotics in CD: prevention of postoperative recurrence

| Study | *N* | Duration | Probiotic | Control | Remission Probiotic; Cont | *P* |
|---|---|---|---|---|---|---|
| Campieri 2000 | 40 | 12 months | Rifaximin × 3 months followed by VSL#3 | 5ASA | Endoscopic 80 %; 60 % | Benefit probiotic |
| Prantera 2002 | 45 | 12 months | *L. rhamnosus* GG | Placebo | Clinical 83 %; 89 % Endoscopic 40 %; 65 % | ns |
| Marteau 2006 | 98 | 6 months | *L. johnsonii* LA1 | Placebo | Endoscopic 51 %; 36 % | ns |
| Van Gossum 2006 | 70 | 3 months | *L. johnsonii* LA1 | Placebo | Endoscopic 21 %; 15 % | ns |
| Fedorak 2015 | 119 | 90 days | VSL#3 | Placebo | Endoscopic 10 %; 26.7 % | ns |

day) for 9 months, or mesalazine (4 g/day) for 12 months. Patients were assessed clinically and endoscopically at 3 and 12 months. Compared with placebo, the combined antibiotic–probiotic treatment was associated with a significantly lower incidence of severe endoscopic recurrence, both at 3 months (10 % vs. 40 %; $p < 0.01$) and 12 months (20 % vs. 40 %; $p < 0.01$) [75].

More recently, VSL#3 at the dose of $1.8 \times 10^{12}$ CFU/day, was shown not to be superior than placebo in maintaining remission in colonic CD, in a 12-month, randomized, double-blind trial [76].

Finally, the ability of VSL#3 to prevent CD recurrence after surgery, was tested in a multicenter, randomized, double-blind, placebo-controlled trial [77].

Patients were randomized, within 30 days after resection, to receive one sachet of VSL#3 (900 billion viable bacteria) ($n = 59$) or placebo ($N = 60$). Ileocolonoscopy was performed after 90 and 365 days; patients with either no or mild recurrence at day 90 received VSL#3 until day 365. There were no statistical differences in endoscopic recurrence at day 90. Patients receiving VSL#3 ha significantly reduced mucosal inflammatory cytokines levels compared with placebo. This together with the lower rate of recurrence among patients who received early VSL#3 (for all 365 days) suggest a possible beneficial effect of this probiotic for prevention of postoperative CD.

## Prebiotics

Prebiotics are dietary substances, usually nondigestible carbohydrates, which beneficially affect the host by selectively stimulating the growth and activity of protective commensal enteric bacteria (Table 46.3) [78]. Fructo-oligosaccharides (FOS), inulin, bran, psyllium, and germinated barley foodstuff (GBF) stimulate the growth of bifidobacteria and lactobacilli, which in turn antagonize pathogenic bacteria by decreasing the luminal pH, inducing colonization resistance, and inhibiting epithelial adhesion and translocation. In addition, these substances increase bacterial fermentation, which produces SCFAs (especially butyrate) that improve epithelial barrier function [79]. These findings suggest that prebiotics are functionally equivalent to probiotic bacteria.

## Studies in Animal Models

A variety of different prebiotic preparations have been tested in animal models of colitis. Lactulose has been shown to attenuate inflammation and to stimulate the growth of lactobacilli in IL-10 knockout mice [18], while administration of inulin and GBF has been shown to inhibit dextran sodium sulfate (DSS)-induced colitis in rats by increasing the luminal concentration of SCFAs, lactobacilli, and bifidobacteria [80, 81]. Experiments on FOS have produced conflicting results. Cherbut et al. reported that FOS attenuates the trinitrobenzene sulfonic acid-induced colitis in rats [82], while Moreau et al. reported no benefit of FOS in the DSS rat model of colitis [83]. Furthermore, a combination of inulin and FOS significantly decreased inflammation in HLA-B27 transgenic rats [84]. Taken together, these findings suggest that combination therapy with different prebiotics may be more effective than monotherapy, due to the fact that each agent has specific biological properties.

