

Probiotics

Mixed messages

David R. Mack, MD, FAAP, FRCPC

In this issue of *Canadian Family Physician*, Drs Reid and Hammond review probiotics and relate them to the current Canadian landscape (page 1487). Probiotic is a catchy word. While it is clear that *antibiotics* are chemicals that are used *against* bacteria, *probiotics* are not chemicals that are used *for the benefit of* bacteria, but rather describe microorganisms administered orally. The World Health Organization defines probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”¹; in order to be labeled a probiotic, scientific evidence for the health benefit would have to be documented.

While the most common microorganisms used as probiotics are from the *Lactobacillus* and *Bifidobacterium* genera, other bacterial genera, including *Enterococcus*, *Streptococcus*, and *Escherichia*, are used. The fungus *Saccharomyces boulardii* is also considered a probiotic and has recently become available in parts of Canada. It is derived from the litchi fruit and is not normally found in the human intestinal tract. *Saccharomyces boulardii* has gained some attention because it grows at normal body temperature and is resistant to antibiotics. It is, therefore, of particular interest for those who need to replace bacteria depleted by antibiotics when antibiotics need to be continued.

Increased interest

Use of probiotics has been proposed for a long time, and there is concern that they have often been adopted without critical appraisal. Various factors have recently increased interest and awareness. First, probiotics and products containing probiotics are becoming more widely available. While this is particularly true in European and Asian markets, there is increasing penetration in the lucrative North American market. People in North America are becoming more interested in taking charge of their health through direct action, and simpler,

unfiltered access to health care information is also fueling the current surge of interest in probiotics. The hope of preserving health in an aging society; concern that some environmental factors and food sources could be detrimental to health; concern about limitations of, effects of, and bacterial resistance to antibiotics; desire for alternative therapies for common conditions; combined with belief that health problems can be limited or reversed by individual health choices also add to the interest in probiotics.

Varying quality of evidence

Many studies examining probiotics have been reported. These studies are of varying quality and have included participants with a host of conditions, including cancer and heart, intestinal, urogenital, and immune system problems. Many of these studies examine small numbers of patients, are not controlled, do not include specific information about the probiotics used, and have been reported in low-impact journals. These problems have plagued much of the research on complementary, nutritional, and alternative health products. Over the last few years, however, better-quality studies and studies using modern research techniques into relevant mechanisms of action for probiotics have emerged. There are no large controlled trials, as we are becoming more familiar with in the medical literature, but smaller controlled trials are being combined to allow for meta-analysis and systematic review of the use of probiotics for some conditions.

For instance, three meta-analyses have been published concerning the use of probiotics in children with acute infectious diarrhea. Essentially, all came to the conclusion that probiotics were beneficial.²⁻⁴ Duration of diarrhea was reduced by 1 day and the number of stools was reduced by about 1.5 per day. Closer examination of these studies reveals some interesting findings. Infants and children

with viral gastroenteritis seem to derive the most benefit from probiotics; those with bloody diarrhea from bacterial enteropathogens did not fare as well.⁵ Furthermore, the earlier the probiotics were initiated, the better the results⁶; by the time patients needed intravenous therapy, little benefit from probiotic therapy could be expected.⁷

Studies examining probiotics' mechanisms of action have determined that administration of probiotics can induce protective mechanisms of the mucosal cells and underlying immune system of the small intestine, which is precisely where viruses, such as rotavirus, induce the sequence of events leading to diarrhea. To date, there has not been a specific meta-analysis examining use of probiotics for prevention of acute infectious diarrhea in infants and children; however, a controlled study was completed in a hospital setting about 10 years ago and demonstrated a benefit.⁸ In contrast, studies regarding the prevention of traveler's diarrhea have yielded mixed results.⁹ The meta-analysis of van Niel et al³ suggested that there was a dose-dependent effect in the prevention of acute diarrhea in infants. There seems to be a window of opportunity where probiotics can be effective for acute infectious diarrhea, and physicians must be circumspect with patients regarding expectations for benefit compared with cost.

Antibiotic-associated diarrhea is another well studied condition. Up to one third of people who take antibiotics develop antibiotic-associated diarrhea. Two meta-analyses have revealed that using probiotics helped prevent this side effect of antibiotic use.^{10,11} Another interesting study explored use of triple-therapy antibiotics for *Helicobacter pylori* infection compared with use of triple-therapy antibiotics combined with probiotics. The latter group of patients had a better outcome, but analysis suggested that this was because these patients were more likely to comply with the triple-therapy regimen.¹²

Questions remain

These meta-analyses are important but also point to other current realities for probiotic therapy. Physicians are accustomed to standardized dosing and specific medications for particular medical problems. With probiotics, for most conditions, there are few or no comparative studies, dosing studies, or duration trials. Thus, for practising physicians, probiotic choices tend to be subjective, extrapolated, imaginative, based on availability, or based on suggestions of the company providing the probiotic.

