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In a nutshell

Inflammatory bowel diseases can involve problems in the development of the gut's immune response. A healthy bowel flora plays an important role in this development, for example through effects on cytokines.

Clinical trials of probiotics for IBD have been predominantly positive for ulcerative colitis and pouchitis, less so for Crohn's disease. So far probiotics appear to be a notably safe therapy, although some theoretical safety issues need to be borne in mind.

Probiotics and bowel inflammation

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NUTRITION RESEARCH REVIEW

Study 1: Probiotics as adjunct in ulcerative colitis

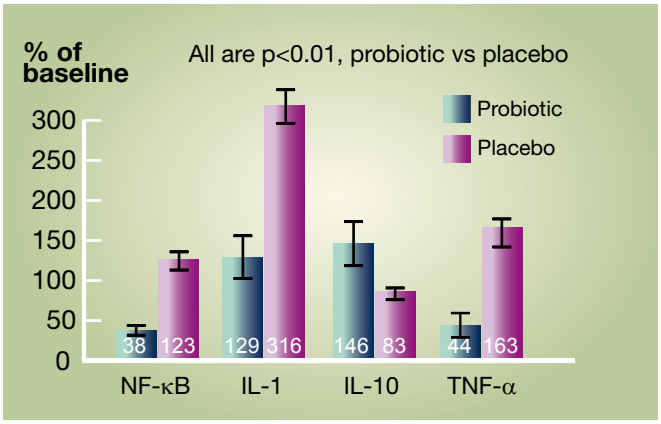
A recent Chinese trial tested probiotics alongside conventional ulcerative colitis (UC) treatment.

Subjects and method: Randomised controlled trial comparing 8 weeks of sulphasalazine/glucocorticoid therapy with or without a probiotic (three *Bifidobacteria*) in 30 UC patients. Colonic tissue was biopsied before and after.

Results: Compared with placebo, the probiotic group had a major improvement in 2 month follow-up relapse rate (20% in probiotic vs 93% in placebo, p<0.01), along with reduced expression of transcriptional factor NF-κB (a regulator of gut inflammatory reactions), lower levels of pro-inflammatory cytokines, and higher levels of anti-inflammatory cytokine IL-10. See Graph.

Ref.: Cui HH. et al. Effects of probiotic on intestinal mucosa of patients with ulcerative colitis. World J Gastroenterol. 2004 May 15;10(10):1521-5.

Graph: Expression of inflammatory factors - (Study 1) values after intervention as % of baseline



Study 2: Probiotics and IBS

A new US trial tested probiotics in treatment of irritable bowel syndrome (IBS).

Subjects and method: RCT of 48 subjects with chronic symptoms indicative of IBS given placebo or a combination probiotic (various *Bifidobacteria*, *Lactobacilli* and *Streptococcus* species) for 4-8 wks.

Results: Compared with placebo, probiotics resulted in significant improvement in subjective flatulence score (25% less than placebo, p=0.01) and colonic transit time (25% more than placebo, p=0.05) but not other symptoms or stool characteristics.

Ref.: Kim HJ. et al. A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. Neurogastroenterol Motil. 2005 Oct;17(5):687-96.

Study 3: Probiotics and ileal pouchitis

A new Swedish trial employed probiotics to counter the side-effect of ileal pouchitis after colonic resection.

Subjects and method: For 4 weeks fermented milk with live probiotic organisms (*Lactobacilli* and *Bifidobacteria*) was given to patients who had had ileal-pouch-anal-anastomosis, 51 due to ulcerative colitis, 10 due to familial polyposis.

Results: A range of symptoms (e.g. from involuntary defaecation to abdominal cramps) and need to use napkins significantly decreased in probiotic patients, with more response in the UC than polyposis patients.

Ref.: Laake KO. et al. Outcome of four weeks' intervention with probiotics on symptoms and endoscopic appearance after surgical reconstruction with a J-configurated ileal-pouch-anal-anastomosis in ulcerative colitis. Scand J Gastroenterol. 2005 Jan;40(1):43-51.

COMMENTARY

These three new trials highlight important aspects of the current research on probiotics in inflammatory bowel diseases (IBD), including Crohn's disease, ulcerative colitis and irritable bowel syndrome. We will consider the evidence on whether probiotics can actually help in treating IBD, what probiotic research tells us about underlying causes, and briefly consider the safety of probiotics.