## Human IBD Studies

A few small, controlled studies have investigated the use of prebiotics in UC, whereas there have been no studies on prebiotics in CD or pouchitis. In a small group of UC patients in remission, psyllium (also known as ispaghula or *Plantago ovata*) was shown to be superior to placebo in decreasing symptom severity, and produced a significant increase in the fecal concentration of bifidobacteria [85]. In an open-label, randomized trial, *Plantago ovata* seeds, which have previously been shown to stimulate the production of SCFAs, were tested as a maintenance treatment in UC patients in remission [86]. In this 12-month study, 105 patients were randomized to receive either *Plantago ovata* seeds alone (10 g twice daily), mesalamine alone (500 mg three times daily), or a combination of *Plantago ovata* seeds plus mesalamine at the same doses administered for monotherapy. Rates of remission were similar for the three groups, and a significant increase in the fecal concentration of butyrate was observed after *Plantago ovata* seed administration.

GBF is comprised of the glutamine- and hemicellulose-rich extracts of spent beer-brewing constituents. Use of this probiotic in patients with mild-to-moderate UC has been investigated in a small pilot study and a placebo-controlled trial [87, 88]. At a dose of 25–30 mg/day, GBF decreased clinical and endoscopic activity in these patients and significantly increased fecal concentrations of bifidobacteria. Similar results were reported by a 24-week, open-label trial [89].

Lindsay et al. [90] performed a small, open-label study in 10 patients with active ileo-colonic CD using a combination of 15 g/day of oligofructose and inulin (ratio 70:30 %). They found a significant reduction in disease activity, concomitant with a significant increase in mucosal bifidobacteria. Interestingly prebiotic treatment increased colonic dendritic cells expressing IL-10, Toll-like receptor (TLR)-2 and TLR-4, indicating that these prebiotics affected the innate mucosal immune response. In a small placebo-controlled study oligofructose-enriched inulin was administered as adjunctive

treatment to mesalazine 3 g/day for 2 weeks in mild to moderate, active UC. This study showed a significant reduction of the fecal calprotectin in prebiotic treated patients compared to placebo [91].

## Antibiotics

### Animal Models

In several rodent models the use of broad-spectrum antibiotics can both prevent onset and treat experimental colitis, whereas metronidazole and ciprofloxacin can only prevent experimental colitis but not reverse established disease [92–96]. Broad-spectrum antibiotics are effective in almost all models of acute and chronic colitis [96–99], and, however, have only a transient efficacy in HLA-B27 transgenic rats [100]. Interestingly ciprofloxacin and metronidazole had selective efficacy in different colonic region in IL-10 knockout mice, suggesting that different bacteria cause inflammation indifferent colonic segments [98]. These studies suggest that most clinical forms of IBD may respond if a proper combination of broad-spectrum antibiotics is used.

### Ulcerative Colitis

Only few trials of antibacterial agents have been carried out in ulcerative colitis (UC) and results are controversial. Most clinicians have used antibiotics as adjuvant therapy in severe UC. Dickinson et al. have carried out a double-blind controlled trial on the use of oral vancomycin as adjuvant therapy in acute exacerbations of idiopathic colitis. No significant difference was found between the two treatment groups with only a trend towards a reduction in the need for surgery in patients treated with vancomycin [101].

Intravenous metronidazole, used as adjunctive treatment to corticosteroids, was similarly effective than placebo to induce remission in patients with severe UC [102].

In a double blind, placebo controlled trial in patients with acute relapse of UC, 84 patients were randomized to receive corticosteroids plus oral tobramycin or placebo. After 1 week of treatment, 74 % of patient in the tobramycin treatment group vs. 43 % in the placebo group ($p < 0.003$) achieved a complete symptomatic remission [103]. Subsequently the combination of tobramycin and metronidazole did not show any beneficial effect when associated to a standard steroid treatment in severely acute UC [104]. Ciprofloxacin has been tested in a randomized, placebo controlled study; 70 patients with mild to moderate active UC were randomized to receive ciprofloxacin 250 mg b.i.d. or placebo for 14 days. At the end of the study, 70.5 % of patients in the ciprofloxacin group vs 72 % in the placebo group achieved remission [105]. Similarly a short course of intravenous ciprofloxacin was not effective as adjunctive treatment to corticosteroids in severe UC in a prospective, randomized, double-blind, placebo-controlled trial [106]. Nevertheless, in a more recent randomized, placebo controlled trial, ciprofloxacin was administered for 6 months to patients with active UC poorly responding to conventional therapy with steroids and mesalamine. At the end of the study, the treatment-failure rate was 21 % in the ciprofloxacin-treated group and 44 % in the placebo group ($p < 0.002$). This difference was detected using clinical criteria; while endoscopic and histological findings showed differences only at 3 months but not at 6 months [107].

