**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**

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.


**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.


**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.

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. 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.

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, as shown in new Study 1. Indeed one trial found that probiotics’ effect on cytokines was directly correlated with its clinical efficacy in IBD. Probiotics can also influence the toll receptors and dendritic cells involved in healthy gut immunity. Other possible therapeutic effects include correction of abnormal intestinal permeability (‘leaky gut’), improved mucus production and production of short chain fatty acids.

Safety
Probiotics do have a long history of apparently safe use. 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). 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. 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.

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, 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, and three others which did not.

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

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.

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), but others did.

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.
<table>
<thead>
<tr>
<th>Year</th>
<th>Disease</th>
<th>n=</th>
<th>Design</th>
<th>Organism</th>
<th>Durn.</th>
<th>Outcome measures</th>
<th>Result</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>2005</td>
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<td>75 kids</td>
<td>RCDBT</td>
<td>Lactob.</td>
<td>8 mo</td>
<td>Relapse</td>
<td>NS</td>
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<td>Remission and relapse</td>
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<td>70% remission</td>
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<td>Mesalazine ± Sacchar.</td>
<td>6 mo</td>
<td>Relapse</td>
<td>Relapse in 6% probiotic vs 38% mesalazine only</td>
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<td>Symptoms, cytokines</td>
<td>Reduction in symptoms and cytokines for bifid. Only</td>
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<td>Symptoms and QOL</td>
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<td>48</td>
<td>RCDBT</td>
<td>VSL#3</td>
<td>4-8 wk</td>
<td>Symptoms, colonic transit</td>
<td>Improved flatulence (p=0.01) and colonic transit (p=0.05), rest NS</td>
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<td>Reduced (42% vs 6%, p=0.015)</td>
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<td>8 mo</td>
<td>Disease activity index</td>
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<td>RCDBT</td>
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<td>Pouchitis risk, QOL</td>
<td>Less risk of pouchitis (p&lt; 0.05) and enhanced QOL</td>
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<td>10</td>
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<td>6 wk</td>
<td>Remission</td>
<td>Remission in 53%</td>
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<td>Sigmoidoscopy, inflamm. factors</td>
<td>Score reduced (p=0.06), inflamm. factors reduced (all p&lt;0.04)</td>
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<td>120</td>
<td>RCT</td>
<td>E.coli vs mesalazine</td>
<td>12 wk</td>
<td>Clinical activity, remission and relapse</td>
<td>Probiotic same as conventional</td>
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<td>Clinical and endoscopic activity</td>
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<td>90</td>
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<td>Convent.Rx ± VSL#3</td>
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<td>Remission</td>
<td>More and faster remission (p&lt;0.02)</td>
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<td>59</td>
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<td>Conven. vs prebiotic</td>
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<td>Arthritis activity score</td>
<td>62% had reduction</td>
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</table>

DB= double blind, RCT=randomised controlled trial, QOL=quality of life, NS= not signif.
References:


