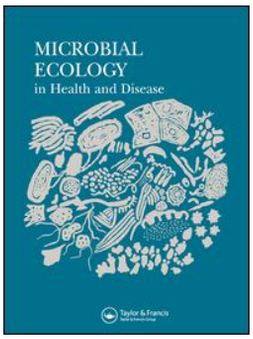

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Probiotics in the Management of Irritable Bowel Syndrome: A Review of Clinical Trials

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Irritable bowel syndrome is a common condition of unknown aetiology, the medical management of which is unsatisfactory. Despite evidence that a disturbance of intestinal flora may be responsible for the initiation and/or chronicity of the distressing symptoms, little attention has been paid to the potential advantages of correcting this imbalance by using probiotics. Results of 12 clinical trials, involving 1371 patients in all, in which probiotic treatment was given have been reviewed. In 10 (five of which were randomized, double-blind and placebo controlled), use of probiotics was beneficial. The probiotic agents, dosage and duration of treatment varied widely between the studies. Despite several shortcomings in terms of study design and publication details, there now seems to be sufficient evidence of the therapeutic efficacy for this inexpensive and safe treatment modality to be tested more widely. *Key words*: Irritable bowel syndrome, probiotic agents, treatment.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common complaint in the Western world, in the order of 15% of the population being affected at some time during their life; it is more often found in females (14–24%) than in males (5–19%) (1). Patients present with various complaints, including abdominal pain, bloating and disturbances of bowel habits (constipation or diarrhoea). The precise aetiology is unknown, but the disorder is undoubtedly multi-factorial and attacks may be triggered by, among other things, items in the diet and emotional stress.

Although the condition is not life-threatening, in comparison with the general population sufferers have a reduced quality of life, use more healthcare resources and are more often absent from work. For example, it has been estimated that IBS may be responsible for 10% of visits to family practitioners and half the number of referrals to gastroenterology clinics (2). There is as yet no satisfactory consensus among the medical profession as to how IBS should be managed, either in the community or in specialist clinics; as a direct result of this, patients may become disillusioned with conventional medicine, illustrated by the fact that up to 70% of those with IBS may not seek medical attention (3). The importance of psychological factors in IBS is underlined by the high improvement rate (30–88%) observed in various clinical trials in control group patients given placebo (1).

In terms of several of the above features, IBS resembles another common condition (but in this case much more closely confined to females), namely the 'urethral syndrome' (4). Indeed, it has been reported (5) that 30% of patients with interstitial cystitis—one cause of the urethral syndrome—also have IBS.

There are good reasons to believe that there may be alterations in the intestinal flora in IBS, although whether this is cause or effect is still unclear. A logical conclusion to this is that manipulation of the flora, for example, by replacement of missing organisms or encouraging a more favourable intestinal milieu, might have beneficial effects. It is the purpose of this review to discuss results of published work where biological therapy, i.e. probiotics, has been used as a management strategy for IBS instead of a pharmacological approach. The use of probiotics has been largely ignored in recent reviews of IBS treatment, partly perhaps because they are considered by some to lie outside the realms of conventional medicine and also because several trials have as yet been reported only as 'abstracts'. With these shortcomings in mind, it is hoped that this review may stimulate a consideration of this type of additional approach to IBS management.

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ASSOCIATION OF INTESTINAL FLORA CHANGES WITH IBS

Direct evidence

There is some direct evidence of changes in the nature of the intestinal flora during IBS. Balsari et al. (6) reported that 20 patients had significantly lower counts of lactobacilli, coliforms and bifidobacteria than healthy control subjects, and Bayliss et al. (7) found a reduction in numbers of bifidobacteria.

Indirect evidence

There are several reports that the disturbances of gut flora resulting from an attack of gastro-enteritis may result in the onset of IBS; McKendrick and Read (8) and Gwee et al. (9) found that one-quarter to one-third of patients (132 were followed in these two studies) who had had infectious gastro-enteritis (due to salmonella, shigella or campylobacter) went on to develop IBS for the first time. In a cohort study, Rodriguez and Ruigomez (10) showed that a first episode of IBS was 10 times more likely to occur following an acute attack of gastro-enteritis than in a control group. Gui (5) has postulated that an episode of intestinal infection produces a local inflammatory response, which may result in mast cell activation, which in turn causes gut hypersensitivity.

