CME

Probiotics

Some evidence of their effectiveness

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ABSTRACT

OBJECTIVE To define the term probiotics, to indicate how to identify products that have been proven beneficial, and to assess the quality of evidence regarding probiotics.

QUALITY OF EVIDENCE A few level I studies support the effectiveness of specific probiotics for certain diagnoses. For most so-called probiotics, however, weak or no evidence supports their effectiveness.

MAIN MESSAGE Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Level I evidence supports use of VSL#3 for maintaining remission of inflammatory colitis. Probiotics for treating vaginal infections, *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14, have level I evidence of effectiveness, but are not available in Canada. Specific probiotics taken for certain indications improve health and have few side effects.

CONCLUSION Limited but good evidence supports the role of certain probiotics in medical practice. Because consumer pressure will undoubtedly stimulate further interest in probiotics, family doctors need to be informed about them so they can advise their patients appropriately.

RÉSUMÉ

OBJECTIF Définir le terme probiotique, indiquer comment identifier les produits dont les effets bénéfiques ont été démontrés et évaluer la qualité des preuves concernant ces agents.

QUALITÉ DES PREUVES L'efficacité de probiotiques spécifiques dans certaines conditions est appuyée par quelques études de niveau I. La majorité des soi-disant probiotiques, toutefois, ont peu ou pas de preuves d'efficacité.

PRINCIPAL MESSAGE Les probiotiques sont des micro-organismes vivants qui, en doses adéquates, sont bénéfiques pour la santé de l'hôte. L'utilisation de VSL#3 pour garder en rémission une colite inflammatoire repose sur des preuves de niveau I. L'efficacité des probiotiques *Lactobacillus rhamnosus* GR-1 et *Lactobacillus reuteri* RC-14 utilisés pour traiter les infections vaginales repose sur des preuves de niveau I, mais ces agents ne sont pas disponibles au Canada. Certains probiotiques spécifiques utilisés pour des indications particulières améliorent la santé et ont peu d'effets secondaires.

CONCLUSION Il existe des preuves limitées mais de bonne qualité à l'effet que les probiotiques ont un rôle à jouer dans la pratique médicale. Les consommateurs voudront nécessairement en savoir davantage sur ces produits et le médecin de famille doit donc se renseigner pour mieux conseiller ses patients à leur sujet.

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The term probiotics is defined by a United Nations and World Health Organization Expert Panel as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[1] The general population's growing interest in natural remedies, including probiotics; the increased scientific and clinical validity of certain probiotic products; and the pending arrival of some of these probiotics in Canada make it important that family physicians understand what probiotics are[2] so they can make reliable recommendations to patients.

A bacterium or product containing bacteria is not a probiotic unless the bacteria have been shown to be viable at time of use in sufficient quantity to confer a physiologic health benefit. The organisms themselves must be speciated using appropriate molecular methods and given a designation, such as *Lactobacillus rhamnosus* GR-1, so that peer-reviewed studies of specific organisms can be followed in PubMed to document the efficacy or lack thereof of the probiotic in defined patient populations. Therefore, *Lactobacillus acidophilus* is not a probiotic, but *L acidophilus* NCFM is a probiotic because it has demonstrated some benefit for people who are lactose intolerant.[3]

Quality of evidence

A PubMed search was conducted using the terms "probiotics," "*Lactobacillus*," and "human clinical trials." The website of the Food and Agriculture Organization of the United Nations was consulted, as were the websites of various commercial probiotic producers. Randomized, placebo-controlled trials (level I evidence) have established the effectiveness of probiotic strains for treatment of diarrhea, maintenance of remission of inflammatory bowel disease, and prevention of urogenital infections.

How do probiotics work?

The concept of treatment with probiotics comes from a belief that modern humans do not consume or replenish the beneficial microbes in their bodies and that they can do so by taking probiotics.[4] Of course, simply eating more bacteria will not in itself guarantee good health. Most probiotic products are foods containing lactobacilli or bifidobacteria, genera with no known virulence that commonly inhabit the healthy gut and vagina. These genera have been used for more than a century in fermented foods.