The nonabsorbable, broad-spectrum antibiotic, rifaximin was tested in a small controlled study to evaluate its efficacy and systemic absorption in patients with moderate to severe active UC refractory to steroid treatment. Twenty-eight patients were randomized to receive rifaximin 400 mg b.i.d. or placebo for 10 days as an adjunct to standard steroid treatment. Although there was no significant difference in clinical efficacy between the two treatments, only rifaximin determined a significant improvement of stool frequency, rectal bleeding, and sigmoidoscopic score [108].

In a more recent systematic review of randomized controlled trials, In active UC, there were nine RCTs with 662 patients and there was a statistically significant benefit for antibiotics inducing remission. However, there was moderate heterogeneity and antibiotics used were all different single or combination drugs [109].

### Crohn's Disease

There are several studies looking at the use of antibiotics as primary therapy for luminal CD. Unfortunately, the majority of these are observational, uncontrolled studies or lack sufficient power to truly detect important differences. Metronidazole has been the mostly investigated agent. In 1978, Blichfeldt et al. in a placebo-controlled, double-blind, crossover trial did not found difference between metronidazole and placebo-treated patients, but a positive trend in favor of metronidazole was observed when only the colon was involved [110]. In the National Cooperative Swedish study, metronidazole was compared to sulfasalazine as primary treatment for Crohn's disease; no significant difference was found between the two group, but, interestingly, in the cross-over section of the study, metronidazole was effective in patients not responders to sulfasalazine [111]. Metronidazole was used as single therapy or associated to cotrimoxazole and compared to cotrimoxazole alone and placebo in patients with a symptomatic relapse of Crohn's Disease. At the end of the 4 weeks of treatment there was no difference in response among the three groups [112]. In a Canadian randomized, placebo-controlled trial, Sutherland et al. have

shown that treatment with metronidazole for 16 weeks significantly decreased the Crohn's Disease Activity Index (CDAI), but no difference was found in the rates of remission compared with placebo; benefit was dose-dependent with 20 mg/kg having a greater benefit than 10 mg/kg [113]. As in the case of the Swedish study, in the Canadian study metronidazole was effective for colonic and ileocolonic Crohn's disease but not for ileitis. Metronidazole has important side effects that include nausea, anorexia, dysgeusia, dyspepsia, and peripheral neuropathy that limit its use in approximately 20 % of patients. An antibiotic association was used in an Italian randomized controlled study in which metronidazole 250 mg four times daily plus ciprofloxacin 500 mg twice daily were compared to a standard steroid treatment for 12 weeks. No differences were reported in the rates of remission between treatments (46 % with ciprofloxacin plus metronidazole vs 63 % with methylprednisolone) suggesting that this antibiotic association could be an alternative to steroid treatment in acute phases of Crohn's disease [114]. Combination of metronidazole and ciprofloxacin was associated with budesonide 9 mg/day in active Crohn's disease; no difference was registered compared to placebo, but surprisingly the overall response in the two groups was lower than the previous studies on budesonide. Also in this study antibiotic treatment was more effective when the colon was involved than for isolated small bowel disease [115].

Ciprofloxacin 1 g/daily was compared to mesalamine 4 g/daily in a controlled study in mild-to-moderate active CD. After 6 weeks an equivalence in efficacy was registered (remission observed in 56 % and 55 % of patients respectively with ciprofloxacin and mesalamine), offering an alternative treatment in active CD [116]. In a small study ciprofloxacin was shown to be effective in association to standard treatment in patients with resistant disease [117]. Other antibiotics have been tested. Shafran et al. carried out an open-label study on the efficacy and safety of rifaximin 600 mg/day for 16 weeks in the treatment of mild-to-moderate active CD. At the end of the study, 59 % of patients were in remission (CDAI < 150) with a significant reduction of the mean CDAI score compared to baseline ($p < 0.0001$) [118]. In an open-label trial, Leiper et al. reported an impressive positive response (64 % patients improved or were in remission after 4 weeks) of clarithromycin in a group of 25 patients with active Crohn's disease, many of whom were unresponsive to other treatments [119]. As stated by European Crohn's Colitis Organization (ECCO), at present, antibiotics are only considered appropriate for septic complications, symptoms attributable to bacterial overgrowth, or perineal disease. Antimycobacterial therapy cannot be recommended on the evidence from controlled trials [120].

