PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

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REVIEW

Antibiotics and probiotics in treatment of inflammatory bowel disease

Paolo Gionchetti, Fernando Rizzello, Karen M Lammers, Claudia Morselli, Lucia Sollazzi, Samuel Davies, Rosy Tambasco, Carlo Calabrese, Massimo Campieri

Paolo Gionchetti, Fernando Rizzello, Karen M Lammers, Claudia Morselli, Lucia Sollazzi, Samuel Davies, Rosy Tambasco, Carlo Calabrese, Massimo Campieri, Department of Internal Medicine and Gastroenterology, University of Bologna, Bologna, Italy
Correspondence to: Paolo Gionchetti, Department of Internal Medicine and Gastroenterology, Policlinico S. Orsola, Via Massarenti 9, 40138 Bologna, Italy. paolo@med.unibo.it
Telephone: +39-51-6364122 Fax: +39-51-392538
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Abstract

Many experimental and clinical observations suggest that intestinal microflora plays a potential role in the pathogenesis of inflammatory bowel disease (IBD). Manipulation of the luminal content using antibiotics or probiotics represents a potentially effective therapeutic option. The available studies do not support the use of antibiotics in ulcerative colitis (UC). Antibiotics are effective in treating septic complications of Crohn's disease (CD) but their use as a primary therapy is more controversial, although this approach is frequently and successfully adopted in clinical practice.

There is evidence that probiotic therapy may be effective in the prevention and treatment of mild to moderate UC. In contrast, a lack of successful study data at present precludes the widespread use of probiotics in the treatment of CD.

Both antibiotics and probiotics appear to play a beneficial role in the treatment and prevention of pouchitis and further trials are warranted to fully quantify their clinical efficacy.

Key words: Inflammatory bowel disease; Intestinal microflora; Antibiotics; Probiotics

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INTRODUCTION

The rationale for using antibiotics and probiotics in the treatment of inflammatory bowel disease (IBD) is based on convincing evidence implicating intestinal bacteria in the pathogenesis of the disease[1].

The distal ileum and the colon are the areas with the highest bacterial concentrations and represent the sites of inflammation in IBD. In addition, pouchitis, the non-specific inflammation of the ileal reservoir after ileo-anal anastomosis, appears to be associated with bacterial overgrowth and dysbiosis. Furthermore, pouchitis does not occur prior to closure of the ileostomy.

Patients with Crohn's disease (CD) consistently respond to diversion of faecal stream, with immediate recurrence of inflammation after restoration of intestinal continuity or infusion of luminal content into the bypassed ileum[2,3]. Moreover, the composition of the enteric flora is altered in patients with IBD, and enteric bacteria or their products have been found within the inflamed mucosa of patients with CD[4]. Increased number of aggressive bacteria such as *Bacteroides,* adherent/invasive *Escherichia coli* and enterococci, and decreased number of protective lactobacilli and bifidobacteria have been observed in IBD[5].

However, the most compelling evidence that intestinal bacteria play a role in IBD has been derived from animal models. Although there is a 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[6]. Indeed, there is evidence that immunological tolerance to commensal bacteria is lost in patients with IBD[7,8]. These findings have led to the proposal that manipulation of intestinal microbiota flora, either with antibiotics or probiotics, may be therapeutic in IBD. Some suggested mechanisms of action of antibiotics and probiotics are shown in Table 1.

There is a growing body of evidence from animal studies and clinical trials that antibiotics and probiotics have therapeutic effects in ulcerative colitis (UC), CD and pouchitis.

ANTIBIOTICS

Animal model studies

In several rodent models the use of broad-spectrum an-

Table 1 Suggested mechanisms of action of antibiotics and probiotics

Antibiotics	Probiotics
Eradication of bacterial antigenic triggers	Inhibition of pathogenic enteric bacteria by:
Elimination of bacterial overgrowth	decreasing luminal pH
Reduction of pro-inflammatory bacterial toxins	secretion of bacteriocidal proteins
Potential immunosuppressive properties of antibiotics	resisting colonization
	blocking epithelial binding
	Improvement in epithelial and mucosal barrier function by:
	production of short-chain fatty acids
	enhancing mucus production
	increasing barrier integrity
	Alteration of immunoregulation by:
	increasing interleukin-10 and TGFβ, and decreasing TNF levels
	increasing IgA production

tibiotics can both prevent and treat experimental colitis, whereas metronidazole and ciprofloxacin can only prevent experimental colitis but cannot reverse the established disease[9-13]. Broad-spectrum antibiotics are effective in almost all models of acute and chronic colitis[13-16], but they have only a transient efficacy in HLA-B27 transgenic rats[17]. Interestingly, ciprofloxacin and metronidazole have selective efficacy in different colonic regions of interleukin-10 (IL-10) knockout mice, suggesting that different bacteria cause inflammation in different colonic segments[15]. These studies suggest that most clinical forms of IBD may respond to a specific combination of broad-spectrum antibiotics.

