The work of Philippe and colleagues[1] provides new insights into the regulation of intestinal inflammation. It raises the possibility of exciting new therapeutic options but also prompts questions regarding the relationship of narcotic use and the natural history of IBD.

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Authors' affiliations
S Collins, M Verma-Gandhu, Intestinal Diseases Research Program, and Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada

Correspondence to: Professor S M Collins, Room 4W8, McMaster University Medical Centre, 1200 Main St West, Hamilton, Ontario L8N 3Z5, Canada; scolins@mcmaster.ca

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Crohn's disease

Probiotics for Crohn's disease: what have we learned?

C Prantera

Probiotics do not seem to be a therapeutic option for patients with Crohn's disease, either in the acute phase or for maintenance

A causative role of bacteria in Crohn's disease (CD) has been surmised for a long time. Only in recent years however has there been a large body of evidence from genetic and bacteriological studies indicating that the intestinal flora is the essential factor in driving the Crohn's inflammatory process in genetically susceptible individuals.[1–5]

The therapeutic arsenal for treating CD assumes the correctness of the above hypothesis. Thus immunosuppressors are used to reduce the host response and antibiotics are used to suppress the bacterial flora, with a consequent decreased activation of the gut immune system.[6] Between the two strategies it should theoretically be better to remove the harmful cause instead of reducing the host defences by inducing a form of immunodeficiency that is susceptible to opportunistic infections.

If the intervention on the gut flora works, substituting antibiotics (which are heavily burdened by side effects) with probiotics is an appealing alternative. Probiotics are defined as a living microbial food ingredient with a beneficial effect on human health[7]; however, the concept that probiotics are a type of long life elixir useful in many pathological conditions needs to be viewed with caution.

In a world medical scenario, where new science develops new drugs and the financial cost increases, natural remedies, relatively cheap and potentially free from side effects, catch the consumer's attention, thereby possibly biasing medical judgement.

To date, diverse probiotics, containing different strains and quantities of bacteria, are sold on the market.[8] Their therapeutic effects may include a competitive action with commensal and pathogenic flora and an influence on the immune response through various mechanisms.[9] Probiotics have been successfully employed in the treatment of antibiotic associated and *Clostridium difficile* diarrhoea,[10–11] traveller's diarrhoea,[12] and rotavirus infection.[13] For inflammatory bowel diseases (IBD), some researchers have reported success with different strains of probiotics in the treatment of ulcerative colitis,[14 15] CD,[16–18] and in pouchitis treatment and prevention.[19 20] *E coli* Nissle 1917, the yeast *Saccharomyces boulardii*, *Lactobacillus rhamnosus* strain GG (LGG), and VSL#3, a cocktail of eight different strains, are the various probiotics employed in these studies. Several significant flaws however limit the importance of many of the

probiotic trials, such as inclusion of too few patients,[16 17] too low a dose of the control drug,[14] or the association of the probiotic with other medicines.[15–18]

Given their potentially high safety profile, the use of probiotics for maintaining CD remission induced by drugs or surgery is particularly appealing. It is suggested that luminal bacteria are the main cause of recurrent lesions after operation.[3] Moreover, preventing recurrent lesions in CD after surgery has removed all of the macroscopic inflamed tracts is the best test for any type of drug.

Consequently, LGG, which has been shown to survive and colonise the human intestine by adhering to intestinal cells, has been challenged in two randomised placebo controlled trials for its efficacy in preventing recurrence after surgery[21] and relapse after medically induced remission.[22]

In the first study, 45 patients operated on for CD were randomly allocated to receive 12 billion LGG or identical placebo for one year.[21] Clinical recurrence was ascertained in 16.6% on *Lactobacillus* and in 10.5% on placebo. Sixty per cent of patients in clinical remission on *Lactobacillus* had endoscopic recurrence in comparison with 35.3% on placebo. There were no significant differences in the severity of lesions between the two groups.

The second trial involved 75 children in medically induced remission.[22] They were randomised to receive 10^{10} LGG bacteria or placebo for two years as an adjunct to standard maintenance treatment. The average time to relapse was 9.8 months in the LGG group and 11 months in the placebo group; 31% and 17% of children on LGG and placebo, respectively, relapsed during the study period. Neither study showed any statistically significant differences between the active and placebo groups.

In this issue of *Gut*, Marteau and colleagues[23] have reported the results of a trial with *Lactobacillus johnsonii* (LA1) for prophylaxis of postoperative recurrence in CD ***(see page 842)***. Ninety eight adult patients were randomised in a double blind, placebo controlled study in which they received 4×10^{9} LA1 or placebo for six months. At the end of this period, 64% of patients on placebo and 49% on probiotic had endoscopic recurrence. Endoscopic scores and clinical recurrences did not differ between the two groups.

Unfortunately, this study is neither decisively negative nor decisively positive. In fact, the lack of statistically significant difference between *Lactobacillus* and placebo might be due either to an insufficiently large sample size or to the follow up period of six months, which may have been too short to demonstrate a larger difference. However, the cumulative result of these three studies is not encouraging, and at the moment probiotics are not a therapeutic option for CD patients either in the acute phase or for maintenance.

Is it curtains, then, for probiotics in CD?

Before dropping the curtain we have to take into account some important points.

- CD is a complex entity. Diverse locations and different disease behaviours may well condition the response to probiotics—for example, colonic location seems to respond better to antibiotics and, consequently, might be more susceptible to flora manipulation.
- The course of CD follows different phases; probiotics might be more effective in the early ones.
- There are many species of probiotic. One type might be more effective than another because strain specific properties might influence the efficacy in different cases and situations.
- The quantity of bacterial content may condition the effectiveness of the probiotic.