Clinical efficacy

The Table (next page) shows that the human trial evidence of clinical benefit in IBD is mixed. Although it includes over two dozen studies involving more than 1500 patients [1-28], we have to discount those that are open trials, to the extent that these disorders have a highly variable natural course and are susceptible to psychological influence. For Crohn's disease this leaves us with just one small trial reporting benefit [4], and three others which did not [1, 2, 5].

For ulcerative colitis, on the other hand, the evidence base is broader and generally encouraging. Three placebo-controlled RCTs showed significant clinical improvement [18, 20, 23], and other studies reported that probiotics (or prebiotics) were at least as effective as conventional treatment in reducing symptoms, obtaining remission and preventing relapse [19, 21, 22, 24-26].

Probiotics may be useful in ileal pouchitis (which can be a complication of surgical colectomy, performed, amongst other things, for severe IBD), although only one trial in the Table was a placebo-controlled RCT [15].

The remaining trials were on the more `non-specific' IBS. That data was hopeful but is not conclusive. Two studies did not find a significant benefit (in part because of a strong placebo effect) [7, 10], but others did [6, 8, 9, 11].

Mechanisms

Although the causes of IBD are still something of a mystery, in order to understand the role of probiotics we need to delve a little bit into this background.

In the complex aetiology of IBD, a strong genetic influence interacts with abnormalities in the development and function of intestinal mucosal immunity, mainly involving T-cells. (Crohn's disease and UC affect different types of helper T-cell). The development and functioning of this gut immunity requires a delicate balance of pro- and anti-inflammatory cytokines (such as the various interleukins, TNF-α etc.), apparently interacting through physiological elements such as toll receptors and dendritic cells [29-31].

The colonic bacterial population is bound up with the development of this immune function in ways only partially understood. For one thing, in animal experiments IBD-like pathology will not occur in a sterile gut [32]. Patients with IBD may have an abnormal microflora, in regard not only to the composition of organisms that make it up, but also their adhesion to and penetration through the intestinal cells [31-33].

Probiotics can potentially counter all these abnormalities. By applying `competitive pressure' they can reduce the population of abnormal organisms (antibiotics have been used for this as well). They can reverse adhesion/penetration abnormalities [33, 34]. On the other hand, the extent to which this abnormal flora is the cause rather than the effect of IBD is still unclear [33].

`Healthy flora' also plays a direct and crucial role in the development of GIT immune balance within the T-cell system. The cytokine elements that keep inflammatory processes in check (e.g. IL-10) have been found to be reduced in IBD [29, 32], and probiotics can counter this imbalance [32, 33], as shown in new Study 1. Indeed one trial found that probiotics' effect on cytokines was directly correlated with its clinical efficacy in IBD [6]. Probiotics can also influence the toll receptors and dendritic cells involved in healthy gut immunity [35]. Other possible therapeutic effects include correction of abnormal intestinal permeability (`leaky gut'), improved mucus production and production of short chain fatty acids [29, 32].

Safety

Probiotics do have a long history of apparently safe use [35, 36]. Even so, the fact that they can exert potentially powerful immune effects should give grounds for some caution until we have more data. This is particularly relevant when we see probiotics being added to infant formula or given to seriously immuno-compromised patients, in whom there have been isolated cases of opportunistic infection from probiotic species (e.g. *Enterococcus* and *Saccharomyces* species [35, 36]).

There is much that is still unknown. Long term trials (> 1 yr) would be welcome. Species- and strain-specificity as well as genetic variations in host susceptibility remain intriguing uncertainties, as we discussed in last week's issue [37]. Until we have more data on such specificity, clinicians might be advised to use the particular probiotics or mixtures proven in RCTs.

Overall we are optimistic about the potential of probiotics to assist patients with IBD. Whilst some uncertainties in the practicalities of prescription remain, this is still a treatment option that clinicians should definitely consider.

Table: Human clinical trials of probiotics for inflammatory bowel diseases
(including Crohn's disease, ulcerative colitis and irritable bowel syndrome - IBS)