Administration of an antibiotic is a well-known cause of alterations in the intestinal flora, and may be associated, anecdotally, with IBS (e.g. (7, 11, 12)). Alun-Jones et al. (13) have documented this phenomenon for metronidazole and various other unnamed antibiotics. Results obtained by Pimentel et al. (14) on the effects of treatment with a variety of antibiotics (most often oral neomycin) strongly suggest that some cases of IBS-like symptoms may be due to bacterial overgrowth in the small intestine, and that elimination of this brings about relief of such symptoms.

King et al. (15) have observed abnormal fermentation by the gut flora in IBS patients; there was excess gas production, mainly hydrogen, compared with control subjects. When the symptoms of IBS were relieved in this case by the use of an exclusion diet, gas production was reduced.

The above reports are highly suggestive of a relationship between IBS and changes in the intestinal flora. The thinking behind the use of probiotics is that it is possible to modulate gut flora by the ingestion of appropriate types of bacteria, usually those that produce lactic acid, such as lactobacilli and bifidobacteria (16). Probiotics also have immunomodulating effects that are assumed to be responsible for therapeutic activity outside the gastro-intestinal tract (e.g. in chronic tonsillitis and sinusitis). The use of probiotics has been shown to be effective in the treatment and prevention of several types of gastro-intestinal infections (17) and in view of the evidence presented above it seems logical to test probiotics in IBS.

CLINICAL TRIALS OF PROBIOTICS IN IBS

Twelve trials have been reported in which 14 probiotic preparations were tested. Six of the studies have been published as full papers (18–21, 25, 27) and six in abstract form only (12, 22–24, 26, 28). Results from a total of 1371 patients were analysed (12, 18–28). A statistically significant improvement was observed in at least one symptom category, and/or by the individual patients' opinion, in 10 of these trials, involving nine different probiotic preparations (Table I section A). In two studies (Table I section B), treatment with a probiotic was not more effective than placebo; it has to be borne in mind, however, that trials producing 'no significant difference' results often go unpublished, so it is possible that there are other studies in IBS that fail to show any benefit from treatment with a probiotic.

A successful result was reported in four trials (21, 23–25) using a single species of lactobacillus (*L. plantarum* 299v in three, and heated-killed *L. acidophilus* LB in one), in three (18, 22, 26) using a single different strain of *E. faecium* (M74, PR88 and SF 68), and in four (12, 19, 20, 26) using a mixture (*E. faecalis* + *E. coli* [killed], *E. coli* [several strains], normal flora [mainly *Bacteroides*], 'mixed lactic acid bacteria'). No beneficial effects were found in trials with *L. acidophilus* NCFM (27), sterile *L. helveticus* (28) and a sterile mixture of two lactobacilli and *E. coli* (28). As can be seen from Table I, there was a wide range in the duration of treatment (from once only to daily for 12 weeks, with a mode of 4 weeks) and in both daily and cumulative dose (in terms of nominal numbers of viable organisms consumed or their equivalent in dead bacteria and/or metabolic products). There was no correlation between either the dosage or the use of live/dead preparations and treatment success.

In five trials (18, 20, 21, 24, 28), rates of placebo response were given: these ranged from 30 to 61%. This is thus in general agreement with the high rates found in trials with other agents (see above).

