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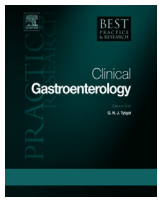

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The current place of probiotics and prebiotics in the treatment of pouchitis

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A B S T R A C T

Pouchitis is a common complication in patients undergoing restorative proctocolectomy for ulcerative colitis. Therapeutic attempts include manipulations of pouch flora composition. In this review, we bring together the evidence supporting the use of probiotics and prebiotics in pouchitis patients, to clarify the place of these treatments in current therapeutic regimens.

Introduction

Ileal-pouch anal anastomosis (IPAA) is the standard reconstruction procedure after total proctocolectomy for medically refractory ulcerative colitis (UC) and UC with dysplasia, as well as for familial adenomatous polyposis (FAP). The pouch is an artificial conduit formed from distal sections of ileum, reconnected to the anus to function as a reservoir in place of the removed rectum. Pouchitis, an inflammation of this conduit, is a common complication in patients operated on for ulcerative colitis,

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and manifest itself with increased stool frequency, rectal bleeding, abdominal cramping, rectal urgency and tenesmus, incontinence, and fever. Endoscopic examination reveals mucosal edema, granularity, loss of vascular pattern and ulceration of the pouch mucosa. While almost half of UC patients undergoing restorative proctocolectomy experience episodes of acute pouchitis [1,2], this complication is only rarely seen in patients with FAP. This selective, nearly exclusive appearance suggests that stasis of intestinal content, in and of itself, is not sufficient to cause inflammation, but only results in pouchitis in genetically and immunologically susceptible patients. In accordance with this hypothesis, carriage of certain alleles of NOD2 [3,4], TLR9 [5], CD14 [5] has been found to be associated with the risk of severe and recurrent pouchitis, whereas carriage of TNF allele 2 [6] and certain alleles of IL-1 receptor antagonist [6,7] is associated with a protective effect, suggesting that intrinsic abnormalities in the immune response against intestinal bacteria may play a role in the pathogenesis of this complication. The impaired ability of intestinal cells to take advantage of butyrate produced by commensal bacteria is another etiological factor associated with pouchitis [8].

As genetic susceptibility is not open to intervention, and stasis of the intestinal content is to be expected in functioning pouches, most attempts to intervene with harmful mucosa–bacteria interactions focus on manipulations of pouch flora composition, by means of either antibiotic, probiotic or prebiotic therapy (or a combination).

In this review, we aim to bring together the evidence supporting the use of of probiotics and prebiotics in pouchitis patients, and to clarify the place of these interventions in current therapeutic regimens. In doing so, we take into consideration different treatment endpoints (induction of remission vs. prevention of relapses), setting (primary vs. secondary prevention), choice of specific microorganism(s), and duration of therapy.

Preventing the onset of pouchitis/primary prevention

Three studies examined the ability of various probiotic regimens to prevent the onset of pouchitis following restorative proctocolectomy [9–11] (Table 1).

Gosselink et al. [9] retrospectively compared 3 year pouchitis-free survival in 39 patients whose treatment with *Lactobacillus rhamnosus GG* preparation commenced immediately after surgery, to that of an historical group of 78 untreated patients. The appearance of pouchitis was documented in 7% and 29% of the patients, respectively ($P = 0.011$), suggesting that LGG exerts a primary preventive effect.

Gionchetti et al. [10] conducted a prospective randomized double-blind, placebo-controlled trial of VSL#3 versus placebo ($n = 40$), in which treatment commenced immediately after closure of protective ileostomy, and was administered for 1 year. Pouchitis occurred in 10% of treated patients, compared with 40% in the placebo group ($P < 0.05$), proving that treatment with VSL#3 is effective in preventing the onset of acute pouchitis. A recent Cochrane meta-analysis confirmed the efficacy of VSL#3 in this connection, with a calculated effect ratio of 1.50 [1.02, 2.21] [12].

In a randomized controlled trial by Yasueda et al. [11], 17 UC patients were randomized to receive the spore-forming bacteria *Clostridium butyricum MIYAIRI* or placebo for 24 months, starting immediately after surgery. Among these patients, 50% of the placebo group and 11% of the *C. butyricum* group developed pouchitis; however, the small size of the study population prevented this difference from reaching statistical significance.

Table 1
Use of probiotics to prevent the onset of pouchitis (primary prevention).

Study	No. of patients	Duration (months)	Probiotic strain	Control	Outcome
Gosselink et al., (2004) [9]	117	36	LGG	No treatment (historical control)	Pouchitis-free survival: 93%, vs. 71% if no treatment ($P = 0.011$)
Gionchetti et al., (2003) [10]	40	12	VSL#3	Placebo	Pouchitis-free survival: 90%, vs. 60% on placebo ($p < 0.05$)
Yasueda et al., (2015) [11]	17	24	*Clostridium butyricum MIYAIRI*	Placebo	Pouchitis-free survival: 89%, vs. 50% on placebo (NS)