

Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: experience in clinical practice

B. SHEN*, A. BRZEZINSKI*, V. W. FAZIO†, F. H. REMZI†, J.-P. ACHKAR*, A. E. BENNETT‡, K. SHERMAN* & B. A. LASHNER*

Departments of *Gastroenterology/Hepatology, †Colorectal Surgery and ‡Anatomic Pathology, The Cleveland Clinic Foundation, Cleveland, OH, USA

Accepted for publication 22 July 2005

SUMMARY

Background: Management of antibiotic-dependent pouchitis is often challenging. Oral bacteriotherapy with probiotics (such as VSL #3) as maintenance treatment has been shown to be effective in relapsing pouchitis in European trials. However, this agent has not been studied in the US, and its applicability in routine clinical practice has not been evaluated.

Aim: To determine compliance and efficacy of probiotic treatment in patients with antibiotic-dependent pouchitis.

Methods: Thirty-one patients with antibiotic-dependent pouchitis were studied. VSL #3 is a patented probiotic preparation of live freeze-dried bacteria. All patients received 2 weeks of ciprofloxacin 500 mg b.d. followed by VSL #3 6 g/day for 8 months. Baseline Pouchitis Disease Activity Index scores were calculated. Patients' symptoms were reassessed at week 3 when VSL #3 therapy was initiated and at the end of the 8-month trial. Some patients underwent repeat pouch endoscopy at the end of the trial.

Results: All 31 patients responded to the 2-week ciprofloxacin trial with resolution of symptoms and they were subsequently treated with VSL #3. The mean

duration of follow-up was 14.5 ± 5.3 months (range: 8–26 months). At the 8-month follow-up, six patients were still on VSL #3 therapy, and the remaining 25 patients had discontinued the therapy due to either recurrence of symptoms while on treatment or development of adverse effects. All six patients who completed the 8-month course with a mean treatment period of 14.3 ± 7.2 months (range: 8–26 months) had repeat clinical and endoscopic evaluation as out-patients. At the end of 8 months, these six patients had a mean Pouchitis Disease Activity Index symptom score of 0.33 ± 0.52 and a mean Pouchitis Disease Activity Index endoscopy score of 1.83 ± 1.72 , which was not statistically different from the baseline Pouchitis Disease Activity Index endoscopy score of 2.83 ± 1.17 ($P = 0.27$).

Conclusion: This study was conducted to evaluate bacteriotherapy in routine care. The use of probiotics has been adopted as part of our routine clinical practice with only anecdotal evidence of efficacy. Our review of patient outcome from the treatment placebo showed that only a minority of patients with antibiotic-dependent pouchitis remained on the probiotic therapy and in symptomatic remission after 8 months.

INTRODUCTION

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice

for patients who have medically refractory ulcerative colitis (UC) or UC with dysplasia or cancer, and for patients with familial adenomatous polyposis.^{1–4} Pouchitis is the most common long-term complication of IPAA in patients with underlying UC.^{1–4} The etiology and pathogenesis of pouchitis are poorly understood. Luminal microflora play a major role in the etiology of inflammatory bowel disease (IBD) and pouchitis, and it

Correspondence to: Dr B. Shen, Department of Gastroenterology/Hepatology-Desk A30, The Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195, USA.
E-mail: shenb@ccf.org

is likely that bacteria perpetuate the inflammatory mucosal reaction in genetically susceptible patients. Given this association, antibiotics and probiotics have been used to treat patients with pouchitis. Pouchitis can be classified into three categories based on the patient response to antibiotic therapy: (i) antibiotic-responsive; (ii) antibiotic-dependent; and (iii) antibiotic-refractory.⁵ The pathogenesis, treatment, and prognosis of these categories of pouchitis may be different.