Ulcerative colitis

Only a few trials on the use of antibacterial agents have been carried out in UC and the results are controversial. Most clinicians have used antibiotics as an adjuvant therapy for severe UC. Dickinson *et al*[18] carried out a double-blind controlled trial on the use of oral vancomycin as an adjunct for acute exacerbations of idiopathic colitis and found that there is no significant difference between the two treatment groups, with only a trend towards a reduction in the need for surgery in patients treated with vancomycin[18].

Intravenous metronidazole used in conjunction with corticosteroids, is as effective as placebo in inducing remission in patients with severe UC[19]. In a double-blind, placebo-controlled trial in patients with acute relapse of UC, Burke *et al*[20] randomized 84 patients to receive corticosteroids plus oral tobramycin or placebo and found that after 1 wk of treatment, 74% of patients in the tobramycin treatment group and 43% in the placebo group ($P < 0.003$) achieve complete symptomatic remission. However, the combination of tobramycin and metronidazole does not have any beneficial effect when compared with a standard steroid treatment in severely acute UC[21].

Mantzaris *et al*[22] investigated ciprofloxacin in a randomised, placebo-controlled study and randomized 70 patients with mild to moderate active UC to receive either 250 mg ciprofloxacin twice a day or placebo for 14 d and found that 70.5% of patients in the ciprofloxacin group and 72% in the placebo group achieve remission. Moreover, a short course of intravenous ciprofloxacin is not effective as an adjunctive treatment to corticosteroids in severe UC[23]. In contrast, some efficacy of ciprofloxan has been observed in a more recent randomised placebo-controlled trial when ciprofloxacin is administered for 6 mo to patients with active UC poorly responding to conventional therapy with steroids and mesalazine[24]. 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 mo but not at 6 mo.

The non-absorbable broad-spectrum antibiotic, rifaximin, was investigated 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 randomised to receive either rifaximin 400 mg twice daily or placebo for 10 d as an adjunct to standard steroid treatment. Although there is no significant difference in the clinical efficacy score between the two treatments, only rifaximin determines a significant improvement in stool frequency, rectal bleeding and sigmoidoscopic score[25].

Whilst rifaximin does not permanently alter the colonic microbiota, resistant *Bifidobacterium* species have been found after 3 intermittent courses in patients with UC[26].

Crohn's disease

Broad-spectrum antibiotics are widely used to treat CD[27], but large controlled trials have not yet been performed (Table 2).

Metronidazole has been the most investigated agent. In 1978, Blichfeldt *et al*[28] found that there is no difference between metronidazole and placebo-treated patients in a placebo-controlled, double-blind, crossover trial. However, a positive trend in favour of metronidazole is observed when only the colon is involved[28]. In the National Cooperative Swedish study, metronidazole has been compared with sulphasalazine as a primary treatment for Crohn's disease. Although no significant difference is found between the two groups, metronidazole is effective in patients who fail to respond to sulphasalazine[29]. In

Table 2 Antibiotics trials in active Crohn's disease

Study	Patients (*n*)	wk	Main outcome	Study design	Treatment schedules
Blichfeldt *et al*[28]	22	8	Improvement (clinical/lab score)	DB crossover study	MZ (+ SASP/CS) Placebo (+ SASP/CS)
Ursing *et al*[29]	22	16	Change in CDAI and orosomucoid	DB crossover study	MZ SASP
Ambrose *et al*[30]	72	4	Improvement (Clinical/lab.score)	DB RCT	MZ CO, MZ/CO, placebo
Sutherland *et al*[31]	99	16	Change in CDAI from baseline	DR RCT	MZ (10/20 mg/kg) Placebo
Prantera *et al*[32]	41	12	Clinical remission (CDAI < 150)	NB RCT	MZ + Cipro Steroids
Colombel *et al*[34]	40	6	Clinical remission (CDAI < 150)	NB RCT	CIPRO 5-ASA
Arnold *et al*[35]	47	24	Change in CDAI	NB RCT	CIPRO (+ conc drugs) Placebo (+ conc drugs)
Steinhart *et al*[33]	134	8	Clinical remission (CDAI < 150)	DB RCT	MZ+CIPRO (+ bud 9 mg) Placebo (+ bud. 9 mg)