DISCUSSION

There have been six reviews recently on the management of IBS (2, 29–33). Three (29, 30, 33) make no mention at all of probiotics, nor are any of the trials discussed here cited. In the other three, Rothstein (32) writes "Probiotics represent another alternative treatment for a variety of gastrointestinal ills and may benefit patients with IBS", but gives no references; Jailwala et al. (31) cite three of the trials identified here (18, 21, 28) under the heading 'miscellaneous', stating that lactobacilli and streptococci were used, but do not indicate that the preparation used by Halpern et al. (21) contained no live bacteria; Akehurst and Kaltenhalter (2) include Lacteol Fort (21) as an 'anti-diarrhoeal drug' and Paraghurt (18) in the 'miscellaneous' category, without mentioning their probiotic na-

Table I

Twelve trials of probiotics IBS, A. reporting significant improvement in patient's condition, B. reporting no significant improvement

Reference	Treatment	Type of study	Number of patients (M/F)		Diagnostic criteria	Signs/symptoms measured	Duration of treatment	Dose	
			Test	Control				Daily	Cumulative
A. Positive outcome									
Gade and Thorn (18)	"Paraghurt" (*Enterococcus faecium* M74)	R, DB, P[a]	32 (5/27)	22 (7/15)	Danish "Medinisk Kompendium"	6 item score sheet	4 weeks	8×10^{6}[b]	2.2×10^{8}
Panijel and Burkhard (19)	"Pro-Symbioflor"[c]	R,DB,P	150	147	Kruis[d]	5 item score sheet	8 weeks	6×10^{7} (mean)	3.4×10^{9}
Schaffstein and Burkhard (20)	"Symbioflor 2"[e]	R, DB, P	149 (63/86)	150 (70/80)	Kruis	5 item score sheet	8 weeks	6×10^{7} (mean)	1.7×10^{9}
Halpern et al. (21)	"Lacteol Fort" (*Lactobacillus acidophilus* LB) (heat-killed)	R,DB,P,C[a]	18		Manning[f]	5 item score sheet	6 weeks	2×10^{10}	1.4×10^{12}
Hunter et al. (22)	*E. faecium* PRSS	O[a]	28		"high volume diarrhoea due to food intolerance"	overall symptoms	12 weeks	10^{10}	8.4×10^{11}
Pearce et al. (12)	Endoscopic instillation of normal flora	O	51 (23/28)		Rome[g]	Likert scale, 4 items	once	not stated	
Young and Vanderhoof (23)	*L. plantarum* 299v	C	12		"paediatric variety of adult IBS"	daily diary of pain and functioning	4 weeks	not stated	
Kordecki and Niedzielin (24)[h]	*L. plantarum* 299v	P	42	20 placebo, 60 anti-spasmodic	"fully symptomatic IBS"	overall condition	4 weeks	2.5×10^{9}	7×10^{10}
Nobaek et al. (25)	*L. plantarum* 299v	R,DB,P	25 (9/16)	27 (7/20)	Rome[g]	daily diary, 3 items; weekly visual analogue score 4 items	4 weeks	2×10^{10}	5.6×10^{11}
De Simone et al. (26)	"VSL # 3"[i]	O	130		Rome	visual analogue score	10 days	3×10^{11}	3×10^{12}
	"Bioflorin"[j]		121					7.5×10^{7}	7.5×10^{8}
B. No improvement									
Newcomer et al. (27)	*L. acidophilus* NCFM	C	61		"typical history and negative tests"	daily 5 item dairy	2 weeks	3×10^{9}	4.2×10^{10}
Hentschel et al. (28)	"Hylac N"[k]	R,DB,P	42	44	"non-ulcer dyspepsia"	4 item score	4 weeks	5×10^{9}	1.4×10^{11}
	"Hylac Forte N"[l]		40					2.5×10^{8}	7×10^{10}