Management of antibiotic-dependent pouchitis can be challenging. Typically, patients initially respond to a short course of antibiotics, but symptoms quickly return after the antibiotic is stopped, and thus long-term maintenance therapy with antibiotics is often needed. However, there are concerns about bacterial resistance in patients who are on long-term maintenance antibiotics. Alternatively, probiotics, as antibiotic-sparing agents, have been used to prevent episodes of pouchitis. A randomized, double-blind, placebo-controlled trial of a probiotic named VSL #3 (Yovis; Sigma-Tau, Pomezia, Italy) was conducted for the maintenance therapy of relapsing pouchitis after remission induced by using ciprofloxacin and rifaximin⁶ and VSL #3 contains viable lyophilized bacteria of four strains of *Lactobacillus*, three *Bifidobacterium* species, *Streptococcus salivarius* subsp. *Thermophilus*. The agent was shown to be highly effective in maintaining remission in patients with relapsing pouchitis^{6, 7} and in preventing the initial episodes of pouchitis after IPAA.⁸ The promising results from prior work have generated continued interest in the use of probiotics in pouchitis. VSL #3 has become commercially available and patients in the US were able to purchase the agent online. Our study was done to determine whether VSL #3 was effective when used in clinical practice.

PATIENTS AND METHODS

Thirty-one consecutive UC patients with antibiotic-dependent pouchitis were recruited from our clinic March 2002 to December 2004. We approached the patients as we normally would, diagnosing and managing their disease according to our standard of practice at our clinic. In order to qualify for the study, patients needed to meet each of the three inclusion criteria: (i) patients with *antibiotic-dependent pouchitis*, defined as patients with four or more episodes of pouchitis per year who quickly responded to a 2-week course of ciprofloxacin or metronidazole, but symp-

toms quickly recurred after stopping the antibiotics; (ii) the patients with frequent episodes or recurrence of pouchitis required long-term continuous low-dose antibiotic therapy or frequent pulse antibiotic therapy to stay on remission; and (iii) patients who are currently symptomatic while having been off any antibiotics or probiotics for at least 2 weeks. Exclusion criteria were patients with antibiotic-refractory pouchitis (defined as failure to respond to a 2-week course of metronidazole or ciprofloxacin) or antibiotic-responsive pouchitis (defined as fewer than four episodes of pouchitis per year which quickly responded to antibiotic therapy);⁹ history of adverse reactions to ciprofloxacin or any brand of probiotics; concurrent pouchitis and cuffitis; irritable pouch syndrome; and Crohn's disease of the pouch. The study was approved by the Institutional Review Board.

A clinical and endoscopic evaluation was conducted at the entry of the trial. The Pouchitis Disease Activity Index (PDAI) instrument¹⁰ was used for the diagnosis of pouchitis (as defined PDAI >7). The 18-point PDAI measures components of symptoms (increased stool frequency, bleeding, fecal urgency or abdominal cramps and fever), endoscopy (edema, granularity, friability, loss of vascular pattern, mucous exudates, ulceration) and histology (polymorphic nuclear leucocyte infiltration and ulceration). Each component has a maximum of six points. Patients who had routinely used non-steroidal anti-inflammatory drugs (NSAID) at the entry of the study were asked to discontinue these agents. Patients were treated with ciprofloxacin 500 mg PO BID for 2 weeks to induce remission, and then started VSL #3 to maintain remission. During the treatment period with ciprofloxacin, the patients obtained VSL #3 from the company's web sites (<http://www.vsl3.com> or <http://www.questcor.com>) and made the agent available for use immediately after the 2-week ciprofloxacin therapy. Patients were advised to follow the manufacturer's instructions, including appropriate refrigeration of the agent. Patients were informed that probiotics are usually not covered by insurance policies. Only patients who were willing to purchase and take the agent were enrolled in the trial. Upon finishing the 2-week ciprofloxacin trial, all patients were contacted either via e-mail or telephone by the primary investigator and treating physician (B.S.) for the assessment of their symptoms and the assurance of their compliance with the next phase of therapy involving VSL #3. If symptoms had been resolved by the end of the 2 week