CDAI: Crohn's disease activity index.

another study, metronidazole was used either as a single therapy or in combination with cotrimoxazole and compared to cotrimoxazole alone and a double placebo in patients with a symptomatic relapse of CD, which shows that after four weeks of treatment there is no difference in response among the three treatment groups[30]. In a Canadian randomised, placebo-controlled trial, Sutherland *et al*[31] demonstrated that treatment with metronidazole for 16 wk significantly decreases the Crohn's disease activity index (CDAI), but no difference is found in the rates of remission compared with placebo. As in the Swedish study[29], the Canadian study found that metronidazole is effective for colonic and ileocolonic CD, but not for ileitis. Unfortunately, metronidazole has numerous side-effects including nausea, anorexia, dysgeusia, dyspepsia and peripheral neuropathy, which limit its use in approximately 20% of patients.

An antibiotic combination was used in an Italian randomised controlled study[32] in which 250 mg metronidazole four times daily plus 500 mg ciprofloxacin twice daily were compared to a standard steroid treatment for 12 wk. No significant differences were reported in the rates of remission between treatments (46% with ciprofloxacin plus metronidazole and 63% with methylprednisolone), suggesting that this antibiotic combination is a potential alternative to steroid treatment in the acute phase of CD[32]. In another trial[33], this combination of metronidazole and ciprofloxacin was supplemented with budesonide (9 mg/d) for active CD. No difference was registered compared to placebo, but the overall response in the two groups was lower than that in previous studies using budesonide, suggesting that antibiotic treatment is more effective in colonic disease than in isolated small bowel disease.

Ciprofloxacin (1 g/d) was compared to mesalazine (4 g/d) in a controlled study[34] of mild to moderate active CD for 6 wk. The results suggest that ciprofloxacin is as efficacious as mesalazine (remission observed in 56% and 55% of patients treated with ciprofloxacin and mesalazine respectively), thus offering a potential alternative treatment for active CD. Furthermore, ciprofloxacin has been shown to be effective when used in combination with standard treatment in patients with resistant disease [35].

Other antibiotics have also been investigated. Shafran *et al*[36] carried out an open-label study on the efficacy and safety of rifaximin (600 mg/d) for 16 wk in the treatment of mild to moderate active CD, and found that at the end of the study, 59% of patients are in remission (CDAI < 150) with a significant reduction of the mean CDAI score compared to baseline ($P < 0.0001$). Leiper *et al*[37] reported that 64% patients have an impressive positive response to clarithromycin, many of whom are unresponsive to other treatments.

Many 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 aetiological agent in CD. Borgaonkar *et al*[38] performed a meta-analysis of all randomised controlled trials in which antimycobacterial therapy was compared with placebo and found that antimycobacterial therapy is only efficacious in the maintenance of remission after a combined treatment of corticosteroids and antimycobacterial agents. However, the investigator emphasised that because of the high incidence of side-effects and the small number of studies included in the meta-analysis, the data are inconclusive and should be interpreted with caution.

The same antibiotics used to treat luminal CD have been reported to be beneficial for the treatment of perianal CD, but no controlled trials are available[39]. Metronidazole (20 mg/kg) can close 62%-83% fistulae[40,41]. The combination of metronidazole and ciprofloxacin results in an improvement in 64% of patients with closure of fistulae in 21%[42]. Unfortunately, fistulae tend to recur in most patients following cessation of treatment. Although the results of these uncontrolled studies are inconclusive, metronidazole and ciprofloxacin alone or in combination, are used by most clinicians as first-line treatments for patients with perianal disease in conjunction with surgical drainage of abscesses.

The use of antibiotics in the prevention of post-

operative disease recurrence has also been investigated. Rutgeerts *et al*[43] have assessed the efficacy of metronidazole at 20 mg/kg per day in a placebo-controlled double-blind study. In their study, sixty patients were randomised to receive either metronidazole or placebo for 12 wk and endoscopic relapse was evaluated by Rutgeerts score at the end of the treatment. They found that metronidazole significantly decreases the incidence of severe endoscopic relapse (grade 3 or 4) and the clinical recurrence rate. More recently, ornidazole used continuously for 1 year, has been shown to be significantly more effective than placebo in the prevention of clinical and endoscopic recurrence in the neoterminal ileum[44].