Antibiotics have been also tested in prevention of postoperative recurrence. Metronidazole at the dose of 20 mg/kg/day was compared with placebo in double-blind, controlled trial by Rutgeerts et al. [121]. Sixty patients were randomized to receive metronidazole or placebo for 12 weeks. At the end of the treatment, endoscopic relapse was evaluated by Rutgeerts score. Metronidazole significantly decreased the incidence of severe endoscopic relapse (grade 3 or 4) in the neoterminal ileum 6 months after surgery and the clinical recurrence rates at 1 year, with a trend towards a protective effect after 3 years. More recently, the similar antibiotic ornidazole, used continuously for 1 year was significantly more effective than placebo in the prevention of severe endoscopic recurrence in the neoterminal ileum both at 3 and 12 months [122].

Imidazole antibiotics, as suggested by the ECCO Consensus on CD management, may be a therapeutic option after ileocolic resection but are poorly tolerated [120].

Campieri et al. performed a randomized trial to evaluate the efficacy in the prevention of postoperative recurrence of rifaximin 1.8 g daily for 3 months followed by a probiotic preparation (VSL#3) 6 g daily for 9 months versus mesalamine 4 g daily for 12 months in 40 patients after curative resection for CD. After 3 months of treatment, rifaximin determined a significant lower incidence of severe endoscopic recurrence compared to mesalamine [2/20 (10 %) versus 8/20 (40 %)]. This difference was maintained since the end of the study using probiotics [4/20 (20 %) versus 8/20 (40 %)] [75].

A lot of studies have tried to evaluate the efficacy of antimycobacterial drugs in patients with CD, pursuing the possibility that a strain of Mycobacterium might be an etiological agent in CD. Borgaonkar et al. [123] evaluated all randomized controlled trials in which antimycobacterial therapy was compared with placebo, suggesting the efficacy of antimycobacterial therapy only as a maintenance treatment in patients who obtained remission after a combined treatment with corticosteroids and antimycobacterial agents. However, the investigator emphasized the high incidence of side effects, and that, because of the small number of studies included in the meta-analysis, the data were not conclusive and should be taken with caution.

The same antibiotics used to treat luminal Crohn's disease have been reported to be beneficial in the treatment of perianal Crohn's disease, but no controlled trial have been performed [124]. Metronidazole 20 mg/kg has shown rates of fistulae closure from 62 % to 83 % [125, 126]. The combination of metronidazole and ciprofloxacin determined an improvement in 64 % of patients and fistulae closure in 21 % [127]. Unfortunately fistulae tend to recur in most patients after stopping treatment. Although the results of these uncontrolled studies are not conclusive, metronidazole, ciprofloxacin, or their combination are used by most clinicians as first-line treatment in patients with perianal disease, in combination with surgical drainage of abscesses.

A systematic review of randomized controlled trials (RCTs) evaluating antibiotics in IBD was carried-out. Studies with any antibiotics alone or in combination using predefined definitions of remission and relapse were included. For active CD, there was a statistically significant effect of antibiotics being superior to placebo. In perianal CD there were three trials using either ciprofloxacin or metronidazole and there was a statistically significant effect in reducing fistula drainage. For quiescent CD, there were 3 RCTs with different antibiotics combinations (all including antimycobacterials) vs. placebo. There was a statistically significant effect in favor of antibiotics vs. placebo. There was moderate heterogeneity between results and a diverse number of antibiotics were tested either alone or in combination and therefore the data are difficult to interpret [109].

We, more recently, performed a multicenter, randomized, double-blind trial of the efficacy and safety of 400, 800, and 1200 mg rifaximin—Extended Ileal Release (EIR), given twice daily to 402 patients with moderately active CD for 12 weeks, compared with placebo [128].