course of ciprofloxacin, patients were instructed to start taking VSL #3 at a dose of 6 g/day immediately (within 1–3 days) following the antibiotic therapy. Patients who did not respond to the 2 weeks of ciprofloxacin were excluded from the protocol. If patients experienced unusual symptoms while on VSL #3 such as intolerable constipation, bloating, bleeding, or worsening abdominal pain or diarrhea, patients were asked to decrease the dose to 3 g daily. If these symptoms persisted for more than 2 weeks, patients were instructed to discontinue VSL #3. Patients who experienced symptoms suggestive of a recurrent episode of pouchitis were advised to discontinue VSL #3. Subsequent treatment was determined by the patients' gastroenterologists. Patients who failed to respond to VSL #3 therapy were asked to return to clinic for evaluation with pouch endoscopy at week 7.

Patients were contacted again by the primary investigator at week 7. At week 7, patients, on VSL #3, who had a symptomatic response with PDAI symptom scores remaining ≤ 1 point continued the therapy. If patients tolerated the VSL #3 therapy, they were periodically contacted (every 1–3 months) by the primary investigator for the assessment of symptoms and assurance of compliance. The VSL #3 trial was designed to last for a duration of 8 months. Up to or after 8 months or later, patients were scheduled to have out-patient clinical and endoscopic evaluations.

Outcome Measurement

The primary outcome measurement was the number of patients who were still on VSL #3 at the end of 8 months. The secondary outcomes included: (i) assessment of symptom response to the antibiotic and probiotic therapy; (ii) assessment of clinical factors that would predict patients' response to VSL #3; and (iii) assessment of adverse effects to VSL #3.

Statistical Analysis

The Student *t*, chi-squared, Fisher's exact tests were used to compare pre- and post-treatment variables. *P* values <0.05 were considered as statistically significant.

RESULTS

All 31 patients who were classified as antibiotic-dependent pouchitis had a typical history of clinical

symptoms and endoscopic inflammation that responded quickly to ciprofloxacin or metronidazole with recurrence of symptoms soon (1.1 ± 1.0 weeks) after discontinuation of the antibiotics. During the current study, all 31 patients who were treated with a 2-week course of ciprofloxacin 500 mg PO BID responded to therapy with improvement in symptoms with a PDAI symptom scores ≤ 1 point and all patients were in remission at week 3 when VSL #3 was started. The mean follow-up was 14.5 ± 5.3 months (range: 8–26 months). At the 8-month follow-up, only six patients (19.4%) were still on VSL #3 (designated as Group A). The remaining 25 patients had discontinued the therapy because of either recurrence of symptoms or development of adverse effects (designated as Group B).

The demographic and clinical data of Groups A and B are shown in Table 1. There were no statistically significant differences in age, gender, duration of UC and IPAA, indication for IPAA, type and stage of IPAA, NSAID use at the entry of the study, smoking, frequency of primary sclerosing cholangitis, or family history of IBD between the two groups. During the study period, none of the patients reported NSAID or other antibiotic use.

At the end of the study period, all six patients, in Group A, who continuously received VSL #3 as a maintenance therapy for a mean period of 14.3 ± 7.2 months (range: 8–26 months) had repeat clinical and endoscopic evaluations. While the six patients were in symptomatic remission with a mean PDAI symptom score of 0.33 ± 0.52 , there was evidence of mild or moderate endoscopic pouch inflammation with a mean PDAI endoscopy score of 1.83 ± 1.72 , which was not statistically different from the baseline PDAI endoscopy score of 2.83 ± 1.17 ($P = 0.27$). This finding suggests that VSL #3 use in these patients may help maintain symptomatic remission, but to a lesser degree VSL #3 use may improve endoscopic inflammation (Table 2).