Pouchitis

The awareness of the crucial importance that faecal stasis and bacterial overgrowth may play a role in the pathogenesis of acute pouchitis has led clinicians to treat patients with antibiotics.

Antibiotics have become the mainstay of treatment for pouchitis, although controlled trials are not available. Metronidazole is the first-line treatment, and most patients with acute pouchitis respond quickly to its administration of 1-1.5 g/d[45,46]. A double-blind, randomised, placebo-controlled, crossover trial was carried out by Madden *et al*[47] to assess the efficacy of 400 mg of metronidazole three times daily *per os* for two weeks in 13 patients (11 completed both arms of the study) with chronic, unremitting pouchitis. The found that metronidazole is significantly more effective than placebo in reducing stool frequency (73% and 9%), even without improvement in endoscopic appearance and histological grade of activity. However, a significant proportion of patients (55%) may experience side-effects while using metronidazole, including nausea, vomiting, abdominal discomfort, headache, skin rash and metallic taste. Recently Shen *et al*[48] compared the efficacy and side-effects of ciprofloxacin and metronidazole in treating acute pouchitis in a randomised clinical trial. Seven patients received ciprofloxacin (1 g/d) and nine patients received metronidazole (20 mg/kg per day) for 2 wk. The results of this study have shown that both ciprofloxacin and metronidazole are efficacious in the treatment of acute pouchitis. Both reduce the total pouchitis disease activity index (PDAI) scores and lead to a significant improvement in symptoms as well as endoscopic and histological scores. However, ciprofloxacin leads to a greater reduction in PDAI scores as well as improvement in symptoms and endoscopic scores. Furthermore ciprofloxacin is better tolerated than metronidazole (33% of metronidazole-treated patients reported adverse effects, compared with none in the ciprofloxacin group).

Given the management difficulties posed by chronic refractory pouchitis, the use of combined antibiotic treatment has been explored. In an open trial, 18 patients with active pouchitis not responding to standard therapy (metronidazole or ciprofloxacin) for 4 wk, were treated orally with rifaximin (2 g/d) plus ciprofloxacin (1 g/d) for 15 d. Symptom assessment, endoscopic and histological evaluations were performed at screening and after 15 d using PDAI scores. The results indicate that 16 out of 18 patients (88.8%) improve ($n = 10$) or go into remission ($n = 6$) with the median PDAI score before and after therapy being 11 and 4 respectively ($P < 0.002$)[49].

More recently, 44 patients with refractory pouchitis received metronidazole (800 mg to 1 g/d) and ciprofloxacin (1 g/d) for 28 d. The results reveal that 66 patients (82%) go into remission with the median PDAI score before and after therapy being 12 and 3 respectively ($P < 0.0001$), and the patients' quality of life is significantly improved after the treatment (median IBD Questionnaire score increased from 96.5 to 175)[50].

Table 3 Organisms associated with probiotic activity

Most commonly	Other bacterial strains	Yeast
Lactobacilli	Enterococci	Saccharomyces boulardii
Bifidobacteria	Non-pathogenic *E. coli*	
Streptococci		

PROBIOTICS

The use of probiotics for the purpose of health maintenance and disease prevention is first proposed by Elie Metchnikoff, the Russian Nobel prize winner[51], who at the turn of the last century suggested that a high concentration of lactobacilli in the intestinal flora is important for the health and longevity of humans. Probiotics are defined as "living organisms, which upon ingestion in a certain number exert health benefits beyond inherent basic nutrition"[52].

A number of bacteria are associated with probiotic activity (Table 3). For clinical application, probiotic strains need to be resistant to acid and bile and the ability to be metabolically active within the luminal flora where they should ideally survive but not persist in the long term. They should be antagonistic to pathogenic bacteria and safe for human use while maintain their viability and beneficial properties during the manufacturing processes[53].

Animal model studies

Encouraging results of probiotic therapy have been obtained in experimental colitis. Administration of *Lactobacillus reuteri* can significantly reduce inflammation in acetic acid-and methotrexate-induced colitis in rats[54,55]. More recently *Lactobacillus sp.* has been shown to be able to prevent the development of spontaneous colitis in IL-10 deficient mice[56], and continuous feeding with *Lactobacillus plantarum* improves an established colitis in the same knockout model[57]. A strain of *Lactobacillus salivarius* (subsp. *salivarius*) reduces the rate of progression from inflammation to dysplasia and colonic cancer in IL-10 deficient mice[58], and *Bifidobacterium infantis* and of *Lactobacillus salivarius* are able to attenuate inflammation and reduce the ability to produce Th1-type cytokines in the IL-10 knockout model[59].