At the end of the 12-week treatment period, 62 % of patients who received the 800-mg dosage of rifaximin-EIR (61 of 98) were in remission, compared with 43 % of patients who received placebo (*P* _ 0.005).

## Pouchitis

Treatment of pouchitis is largely empirical and only small placebo-controlled trials have been conducted. The awareness of the crucial importance that fecal stasis and the bacterial overgrowth may represent in the pathogenesis of acute pouchitis has led the clinicians to treat patients with antibiotics, which have become the mainstay of treatment, in absence of controlled trials. Table 46.8 summarizes results of trials carried-out with antibiotics in pouchitis. Usually metronidazole and ciprofloxacin are the most common initial approaches, often resulting in a rapid response [129].

However, randomized trials of both metronidazole and ciprofloxacin are small. A double-blind, randomized, placebo-controlled, crossover trial was carried out by Madden et al. to assess the efficacy of 400 mg three times a day of metronidazole per os in 13 patients (11 completed both arms of the study) with chronic, unremitting pouchitis. Patients were treated for 2 weeks, and metronidazole was significantly more effective than placebo in reducing the stool frequency (73 % vs. 9 %), even without improvement of endoscopic appearance and histologic grade of activity. Some patients (55 %) experienced side effects of metronidazole including nausea, vomiting, abdominal discomfort, headache, skin rash, and metallic taste [130].

Metronidazole and ciprofloxacin have been compared in another small randomized trial [131]. Seven patients received ciprofloxacin 1 g/day and nine patients metronidazole 20 mg/kg/day for a period of 2 weeks. Ciprofloxacin lowered the PDAI score from 10.1 ± 2.3 to 3.3 ± 1.7 ($p = 0.0001$), whereas metronidazole reduced the PDAI score from 9.7 ± 2.3 to 5.8 ± 1.7 ($p = 0.0002$). There was a significantly greater benefit with ciprofloxacin compared to metronidazole in terms of the total PDAI ($p = 0.002$), symptom score ($p = 0.03$) and endoscopic score ($p = 0.03$), as well as fewer adverse events (33 % of metronidazole-treated patients reported side-effects, but none on ciprofloxacin).

The treatment and prevention of pouchitis has been systematically reviewed in 2010 by a Cochrane analysis [66]. For the treatment of acute pouchitis (four RCTS, five agents) ciprofloxacin was more effective at inducing remission than metronidazole.

Patients with chronic, refractory pouchitis do not respond to conventional therapy and often have ongoing symptoms; this is a common cause of pouch failure. Combined antibiotic therapy may be effective [45]. Sixteen consecutive

**Table 46.8** Antibiotics in pouchitis

| Study | *N* | Duration | Antibiotic | Control | Results<br>Antibiotic; Control |
|---|---|---|---|---|---|
| *Madden 1994*<br>[acute pouchitis] | 11 | 1 week | Metronidazole | Placebo | 79 %; 9 %<br>(reduction of stool frequency) |
| *Gionchetti 1999*<br>[chronic pouchitis] | 18 | 2 weeks | Rifaximin + ciprofloxacin | Open label | 88.8 % improvement or remission<br>(total PDAI significant reduction) |
| *Shen 2001*<br>[acute pouchitis] | 16 | 2 weeks | Ciprofloxacin vs metronidazole | Double-blind | Significant reduction in total PDAI in both groups |
| *Mimura 2002*<br>[chronic pouchitis] | 44 | 4 weeks | Ciprofloxacin + metronidazole | Open label | 82 % in complete remission<br>(total PDAI significant reduction) |
| *Abdelrazeq 2005*<br>[chronic pouchitis] | 8 | 2 weeks | Rifaximin + ciprofloxacin | Open label | Seven of eight patients in complete remission<br>(total PDAI significant reduction) |
| *Shen 2007*<br>[chronic pouchitis] | 16 | 4 weeks | Tinidazole + ciprofloxacin | Open label | 87.5 % in complete remission<br>(total PDAI significant reduction) |