Similar to Group A, all 25 patients in Group B reached symptomatic remission after the 2-week course of ciprofloxacin and initiated VSL #3 therapy (Table 2). However, VSL #3 was discontinued in all 25 patients by 8 months into the study. Of the 25 patients, 23 discontinued the agent because of recurrence of symptoms and two discontinued because of the development of adverse effects (Table 3). The mean duration of VSL #3 use in the Group B was 1.2 ± 1.2 months (range: 0.5–6.5 months). By week 7, nine patients (36%) had discontinued VSL #3 because of either relapse of

	Group A <i>n</i> = 6	Group B <i>n</i> = 25	<i>P</i> -value
Age, years, \pm s.d.	40.0 \pm 11.5	42.9 \pm 13.4	0.63
Male gender, <i>n</i> (%)	4 (66.7)	14 (56.0)	0.63
Duration of UC, years, \pm s.d.	10.3 \pm 8.5	14.0 \pm 9.9	0.42
Duration of IPAA, years, \pm s.d.	3.3 \pm 2.5	2.0 \pm 0.9	0.15
Fulminant colitis, <i>n</i> (%)	1 (16.7)	2 (8.0)	0.52
Indications for colectomy, <i>n</i> (%)			
Refractory/steroid-dependency UC	5 (83.3)	18 (72.0%)	0.57
UC with dysplasia or cancer	1 (16.7)	7 (28.0)	
J-shaped pouch, <i>n</i> (%)	6 (100)	25 (100)	<0.99
Pancolitis, <i>n</i> (%)	6 (100)	24 (96.0)	0.62
Stages of IPAA, <i>n</i> (%)			
2	3 (50.0)	21 (84.0)	
3	2 (33.3)	2 (8.0)	
Redo pouch	1 (16.7)	2 (8.0)	0.17
NSAIDS more often than monthly, <i>n</i> (%)	2 (33.3)	11 (44.0)	0.63
Current smoking, <i>n</i> (%)	1 (16.7)	0	0.19
Primary sclerosing cholangitis, <i>n</i> (%)	1 (16.7)	1 (4.0)	0.26
IBD in first-degree relatives, <i>n</i> (%)	0	4 (16.0)	0.29
Duration on VSL #3 months, \pm s.d.	14.3 \pm 7.2	1.2 \pm 1.2	<0.001

Table 1. Comparison of demographic and clinical data between Group A and Group B

	Week 0 (At starting ciprofloxacin)	Week 3 (At starting VSL #3)	End of 8-month VSL #3 trial
Group A (<i>n</i> = 6)			
PDAI symptom score	2.67 \pm 0.52*	0*	0.33 \pm 0.52*
PDAI endoscopy score	2.83 \pm 1.17	N/A	1.83 \pm 1.72
Group B (<i>n</i> = 25)			
PDAI symptom score	3.17 \pm 1.49†	0.46 \pm 0.51†	2.83 \pm 1.43‡
PDAI endoscopy score	2.89 \pm 1.73	N/A	2.11 \pm 2.09‡

Table 2. Treatment response in the Group A and Group B

* Baseline vs. starting VSL #3 and on VSL #3 *P* < 0.001.

† Baseline and on VSL #3 vs. starting VSL #3 *P* < 0.001.

‡ Nine patients in the group B had repeat pouch endoscopy at week 7 for evaluation of recurrent symptoms.

symptoms or development of adverse effects. At week 7, the majority of patients in the group became symptomatic, with a mean PDAI symptom score of 2.83 \pm 1.43, which was not statistically different from the baseline score of 3.17 \pm 1.49 at the initiation of the sequential ciprofloxacin-VSL #3 therapy (*P* = 0.43). The nine patients in the Group B underwent repeat

pouch endoscopy at week 7 because of persistent symptoms and the mean PDAI endoscopy score was 2.11 \pm 2.09, which was not statistically different from the baseline endoscopy score of 2.89 \pm 1.73 (*P* = 0.29). At the time of repeat pouch endoscopy at Week 7, all the nine patients were already back on antibiotic therapy after they discontinued VSL #3. According to our clinical practice algorithm, the re-administration of antibiotics was allowed if patients discontinued VSL #3 because of recurrence of symptoms or development of adverse effects of VSL #3. The re-administration of antibiotics might have resulted in falsely improved PDAI symptom and endoscopy scores (Table 2). The remaining 16 patients (64%) discontinued VSL #3 after week 7, with the longest duration of treatment with VSL #3