VSL#3 is characterised by a very high bacterial concentration (each packet containing 450 billion viable bacteria) and the presence of a cocktail of eight different bacterial species. This product contains viable lyophilised bacteria 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*. Rachmilewitz and colleagues[60] found that VSL#3 results in a significant attenuation of inflammation with a decrease of myeloperoxidase and nitric oxide synthase activity of the iodoacetamide-induced colitis. Madsen and colleagues[61] have reported a significant improvement in inflammation together with a reduction in mucosal levels of pro-inflammatory cytokines and normalisation of colonic barrier integrity in IL-10 knockout mice.

Ulcerative colitis

Promising results of probiotics have been found in the treatment of UC. In 3 recent trials involving the non-pathogenic strain of *Escherichia coli* Nissle 1917, similar efficacy has been observed to that of mesalazine in the maintenance treatment of UC[62-64].

We carried out a pilot study using the probiotic cocktail, VSL#3, as maintenance treatment for patients with UC in remission, allergic or intolerant to sulphasalazine and mesalazine, to assess its impact on the faecal flora. Twenty patients received 6 g a day of VSL#3 (1800 billion bacteria) for 12 mo and were assessed clinically and endoscopically at baseline, at 6 and 12 mo, and in the event of a relapse. Stool culture and determination of faecal pH were also performed at different intervals[65]. Microbiological determination showed a significant increase in concentration of lactobacilli, bifidobacteria and *Streptococcus thermophilus,* evident after just 20 d, which persisted throughout the treatment period, and returned to basal levels within 15 d after treatment. Faecal concentration of *Bacteroides*, enterococci, coliforms, *Clostridia* and total anaerobes and aerobes was not affected, but faecal pH was significantly reduced by the treatment. Fifteen of the twenty patients (75%) remained in remission throughout the treatment period[65].

Furthermore, VSL#3 at very high dosage (3600 billion bacteria/d) can induce remission in 63%, with a positive response in a further 23% of patients with active mild to moderate disease[66].

In addition, an open uncontrolled 4-wk study found that the yeast *Saccharomyces boulardii* could induce remission in 71% of patients with mild to moderate UC[67]. These studies highlight the wide range of organisms that may be beneficial as probiotic therapy for UC.

Crohn's disease

Campieri *et al*[68] performed a randomised trial to evaluate the efficacy of a combination of rifaximin and the probiotic preparation, VSL#3, in the prevention of post-operative recurrence of CD. Rifaximin (1.8 g/d) for 3 mo, followed by VSL#3 (6 g daily) for 9 mo, was compared with mesalazine (4 g/d) for 12 mo in 40 patients after curative resection for CD. After 3 mo of treatment, the antibiotic-probiotic combination resulted in a significantly lower incidence of severe endoscopic recurrence compared to mesalazine [2/20 (10%) *vs* 8/20 (40%)]. This difference was maintained throughout the study period [4/20 (20%) *vs* 8/20 (40%)][68].

No such clinical effect was seen in a study by Prantera *et al*[69] who reported that the probiotic *Lactobacillus GG* could not prevent post-operative disease recurrence in an 1-year double-blind, placebo-controlled trial. Similar negative results have been recently reported by the GETAID French group. A randomised double-blind, placebo-controlled study showed that *Lactobacillus johnsonii* LA1 ($4x10^9$ cfu/d) is not superior to placebo in preventing endoscopic recurrence of CD[70].

In a small pilot study[71], treatment with capsules containing *E.coli* Nissle 1917 was compared to placebo in the maintenance of steroid-induced remission of colonic CD. Twelve patients were treated with *E.coli* Nissle and 11 with placebo. The results showed that at the end of the 12-wk treatment period, the relapse rate is 33% in the *E.coli* group and 63% in the placebo group. Unfortunately, because of the small number of patients treated, this difference did not reach statistical significance.

However, a small comparative open study[72] showed that the combination of *Saccharomyces boulardii* (1 g/d) and mesalazine (2 g/d) is significantly superior to mesalazine (3 g/d) in maintenance of remission, suggesting that probiotic treatment in CD may be beneficial. More recently, a double-blind trial showed that *Lactobacillus* GG is not superior to placebo in prolonging remission in children with CD when given as an adjunct to standard therapy[73].