In short, it seems advisable to wait for results from some larger controlled trials, some of which are already underway.

Setting aside the question of probiotic effectiveness however, is their use absolutely safe? In CD, antigenic stimuli contribute towards maintaining gut inflammation, and any bacteria can become a stimulus. In the two studies with LGG, recurrence rates were lower in the placebo groups than in the groups treated with probiotics.[21–22]

Moreover, some anecdotal reports of infections probably caused by probiotics have been published.[24–25] Probiotic strains adhering to the intestinal mucosa could translocate, inducing bacteraemia and sepsis. This risk can be increased in patients with severe disease or deeply immunosuppressed.

So, in conclusion, is all news about probiotics in CD negative? A possible future scenario on probiotics use in this disease has come from data extrapolated from allergic paediatric patients. In children with atopic dermatitis, probiotics seem to stabilise intestinal barrier function and decrease gastrointestinal symptoms.[26–29]

In CD, enhanced mucosa permeability may play a pivotal role in causing and perpetuating intestinal inflammation.[30] It is possible therefore that administration of probiotics in the very early phases of CD may limit pathological damage and aggravation of symptoms by stabilising the intestinal barrier.

We can also speculate that children with IBD familiarity, who are at risk of developing CD, could be treated by probiotics to reduce intestinal permeability and counterbalance the hypothetical ''harmful'' species. For this purpose, identification of subjects at risk of developing CD could be done by analysis of genetic characteristics, such as NO2 and other genes still to be identified. In this case, genetic studies in IBD could be promoted from the laboratory to practical usefulness.

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Correspondence to: Dr C Prantera, Division of Gastroenterology, Azienda Ospedaliera S Camillo-Forlanini, 00149 Roma, Italia; prantera@tin.it

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Colorectal cancer

Prospective evaluation of fluorouracil chemotherapy based on the genetic makeup of colorectal cancer

J M Carethers

Evaluation of 5-fluorouracil chemotherapy and survival, based on mismatch repair (MMR) status, indicates that patients with MMR proficient colorectal tumours benefit from 5-fluorouracil treatment while patients with MMR deficient tumours do not

The current gold standard for treating patients with advanced colon cancer is chemotherapy with 5-fluorouracil (5-FU) based regimens.[1] This standard is based on compelling clinical trials utilising 5-FU and levamisole, and demonstrating a survival benefit for patients with TNM stage III (Dukes-Aston Collier stage C) colon cancer.[2–4] Although there is no set standard for treating stage II patients, some stage II patients do receive 5-FU chemotherapy, albeit the natural history of this stage of colon cancer is reasonably favourable at more than 70% five year survival.[1] Patients with rectal cancer may receive neoadjuvant or adjuvant chemotherapy for stage II or III disease, as treatment in both of these stages of tumour benefit patient survival.[1] Stage I patients with colorectal cancer do not receive 5-FU as their prognosis is excellent with removal of the tumour, and stage IV patients may receive 5-FU for palliation. Overall, determination for use of 5-FU based chemotherapy is completely based on the stage of the colorectal cancer in the patient at presentation.

The past decade has brought a fruitful understanding of the genetic and biological behaviour of colorectal cancer, and our knowledge is still growing in this aspect. Colorectal cancer is a genetic disease, with changes in the genome of the tumour cell that are favourable for the tumour's growth and remote spread. Taking knowledge learned from hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome) in which a germline mutation occurs in genes that encode proteins for DNA mismatch repair (MMR), it was discovered that approximately 15% of sporadic colorectal cancers lack intact MMR due to the epigenetic inactivation of the MMR protein *hMLH1* without genetic mutation.[5] Sporadic colorectal cancers can thus be categorised into two groups: those that are MMR proficient (that is, cancers that express all components of the MMR system) and those that are MMR deficient (that is, cancers that lack a component of the MMR system, such as *hMLH1*, and exhibit microsatellite instability, a marker for loss of MMR function). Intact DNA MMR will repair DNA polymerase mistakes to maintain the fidelity of replicating DNA. Additionally, the MMR system can recognise certain chemotherapeutic agents that intercalate or get incorporated into DNA, and may be an important trigger to execute cell death.[6–9] With MMR deficiency, repair of polymerase mistakes are lacking and affected cells accumulate mutations that may drive tumorigenesis.[5 10] Importantly, MMR deficiency may prevent the recognition of DNA damaging chemotherapy to initiate cell killing by that agent.[8 11 12]

There are differences in the biological behaviour of MMR deficient tumours compared with MMR proficient tumours. MMR deficient tumours are more likely to be located in the proximal (right) colon, and on histology are more likely to demonstrate the presence of mucin, have a surrounding lymphoid reaction, and be of poor histological grade.[5] Despite this poor histological grade, there is some evidence that patients with MMR deficient tumours have a more favourable prognosis for survival. This has been particularly shown in patients with MMR deficient tumours who were under the age of 50 years,[13] but extends to older ages as well in some studies.[14 15] Pooling multiple studies confirmed the relationship between MMR deficiency and patient survival, with a combined hazard ratio for overall survival associated with MMR deficiency of 0.65 (95% confidence interval 0.59–0.71).[16]

The fact that patients with MMR deficient tumours may have a better prognosis over patients with MMR proficient tumours confounded some original studies examining 5-FU chemotherapy and benefit, with most lacking the appropriate control group for comparative purposes.[17–19] Indeed, these reports appeared to indicate that 5-FU adjuvant chemotherapy was beneficial for patients with MMR deficient colorectal cancer, but without control groups it was not clear if the survival benefit was derived from the chemotherapy or from the presence of the MMR deficient tumour itself. Two