Table 3. Outcome of VSL 3 therapy

Outcome	Cases (%)
Discontinued because of reported recurrent symptoms	23 (74.2)
Discontinued because of adverse effects	2 (6.5)
Remained on VSL #3	6 (19.4)
Total	31 (100)

of 6.5 months in Group B (Table 2). The 16 patients were back on antibiotics when follow-up PDAI symptoms were recalculated. Again, the antibiotic use might have caused falsely improved symptom scores. However, this would not affect the primary or secondary outcome measures in this study.

The PDAI symptom score was used to assess response at the end of the 2-week of ciprofloxacin trial (i.e. at the beginning of the probiotic) and at the end of 8-month trial. Unfortunately, accurate PDAI symptom scores were available only in six patients who were still on VSL #3 at the end of 8 months (Table 2). Although the PDAI symptom scores were available in the 25 patients in Group B at the end of 8 months (Table 2), the scores might have been falsely improved, as all the 25 patients were on antibiotics rather than VSL #3.

VSL #3 was generally well tolerated, and only two patients experienced intolerable adverse effects. One patient developed bloody bowel movements immediately after starting VSL #3; and one patient experienced severe constipation, bloating, and gas. The main reason for discontinuation of VSL #3 was recurrent symptoms (Table 3).

DISCUSSION

Pouchitis likely represents a spectrum of disease processes ranging from an acute antibiotic-responsive type to a chronic antibiotic-refractory entity. Management of pouchitis, especially antibiotic-dependent pouchitis and antibiotic-refractory pouchitis, is often challenging. For patients with antibiotic-dependent pouchitis, probiotics may be beneficial in correcting luminal microbial imbalance, which is considered to play an important role in its pathogenesis.^{11,12} Previous randomized, placebo-controlled trials showed that a probiotic agent VSL #3 was safe and highly effective in preventing pouchitis.⁶⁻⁸ This open-labelled study was intended to incorporate those promising results into routine clinical practice. This study showed that all patients with antibiotic-dependent pouchitis achieved symptom remission by means of a 2-week course of ciprofloxacin, but the majority of patients (80.6%) were not able to continue the probiotic therapy because of reported relapse of symptoms or development of adverse effects. Only six of 31 patients (19.4%) were able to continue the long-term use of the agent. However, even in the six patients whose symptoms were in clinical remission, a

follow-up pouch endoscopy showed inflammation with a mean PDAI endoscopy score of 1.83 ± 1.72 , which was not statistically different from that of the baseline (2.83 ± 1.17). The discrepancy between symptomatic and endoscopic responses may reflect the known lack of correlation between symptoms and endoscopic findings in pouchitis.

While most patients with acute pouchitis respond promptly to antibiotic therapy, 5–19% develop refractory or rapidly relapsing symptoms that require protracted therapy.¹³⁻¹⁵ Of the patients with acute pouchitis, 39% have a single acute episode that responds to treatment with antibiotics whereas the remaining 61% of patients go on to develop at least one recurrence.¹⁶ Treatment and prevention of relapsing pouchitis or antibiotic-dependent pouchitis are often challenging. These patients require frequent antibiotic treatment, to keep the disease in remission, either with a low-dose maintenance therapy or with a full-dose pulse therapy. However, this approach to maintain remission is empiric and there are no published trials of long-term antibiotic therapy. Probiotic therapy would be a good alternative given that it would eliminate the concern of development of bacterial resistance because of chronic antibiotic use. During the 9-month trial of 40 patients with relapsing pouchitis (defined as >3 relapses per year), only three of 20 patients (15%) in the VSL #3 group relapsed during the follow-up, whereas all 20 patients (100%) in the placebo group relapsed.⁶ Patients who received VSL #3 had better quality of life scores than those who received placebo.⁷ In another trial, the same group of investigators studied 40 patients to determine the efficacy of VSL #3 in the primary prophylaxis for initial episodes of pouchitis after IPAA.⁸ Within 1 week after ileostomy closure, 40 patients with IPAA were randomized to receive either placebo or VSL #3. Of the 20 patients in the placebo group, eight (40%) had an episode of acute pouchitis during the 1-year follow-up while only two of the 20 patients (10%) in the VSL #3 group had such an occurrence.⁸ However, in our clinical practice, the majority of patients with antibiotic-dependent pouchitis discontinued its use because of lack of clinical efficacy. We have attempted to optimize the clinical practice model for the management of the disease, by means of endoscopic evaluation and frequent contact with the patients. Prior to entering the study, it was established that all 31 patients had a history of antibiotic-dependent pouchitis, i.e. symptoms quickly responded to antibiotic therapy but quickly