Studies of specific conditions provide insight into other issues surrounding probiotics. For patients with ulcerative colitis who have undergone subtotal colectomy with ileo-anal anastomosis and creation of an ileal pouch, recurrent pouchitis can develop. A small, well-done study demonstrated that a combination of probiotics taken orally stopped the recurrence of pouchitis.¹³ Another study of this condition used a single probiotic microbe at a lower dose and did not demonstrate this benefit.¹⁴ Patients in the former study, however, had already responded to antibiotics, while those patients who had previously received antibiotics were excluded from the latter study. Studies such as these raise the question of what role endogenous flora play in disease development (eg, atopic dermatitis¹⁵). There is no information regarding antibiotic and probiotic combinations, long-term consequences of probiotic administration, or whether these types of therapies are even needed.

Government heavily regulates and monitors physicians and the pharmaceutical industry. The probiotic industry is largely unregulated. While humans have been consuming fermented food products for a long time, consumption of concentrated probiotics

on a daily basis for specific medical conditions is a new phenomenon. Certainly, safety studies, such as that by Saavedra and colleagues,¹⁶ are welcome, but they are rare in the medical literature. There are reports



of development of sepsis from bacterial probiotics and fungemia following use of *S boulardii*. These reports are uncommon and usually associated with patients with central access catheters in intensive care. It would be prudent, however, to be cautious in routine home probiotic administration for those at increased risk of translocation-related problems (eg, central venous catheters, artificial heart valves), those at high risk of developing sepsis (eg, low white blood cell count), very young infants, or those with bowel immotility problems (eg, using D-lactic acid-producing probiotics). All should be told of the unlikely but potential risk of bacterial translocation.

Until issues surrounding regulation, quality assurance, and treatment (probiotic strain, dose, duration, timing, and indications) are agreed upon, practising physicians are going to struggle to confidently recommend probiotics as efficacious therapy in Canada. 

Dr Mack is Chief of Gastroenterology at the Children's Hospital of Eastern Ontario in Ottawa.

Correspondence to: Dr David Mack, Chief of Gastroenterology, Children's Hospital of Eastern Ontario, 401 Smith Rd, Ottawa, ON K1H 8L1; telephone (613) 737-2516; fax (613) 738-4854; e-mail dmack@cheo.on.ca

The opinions expressed in editorials are those of the authors and do not imply endorsement by the College of Family Physicians of Canada.

References

1. Food and Agriculture Organization and World Health Organization Expert Consultation. *Evaluation of health and nutritional properties of powder milk and live lactic acid bacteria*. Córdoba, Argentina: Food and Agriculture Organization of the United Nations and World Health Organization; 2001. Available from: ftp://ftp.fao.org/esn/food/probio_report_en.pdf. Accessed 2005 September 8.
2. Huang JS, Bousvaros A, Lee JW, Diaz A, Davidson EJ. Efficacy of probiotic use in acute diarrhea in children: a meta-analysis. *Dig Dis Sci* 2002;47:2625-34.
3. Van Niel CW, Feudtner C, Garrison MM, Christakis DA. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics* 2002;109:678-84.
4. Szajewska H, Mrukowicz JZ. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, double-blind, placebo-controlled trials. *J Pediatr Gastroenterol Nutr* 2001;33(Suppl 2):S17-25.
5. Guandalini S, Pensabene L, Zikri MA, Dias JA, Casali LG, Hoekstra H, et al. Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. *J Pediatr Gastroenterol Nutr* 2000;30:54-60.
6. Rosenfeldt V, Michaelsen KF, Jakobsen M, Larsen CN, Moller PL, Tvede M, et al. Effect of probiotic Lactobacillus strains on acute diarrhea in a cohort of nonhospitalized children attending day-care centers. *Pediatr Infect Dis J* 2002;21:417-9.
7. Costa-Ribeiro H, Ribeiro TC, Mattos AP, Valois SS, Neri DA, Almeida P, et al. Limitations of probiotic therapy in acute, severe dehydrating diarrhea. *J Pediatr Gastroenterol Nutr* 2003;36:112-5.
8. Saavedra JM, Bauman NA, Oung I, Perman JA, Yolken RH. Feeding of *Bifidobacterium bifidum* and *Streptococcus thermophilus* to infants in hospital for prevention of diarrhoea and shedding of rotavirus. *Lancet* 1994;344:1046-9.
9. Marteau PR, de Vrese M, Cellier CJ, Schrezenmeir J. Protection from gastrointestinal diseases with the use of probiotics. *Am J Clin Nutr* 2001;73(2 Suppl):430S-6S.
10. Cremonini F, Di Caro S, Nista EC, Bartolozzi F, Capelli G, Gasbarrini G, et al. Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea. *Aliment Pharmacol Ther* 2002;16:1461-7.
11. D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ* 2002;324:1361.
12. Sheu BS, Wu JJ, Lo CY, Wu HW, Chen JH, Lin YS, et al. Impact of supplement with Lactobacillus and Bifidobacterium-containing yogurt on triple therapy for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2002;16:1669-75.
13. Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic recurrent pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:305-9.
14. Kuisma J, Mentula S, Jarvinen H, Kahri A, Saxelin M, Farkkila M. Effect of *Lactobacillus rhamnosus* GG on ileal pouch inflammation and microbial flora. *Aliment Pharmacol Ther* 2003;17:509-15.
15. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357:1076-9.
16. Saavedra JM, Abi-Hanna A, Moore N, Yolken RH. Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety. *Am J Clin Nutr* 2004;79:261-7.