Pouchitis

Although probiotics are less widely used in clinical practice than antibiotics, they may be efficacious in the prevention and treatment of pouchitis. We have compared the efficacy of VSL#3 with placebo in the maintenance and treatment of chronic pouchitis[74]. Forty patients who obtained clinical and endoscopic remission after 1 mo of combined antibiotic treatment (rifaximin 2 g/d + ciprofloxacin 1 g/d) were randomised to receive VSL#3, 6 g daily (1800 billion bacteria/d) or a placebo of identical appearance for 9 mo. Clinical assessment was carried out every month, endoscopic and histological assessments were performed at entry and subsequently every two months. Stool samples were cultured before and after antibiotic treatment and subsequently every month during maintenance treatment. Relapse was defined as an increase of at least 2 points in the clinical portion of the PDAI and confirmed endoscopically and histologically. Whilst all 20 patients treated with placebo had a relapse during the 9 mo follow-up period, 17 of the 20 (85%) patients treated with VSL#3 remained in remission at this point. Interestingly, all these 17 patients had a relapse within 4 mo after the active treatment. Faecal concentrations of lactobacilli, bifidobacteria and *Streptococcus salivarius* subsp. *thermophilus* were significantly increased within 1 mo after VSL#3 treatment, and remained stable throughout the study. However, this increase did not affect the concentration of the other bacterial groups, suggesting that the beneficial effect of treatment is not mediated by suppression of endogenous luminal bacteria.

A recent study examining the maintenance of remission in patients with refractory or recurrent pouchitis showed that remission is achieved in 85% of patients treated with VSL#3, 6 g/d (1800 billion bacteria/d) and 6% in

the placebo group after 1 year of treatment[75]. In addition, continuous administration of VSL#3 results in a significant increase in IL-10 tissue levels, a significant decrease in tissue levels of the pro-inflammatory cytokines (TNF alpha, IL-1 and IFN gamma) and a decrease in matrix metalloproteinase activity[76]. This may aid our understanding of the mechanisms of action by which VSL#3 maintains remission in pouchitis. In contrast, *Lactobacillus GG* is ineffective in preventing relapse in patients with chronic pouchitis[77].

We have also carried out a double-blind, placebo-controlled trial to evaluate the efficacy of VSL#3 in preventing pouchitis onset following ileal-anal anastomosis for UC[76]. Forty patients were randomised to receive VSL#3, 3 g per day (900 billion bacteria/d) or an identical placebo for 12 mo. Patients were assessed clinically, endoscopically and histologically at 1, 3, 6, 9 and 12 mo according to the PDAI. The results indicate that patients treated with VSL#3 have a significantly lower incidence of acute pouchitis compared with those treated with placebo during the first year of ileostomy closure (10% *vs* 40%; $P < 0.05$). Moreover, the IBD Questionnaire score is significantly improved in the group treated with VSL#3, and the median stool frequency in patients not developing pouchitis, is significantly less in the VSL#3 group compared with the placebo group[78].

CONCLUSION

There is strong evidence that enteric commensal bacteria are involved in the pathogenesis of IBD. Therefore, modification of the gut bacterial flora by antibiotics and probiotics may be effective in treating UC, CD and pouchitis.

Antibiotics are a well established, efficacious treatment option for various manifestations of IBD. Antibiotics play an essential role in treating the septic complications of CD, including intra-abdominal and perianal abscesses and perianal fistulae, although their use in CD as a primary therapy is poorly documented. There is good evidence that ciprofloxacin, metronidazole or their combination is effective in Crohn's colitis and ileocolitis, though not in isolated ileal disease. Large controlled trials are needed to define optimal antibiotic regimens. In addition, their use in UC is not supported by the available studies and large trials with broad-spectrum agents are required. Although proper controlled trials have not yet been conducted, the use of antibiotics in pouchitis is largely justified.

Probiotics provide an attractive alternative to antibiotics in the treatment of IBD as trials to date have shown that they safe and have no side-effects. Promising results have been obtained from studies using probiotics, in both the prevention of relapse and the treatment of mild to moderate attacks of UC. Studies using probiotics in the treatment of CD are less clear due to conflicting and limited data. There is also considerable evidence that the highly concentrated cocktail of probiotics, VSL#3 is efficacious in preventing pouchitis onset and relapse.

Studies have highlighted the importance of selecting a well characterised probiotic preparation for treatment. In fact, viability and survival of bacteria in many available preparations are unproven. It should be remembered 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 its unique biological properties.

There is a need to improve our understanding of the composition of the enteric flora and the relationship between intestinal physiology and the luminal ecosystem. Only then can we truly optimise the bacteria-modifying treatments now available to effectively treat IBD.

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