recurred after stopping antibiotics. If the probiotic agent were effective, we would expect that it would have at least postponed the recurrence of symptoms. The mean duration of VSL #3 use by the patients in Group B was only 1.2 ± 1.2 months, and these patients stopped the agent because of reported recurrence of symptoms or the development of adverse effects.

Previous randomized trials have demonstrated that VSL #3 was highly effective in maintaining remission of pouchitis.^{6–8} The mechanism of action of probiotics in patients with pouchitis is not well understood. During probiotic treatment, fecal concentrations of *Lactobacillus*, *Bifidobacterium* and *S. salivarius* increased with no change in other commensal bacteria.⁶ It was speculated that probiotics may help maintain remission in patients with pouchitis by: (i) suppressing resident pathogenic bacteria; (ii) stimulating mucin glycoprotein production by intestinal epithelial cells; (iii) preventing adhesion of pathogenic strains to epithelial cells; and (iv) inducing host immune responses.¹¹ Being able to prevent relapse of pouchitis using non-toxic, physiologic bacterial agents would be a significant clinical advance.

The results of our current open-label study differ from that of the previous randomized trials.^{6–8} The open-label design of the current study was not intended to verify or validate the randomized trials. The goal of this study was done to determine whether VSL #3 was effective when used in clinical practice. Unfortunately, only a small number of patients remained in clinical response to VSL #3 for the 8-month duration of the trial. The reported causes for discontinuation of VSL #3 were recurrence of symptoms and the development of adverse effects. The discrepancy between this study and the previous studies could be because of several possibilities. Firstly, the diagnostic criteria and the classification used in the study populations, especially in distinguishing relapsing pouchitis (defined as >3 relapses per year)⁶ and antibiotic-dependent pouchitis, could differ. It is best to acknowledge that the difference in results may be related to the difference in patient population. It can easily be argued that patients with relapsing pouchitis have a different clinical disease from patients with antibiotic-dependent pouchitis. Secondly, the gut flora may be different in European and in US patients because of differences in diet.^{17–19} Another discrepancy could be because of the fact that NSAID use was common in our study population at the entry of the study, while NSAID use was not mentioned in all the previous studies.^{6, 7} In this trial, NSAID use was not allowed. As our

previous study indicated, NSAID use is an independent risk factor for pouchitis.²⁰ Whether NSAID-induced pouchitis is a subset of antibiotic-dependent pouchitis is not known. The description of NSAID use in this study was intended to acknowledge potential difference in patient populations between this and previous trials. In addition, antibiotic use for the induction of remission was different. In our trial, we used a 2-week course of ciprofloxacin, while the previous trials^{6–8} used a 4-week course of combined ciprofloxacin and rifaximin. Whether the number and/or type of antibiotics and the duration of treatment as an induction therapy affect the outcome of VSL #3 as a maintenance therapy is not known. Another possibility is that the potency of the agent purchased from the US may be different from that of the Europe. One final source of discrepancy could be the methods used to obtain VSL #3. In this study, the patients were instructed to purchase the agent through the Internet by themselves, which was the only way patients could obtain the agent in the US. In contrast, the agent was given free of charge to the patients in the previous randomized trials. This would raise the concern about patients' adherence in our trial.