Year	Disease	n=	Design	Organism	Durn.	Outcome measures	Result	Ref.
2005	Crohn's	75 kids	RCDBT	*Lactob.*	8 mo	Relapse	NS	1
2004	Crohn's	11	RCDBT	*Lactob.*	6 mo	Remission and relapse	NS	2
2003	Crohn's	25	Open trial	*Sacchar.*	4 wk	Remission	70% remission	3
2000	Crohn's	32	RCT	Mesalazine ± *Sacchar.*	6 mo	Relapse	Relapse in 6% probiotic vs 38% mesalazine only	4
2002	Crohn's	45	RCDBT	*Lactob.*	12 mo	Relapse after surgery	NS	5
2005	IBS	77	RCDBT	*Lactob.*or *Bifidob.*	8 wk	Symptoms, cytokines	Reduction in symptoms and cytokines for bifid. Only	6
2005	IBS	54	RCDBT	*Lactob.*	6 mo	Symptoms and QOL	NS	7
2005	IBS	48	RCDBT	VSL#3	4-8 wk	Symptoms, colonic transit	Improved flatulence (p=0.01) and colonic transit (p=0.05), rest NS	8
2005	IBS	103	RCDBT	Mixture	6 mo	Symptoms	Reduced (42% vs 6%, p=0.015)	9
2005	IBS	50 kids	RCDBT	*Lactob.*	6 wk	Symptoms	NS	10
2005	IBS	25	RCDBT	Synbiotic	2 wk	3 specific symptoms	All reduced (p=0.042 p=0.008, p=0.003)	11
2005	Pouchitis	31	Open trial	VSL#3	8 mo	Disease activity index	NS	12
2005	Pouchitis	61	Open trial	*Lactob.*& *Bifidob*.	4 wk	Symptoms	Reduction in range of symptoms	13
2004	Pouchitis	51	Open trial	*Lactob.*	4 wk	Mucosal inflammation and blood flow	Reduced blood flow	14
2003	Pouchitis	40	RCDBT	VSL#3	12 mo	Pouchitis risk, QOL	Less risk of pouchitis (p< 0.05) and enhanced QOL	15
2003	Pouchitis	10	Open trial	*Lactob.*+ *Bifidob*.	4 wk	Endoscopic inflammation	Reduced	16
2005	UC	34	Open trial	VSL#3	6 wk	Remission	Remission in 53%	17
2005	UC	18	RCDBT	Synbiotic	1 mo	Sigmoidoscopy, inflamm. factors	Score reduced (p=0.06), inflamm. factors reduced (all p<0.04)	18
2004	UC	120	RCT	*E.coli* vs mesalazine	12 wk	Clinical activity, remission and relapse	Probiotic same as conventional	19
2004	UC	20	RCDBT	*Bifidob.*	12 wk	Clinical and endoscopic activity	Reductions in probiotic only	20
2004	UC	327	RCT	*E.coli* vs mesalazine	12 mo	Relapse	Probiotic same as conventional	21
2004	UC	90	RCT	Convent.Rx ± VSL#3	8 wk	Remission	More and faster remission (p<0.02)	22
2004	UC	30	RCDBT	*Bifidob*.	2 mo	Relapse, cytokines	Less relapse, cytokines (all (p<0.01)	23
2004	UC	59	RCT	*Conven. vs prebiotic*	12 mo	Disease activity index, relapse	Significantly better	24
2003	UC	21	RCT	*Bifidob.*	12 mo	Exacerbation rate	Reduced (p<0.02)	25
1999	UC	120	RCDBT	*E.coli* vs mesalazine	to 12 mo	Relapse	Probiotic same as conventional	26
1999	UC	20	Open trial	VSL#3	12 mo	Remission	75% remission	27
2005	UC and Crohn's	29	Open trial	VSL#3	Pilot study	Arthritis activity score	62% had reduction	28
			DB= double blind, RCT=randomised controlled trial			QOL=quality of iife	NS= not signif.	