[a] R, randomized; DB, double-blind; P, placebo controlled; C, crossover; O, open, historical controls.
[b] This count is based on the present author's assay of Paraghurt tablets.
[c] "Pro-Symbioflor" is a sterile autolysate of *Enterococcus faecalis* and 10 strains of *Escherichia coli.*
[b] Kruis W, Thieme C, Weinzieri M, Schlusser P, Holl J, Paulus W. A diagnostic score for the irritable bowel syndrome. Its value in the exclusion of organic disease. Gastroenterology 1984; 87: 1–7.
[e] "Symbioflor 2" is an autolysate and live cells of several strains of *E. coli*. The present author's assay showed a viable count of 7×10^{6} cells per ml.
[f] Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. Br Med J 1978; ii: 653–54.
[g] Thompson WG, Dotevail G, Drossman DA, Heaton KW, Kruis W. Irritable bowel syndrome: guidelines for diagnosis. Gastroenterol Int 1989; 2: 92–95.
[h] Information given in a personal communication from Professor HJ Kordecki has been added
[i] "VSL # 3" contains 10^{11} live bacteria per ml, consisting of seven species: *L. acidophilus*, *L. plantarum*, *L. casei*, *L. delbrueckii*, *Streptococcus thermophilus*, *E. faecium* and bifidobacteria.
[j] "Bioflorin" is 2.5×10^{7} cells per ml of *E. faecium* SF68.
[k] "Hylac N": 1 ml contains metabolic products from 2×10^{9} *L. helveticus.*
[l] "Hylac N Forte": 1 ml contains metabolic products from 10^{9} *L. helveticus*, 10^{7} *L. acidophilus* and 8×10^{7} *E. coli* (present author finds it contains no viable bacteria).

ture. The trials carried out by Panijel and Burkhard (19) and Schaffstein and Burkhard (20) were published in German, and so were not considered by Jailwala et al. (31), who searched only for English language papers, and by Akehurst and Kaltenhalter (2) presumably because the journals used are not listed on the databases searched.

While it is clear that the reporting of several of the 14 trials reviewed above leaves much to be desired, the overall picture is that probiotics may offer some relief to sufferers of IBS. Particularly convincing are the five studies (18–21, 25) that were randomized, double-blinded and placebo-controlled, involving 720 patients. All five trials showed a statistically significant outcome benefit from taking probiotics.

It can be speculated, as outlined above, that the success of the trials using live probiotics (12, 18, 20, 22–26) may be due to recolonization of the intestines with a more suitable flora. On the other hand, there is clearly an immunological contribution, as indicated by the positive outcomes reported in two studies (19, 21) using killed probiotic bacteria. For example, the strain of *E. faecalis* used by Panijel and Burkhard (19) has been shown to stimulate lymphocytes to produce interleukins and γ-interferon (34); immunomodulating properties of probiotics are especially marked in relation to the intestine (35).

Much more work needs to be done, specifically to determine which type of probiotic is best, the optimal regimen in terms of length and dosage and whether one of the three IBS patient subgroups (constipation, diarrhoea or alternating between the two) may benefit more than another. More detailed microbiological examination of flora in treatment and placebo groups would give much valuable information. A surprising shortcoming in the study design of almost all the trials analysed above is a lack of long-term follow-up. If the hypothesis is correct, that IBS may be due to a disturbance in gut flora, it is obviously important to determine whether supplementation of this flora for, say 4 weeks, has a permanent or merely a temporary effect. Long-term follow-up was reported in only two of the trials listed in Table I: Pearce et al. (12) found that 65% of patients treated by flora replacement continued to be improved 3 months after treatment, and Nobaek et al. (25) showed that symptomatic scores 12 months after the completion of the study were significantly better in patients who had been treated with the active preparation (*L. plantarum* 299v) than in the placebo group.

It is well recognized that current conventional medical treatment of IBS is unsatisfactory, and indeed in many cases of no proven value at all (29). One clear advantage of using probiotics is the minimal incidence of adverse events, and many practitioners and patients may consider a course of probiotics, in the form of a supplement of satisfactory quality (36) or a functional food (e.g. a bioyoghurt or fermented milk), to be worth trying in this difficult condition. Unfortunately, many of the probiotics shown to be useful in IBS (Table I section A) are not generally available: for example, *E. faecium* PR88 (22) is a cheese starter culture, not on sale to the public, while Lacteol Fort (21), Symbioflor products (19, 20) and VSL#3 and Bioflorin (26) may be difficult to obtain outside the countries of their manufacture, respectively, France, Germany and Italy. This emphasizes the need for further studies with probiotics that are more widely available (e.g. Lactobacillus GG, *L. casei* Shirota, *L. johnsoni* La1). Even those practitioners who remain completely unconvinced as to the efficacy of probiotics in IBS may care to take advantage of the placebo effect, which, although frustrating and misleading to those seeking the underlying causes of IBS, is nevertheless of considerable benefit to the patient.

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