We chose a 2-week course of ciprofloxacin as an induction therapy because of the excellent outcome in our previous randomized trial of ciprofloxacin vs. metronidazole in treating acute pouchitis.²¹ A 2-week single-agent antibiotic (ciprofloxacin or metronidazole) has also been shown to be effective in treating acute pouchitis by other investigators.^{22, 23} In clinical practice, ciprofloxacin with a dose of 500–1500 mg/day is a commonly used therapy. In contrast, the European studies used a 4-week ciprofloxacin and rifaximin regimen for induction therapy in relapsing pouchitis^{6, 7} – the same regimen they used to treat patients with chronic, treatment resistant pouchitis.²⁴

This study was intended to test the efficacy of VSL #3 in antibiotic-dependent pouchitis in routine clinical practice. With this in mind, there are inherent limitations to the study. Firstly, some patients in this series voiced the concern about cost, as VSL #3 is not considered a medicine, and it is rarely covered by insurance policies. This would raise the question of adherence to therapy. However, the patients were informed of the cost before entering the study, and they were also aware of possible alternatives to probiotics, including long-term antibiotic therapy. The majority of patients discontinued VSL #3 within 1–2 months after the initiation of the therapy because of reported relapse

of symptoms or adverse effects; none of the patients reported discontinuation of the agent because of the cost. Secondly, the study agent VSL #3 was self-administered by patients after they obtained the agent over the Internet. Medicine counts and evaluation of prescription records were impossible. Unlike the previous trials, fecal bacteriology was not conducted. This would further raise the issue about patients' adherence. However, we have attempted to create the best possible scenario for routine clinical practice, by providing out-patient evaluation and keeping frequent contact with patients during the trial.

Another issue is that although all patients underwent a baseline evaluation before the initiation of the sequential antibiotic-probiotic therapy that included pouch endoscopy and biopsy, none of them had pouch endoscopy at the beginning of the VSL #3 trial to document a complete resolution of endoscopic inflammation of the pouch. This would have missed residual pouch inflammation in some patients, although our previous study showed that a 2-week course of ciprofloxacin achieved remission rate of 100% in active pouchitis patients.²¹ A final limitation to the study is the fact that the determination of patients' response to the antibiotic or the probiotic was largely based on symptoms. It is important to acknowledge that the recurrence of symptoms on VSL #3 does not necessarily indicate the presence of pouchitis.^{25, 26} Symptoms may be related to irritable pouch syndrome, cuffitis, and proximal small bowel bacterial overgrowth. Despite the limitations, the results of this study reflect the reality of the effects, which the sequential use of antibiotic-probiotic therapy would have on our daily clinical practice.

In conclusion, we demonstrated in the study that although symptomatic remission was achieved by a 2-week therapy with ciprofloxacin in all patients, the majority of patients were not able to continue the long-term maintenance probiotic therapy. More studies are warranted to further evaluate the safety and efficacy of probiotic agents. Several hurdles need to be overcome before we incorporate the routine use of probiotics into our daily clinical practice for managing pouchitis.

ACKNOWLEDGEMENT

No external funding was received for this study.