*PDAI* Pouchitis Disease Activity Index

patients with chronic, refractory pouchitis (disease >4 weeks and failure to respond to >4 weeks of single-antibiotic therapy) were treated with ciprofloxacin 1 g/day and tinidazole 15 mg/kg/day for 4 weeks [132]. A historic cohort of ten consecutive patients with chronic refractory pouchitis treated with high dose oral and topical mesalazine daily was used as a comparator. These treatment-refractory patients had a significant reduction in the total PDAI score and a significant improvement in quality-of-life score ($p<0.002$) when taking ciprofloxacin and tinidazole, compared to baseline. The rate of clinical remission in the antibiotic group was 87.5 % and for the mesalazine group was 50 %. In another study, 18 patients refractory to metronidazole, ciprofloxacin or amoxicillin/clavulanic acid for 4 weeks were treated orally with rifaximin 2 g/day (a nonabsorbable, broad-spectrum antibiotic) and ciprofloxacin 1 g/day for 15 days. Improvement was defined as a decrease of at least 3 points in the PDAI and remission as a PDAI score of 0. Sixteen out of 18 patients (88.8 %) either improved ($n=10$) or went into remission ($n=6$) [133]. Median PDAI scores before and after therapy were 11 (range 9–17) and 4 (range 0–16), respectively ($p<0.002$). A British group observed similar benefit in just 8 patients with chronic active refractory pouchitis using the same combination of antibiotics, for the same period, and the same definition of improvement and remission. Seven of the eight patients either went into remission ($n=5$) or improved ($n=2$). The median (range) PDAI scores before and after therapy were 12 (9–18) and 0 (0–15), respectively, ($p=0.018$). All patients were compliant and no side effects were reported [134]. In another combination study, 44 patients with refractory pouchitis received metronidazole 800 mg–1 g/day and ciprofloxacin 1 g/day for 28 days [135]. Remission was defined as a combination of a PDAI clinical score of ≤2, endoscopic score of ≤1 and total score of ≤4. Forty four patients entered the trial and completed treatment. Thirty-six (82 %) went into remission. The median Pouchitis Disease Activity Index scores before and after therapy were 12 (range, 8–17) and 3 (range, 1–10), respectively ($p<0.0001$). The median Inflammatory Bowel Disease Questionnaire score also significantly improved from 96.5 (range, 74–183) to 175 (range, 76–215) with this therapy ($p<0.0001$). The eight patients (five male, three female) who did not go into remission were significantly older (median 47.5 vs. 35 years; $p<0.007$), had a longer history of pouchitis (95.5 vs. 26 months; $p<0.0008$), and tended to have a higher Pouchitis Disease Activity Index score before treatment (median 14.5 vs. 12; $p<0.13$) than those who went into remission.

## Conclusions

Many clinical and experimental observations indicate that the intestinal microflora are involved in the pathogenesis of IBD.

Probiotics may provide a simple and attractive way of preventing or treating IBD, and patients find the probiotic concept appealing because it is safe, nontoxic, and natural. VSL#3, a highly concentrated cocktail of probiotics has been shown to be effective in the prevention of pouchitis onset and relapses. Results on the use of this probiotic in UC are promising, both in terms of the prevention of relapses and the treatment of mild-to-moderate attacks. Results with probiotics in CD are poor and there is the need of well-performed studies.

It is important to select a well-characterized probiotic preparation, in view of the fact that the viability and survival of bacteria in many of the currently available preparations are unproven. It should be noted that the beneficial effect of one probiotic preparation does not imply efficacy of other preparations containing different bacterial strains, because each individual probiotic strain has unique biological properties.

Prebiotics are an exciting potential treatment for IBD patients. They offer a safe and cost-effective approach and may be considered for long-term treatment. However, experimental evidence supporting the use of these nutraceuticals is still limited. We need to improve our knowledge on the composition of enteric flora or "the neglected organ" and on the intestinal physiology and its relationship with the luminal ecosystem.

The use of antibiotics in UC is not supported by the available studies, although large studies with broad-spectrum agents are required. Antibiotics have an essential role in treating the septic complications of Crohn's disease, including intrabdominal and perianal abscesses and perianal fistulae.

There is evidence that ciprofloxacin, metronidazole, or their combination are effective in Crohn's colitis and ileocolitis, but not in isolated ileal disease; however, use of antibiotics as primary therapy in Crohn's disease is poorly documented, and large, controlled trials are needed for defining the optimal antibiotic regimens.

The use of antibiotics in pouchitis is largely justified although proper controlled trials have not been conducted.

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