References:
1. Bousvaros A. et al. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. Inflamm Bowel Dis. 2005 Sep;11(9):833-9.
2. Schultz M. et al. Lactobacillus GG in inducing and maintaining remission of Crohn's disease. BMC Gastroenterol. 2004 Mar 15;4:5.
3. Guslandi M. et al. A pilot trial of Saccharomyces boulardii in ulcerative colitis. Eur J Gastroenterol Hepatol. 2003 Jun;15(6):697-8.
4. Guslandi M. et al. Saccharomyces boulardii in maintenance treatment of Crohn's disease. Dig Dis Sci. 2000 Jul;45(7):1462-4.
5. Prantera C. et al. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut. 2002 Sep;51(3):405-9.
6. O'Mahony L. et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology. 2005 Mar;128(3):541-51.
7. Niv E. et al. The efficacy of Lactobacillus reuteri ATCC 55730 in the treatment of patients with irritable bowel syndrome--a double blind, placebo-controlled, randomized study. Clin Nutr. 2005 Dec;24(6):925-31.
8. Cui HH. et al. Effects of probiotic on intestinal mucosa of patients with ulcerative colitis. World J Gastroenterol. 2004 May 15;10(10):1521-5.
9. Kajander K. et al. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. Aliment Pharmacol Ther. 2005 Sep 1;22(5):387-94.
10. Bausserman M. et al. The use of Lactobacillus GG in irritable bowel syndrome in children: a double-blind randomized control trial. J Pediatr. 2005 Aug;147(2):197-201.
11. Bittner AC. et al. Prescript-Assist probiotic-prebiotic treatment for irritable bowel syndrome: a methodologically oriented, 2-week, randomized, placebo-controlled, double-blind clinical study. Clin Ther. 2005 Jun;27(6):755-61.
12. Shen B. et al. Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: experience in clinical practice. Aliment Pharmacol Ther. 2005 Oct 15;22(8):721-8.
13. Kim HJ. et al. A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. Neurogastroenterol Motil. 2005 Oct;17(5):687-96.
14. Laake KO. et al. Assessment of mucosal inflammation and blood flow in response to four weeks' intervention with probiotics in patients operated with a J-configurated ileal-pouch-anal-anastomosis (IPAA). Scand J Gastroenterol. 2004 Dec;39(12):1228-35.
15. Gionchetti P. et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. Gastroenterology. 2003 May;124(5):1202-9.
16. Laake KO. et al. Assessment of mucosal inflammation and circulation in response to probiotics in patients operated with ileal pouch anal anastomosis for ulcerative colitis. Scand J Gastroenterol. 2003 Apr;38(4):409-14.
17. Bibiloni R. et al. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. Am J Gastroenterol. 2005 Jul;100(7):1539-46.
18. Furrie E. et al. Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. Gut. 2005 Feb;54(2):242-9.
19. Kruis W. et al. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 1997 Oct;11(5):853-8.
20. Kato K. et al. Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. Aliment Pharmacol Ther. 2004 Nov 15;20(10):1133-41.
21. Kruis W. et al. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. Gut. 2004 Nov;53(11):1617-23.
22. Tursi A. et al. Low-dose balsalazide plus a high-potency probiotic preparation is more effective than balsalazide alone or mesalazine in the treatment of acute mild-to-moderate ulcerative colitis. Med Sci Monit. 2004 Nov;10(11):PI126-31.
23. Laake KO. et al. Outcome of four weeks' intervention with probiotics on symptoms and endoscopic appearance after surgical reconstruction with a J-configurated ileal-pouch-anal-anastomosis in ulcerative colitis. Scand J Gastroenterol. 2005 Jan;40(1):43-51.
24. Hanai H. et al. Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. Int J Mol Med. 2004 May;13(5):643-7.
25. Ishikawa H. et al. Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. J Am Coll Nutr. 2003 Feb;22(1):56-63.
26. Rembacken BJ. et al. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. Lancet. 1999 Aug 21;354(9179):635-9.
27. Venturi A. et al. Impact on the composition of the faecal flora by a new probiotic preparation: preliminary data on maintenance treatment of patients with ulcerative colitis. Aliment Pharmacol Ther. 1999 Aug;13(8):1103-8.
28. Karimi O. et al. Probiotics (VSL#3) in arthralgia in patients with ulcerative colitis and Crohn's disease: a pilot study. Drugs Today (Barc). 2005 Jul;41(7):453-9.
29. Korzenik JR. et al. Evolving knowledge and therapy of inflammatory bowel disease. Nat Rev Drug Discov. 2006 Mar;5(3):197-209.
30. Rook GA. et al. Microbes, immunoregulation, and the gut. Gut. 2005 Mar;54(3):317-20.
31. Jonkers D. et al. Probiotics and inflammatory bowel disease. J R Soc Med. 2003 Apr;96(4):167-71.
32. Campieri M. et al. Bacteria as the cause of ulcerative colitis. Gut. 2001 Jan;48(1):132-5.
33. Ghosh S. et al. Probiotics in inflammatory bowel disease: is it all gut flora modulation? Gut. 2004 May;53(5):620-2.
34. Ingrassia I. et al. Lactobacillus casei DN-114 001 inhibits the ability of adherent-invasive Escherichia coli isolated from Crohn's disease patients to adhere to and to invade intestinal epithelial cells. Appl Environ Microbiol. 2005 Jun;71(6):2880-7.
35. Ezendam J. et al. Probiotics: immunomodulation and evaluation of safety and efficacy. Nutr Rev. 2006 Jan;64(1):1-14.
36. Senok AC. et al. Probiotics: facts and myths. Clin Microbiol Infect. 2005 Dec;11(12):958-66.
37. Helman A. Probiotics, immunity and allergy. Arbor Clin Nutr Updates. 2006;246:1-5.

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