REFERENCES

- Sandborn WJ. Pouchitis following ileal pouch-anal anastomosis. Definition, pathogenesis, and treatment. *Gastroenterology* 1994; 107: 1856–60.
- Zuccaro G, Fazio VW, Church JM, Lavery IC, Ruderman WB, Farmer RG. Pouch ileitis. *Dig Dis Sci* 1989; 34: 1505–10.
- Fazio VW, Ziv Y, Church JM, *et al.* Ileal pouch-anal anastomosis complications and function in 1005 patients. *Ann Surg* 1995; 222: 120–7.
- Mahadevan U, Sandborn WJ. Diagnosis and management of pouchitis [Review]. *Gastroenterology* 2003; 124: 1636–50.
- Shen B. Diagnosis and management of patients with pouchitis. *Drugs* 2003; 65: 453–61.
- Gionchetti P, Rizzello F, Venturi A, *et al.* Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; 119: 305–9.
- Mimura T, Rizzello F, Helwig U, *et al.* Once daily high dose probiotic therapy (VSL 3) for maintaining remission in recurrent or refractory pouchitis. *Gut* 2004; 53: 108–14.
- Gionchetti P, Rizzello F, Helwig U, *et al.* Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology* 2003; 124: 1202–9.
- Shen B, Fazio VW, Remzi FH, *et al.* Comprehensive evaluation of inflammatory and non-inflammatory sequelae of ileal pouch-anal anastomosis. *Am J Gastroenterol* 2004; 100: 93–101.
- Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a pouchitis disease activity index. *Mayo Clin Proc* 1994; 69: 409–15.
- Sartor RB. Probiotics in chronic pouchitis. Restoring luminal microbial balance. *Gastroenterology* 2000; 119: 584–5.
- Shen B, Lashner BA. Can we immunogenotypically and immunotypically profile patients who are at risk for pouchitis? *Am J Gastroenterol* 2004; 99: 442–4.
- Mowschenson PM, Critchlow JF, Peppercorn MA. Ileoanal pouch operation: long-term outcome with or without diverting ileostomy. *Arch Surg* 2000; 135: 463–5.
- Hurst RD, Chung TP, Rubin M, Michelassi F. Implications of acute pouchitis on the long-term functional results after restorative proctocolectomy. *Inflamm Bowel Dis* 1998; 4: 280–4.
- Madiba TE, Bartolo DC. Pouchitis following restorative proctocolectomy for ulcerative colitis: incidence and therapeutic outcome. *J Royal Coll Surg Edinburgh* 2001; 46: 334–7.
- Lohmuller JL, Perberton JH, Dozois RR, Dozois FF, Ilstrup D, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. *Ann Surg* 1990; 211: 622–9.
- Hill MJ. Diet and the human intestinal flora. *Cancer Res* 1981; 41: 3778–80.
- Hayashi H, Sakamoto M, Benno Y. Fecal microbial diversity in a strict vegetarian as determined by molecular analysis and cultivation. *Microbiol Immunol* 2002; 46: 819–31.

- 19 Peltonen R, Nenonen M, Helve T, Hanninen O, Toivanen P, Eerola E. Faecal microbial flora and disease activity in rheumatoid arthritis during a vegan diet. *Br J Rheumatol* 1997; 36: 64–8.
- 20 Achkar J-P, Al-Haddad M, Lashner BA, *et al.* Differentiating risk factors for acute and chronic pouchitis. *Clin Gastroenterol Hepatol* 2005; 3: 60–6.
- 21 Shen B, Achkar JP, Lashner BA, *et al.* A randomized trial of ciprofloxacin and metronidazole in treating acute pouchitis. *Inflamm Bowel Dis* 2001; 7: 301–5.
- 22 Madden MV, McIntyre AS, Nicholls RJ. Double-blinded crossover trial of metronidazole versus placebo in chronic unremitting pouchitis. *Dig Dis Sci* 1994; 39: 1193–6.
- 23 Hurst RD, Molinari M, Chung TP, Rubin M, Michelassi F. Prospective study of the incidence, timing, and treatment of pouchitis in 104 consecutive patients after restorative proctocolectomy. *Arch Surg* 1996; 131: 497–502.
- 24 Gionchetti P, Rizzello F, Venturi A, *et al.* Antibiotic combination therapy in patients with chronic, treatment resistant pouchitis. *Aliment Pharmacol Ther* 1999; 13: 713–8.
- 25 Shen B, Achkar J-P, Lashner BA, *et al.* Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. *Gastroenterology* 2001; 121: 261–7.
- 26 Shen B, Achkar JP, Lashner BA, *et al.* Irritable pouch syndrome: a new category of diagnosis for symptomatic patients with ileal pouch-anal anastomosis. *Am J Gastroenterol* 2002; 97: 972–7.