Historically, ingested probiotic strains were believed to adhere to the gut wall, to block pathogen adhesion and growth,[5] and also to give a nonspecific boost to immunity.[6] Current thinking suggests that probiotics have other functions, including producing anti-infectives, such as hydrogen peroxide and bacteriocins[7]; cell signals that strengthen host-cell mucus barriers against pathogen invasion[8]; and other signals that prevent virulent factors, such as toxins, from being released.

It was once believed that probiotic strains needed to be resistant to acid and bile. If they were not, strains of *Lactobacillus delbruekii* subsp. *bulgaricus* and *Streptococcus thermophilus* in yogurt often would not survive well in the gut. Delivery systems, such as gel matrix coatings on the bacteria themselves and enterocoated capsules, allow

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

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bacteria to get past the stomach and to hydrate the small intestine. For example, *Lactobacillus* strains GR-1 and RC-14 can function in the gut, survive passage, and be excreted in feces.[9,10]

Treatment of diarrhea

Level I evidence shows that the probiotic strains *L rhamnosus* GG and *Lactobacillus reuteri* DSM 12246 (not available in Canada) can reduce the risk of diarrhea in children. A study of 204 undernourished children 6 to 24 months old in Peru showed that once-daily intake of *L rhamnosus* GG 6 days a week for 15 months resulted in significantly fewer episodes of diarrhea per child per year (5.21 in the treatment group compared with 6.02 in the placebo group, $P = .028$).[11] A prospective, double-blind, randomized, placebo-controlled study of 118 infants (aged 3 to 4 months) showed that consumption of a milk-based formula with or without 1 x 10^7 colony-forming units/g each of *Bifidobacterium lactis* BB12 and *S thermophilus* for 210 ± 127 days resulted in less frequent reports of colic or irritability ($P < .001$) and less frequent antibiotic use ($P < .001$).[12]

Level I evidence exists for probiotic treatment of diarrhea. After 4 to 6 hours of oral rehydration, 140 children aged 1 to 3 months randomly assigned to receive milk with placebo or with *L rhamnosus* GG had shorter bouts of diarrhea when they were given the probiotics. Duration of diarrhea was reduced from a mean of 3 days to 2.4 days ($P = .03$).[13] In a randomized, placebo-controlled study of 40 patients (6 to 36 months old) with acute diarrhea (75% rotavirus) treatment with *L reuteri* DSM 12246 for up to 5 days resulted in reduced duration of watery stools (1.6 days in the treatment group compared with 2.9 days in the placebo group, $P = .07$).[14]

A systematic review of published, randomized, double-blind, placebo-controlled trials of probiotics for treatment or prevention of acute diarrhea, defined as more than three loose or watery stools in 24 hours in infants and children, showed that probiotics significantly reduced risk of diarrhea lasting more than 3 days.[15] A subsequent meta-analysis of 18 eligible studies indicated that coadministration of probiotics and standard rehydration therapy reduced duration of acute diarrhea by approximately 1 day (random-effects pooled estimate -0.8 days [-1.1 to -0.6], $P < .001$).[16]

In Canada, if we estimate that 1 million cases of gastroenteritis occur each year, the potential for preventing it or improving treatment with probiotics is worthy of consideration, but only if suitable probiotic products are made available here. The Walkerton, Ont, tragedy highlighted the dangers of gastroenteritis. While a vaccine might reduce *Escherichia coli* O157 shedding 30% (versus 78% with placebo) 2 days after injection[17] in some cows, it is unlikely to address the sporadic nature of shedding or carcass contamination.[18,19] Meanwhile, *E coli* O157:H7 was twice as likely to be detected in control animals' hides as in those of animals receiving *L acidophilus* NPC 747.[20,21] Probiotic supplementation significantly decreased the number of hides testing positive for *E coli* O157:H7 ($P < .05$). Also, adding *L acidophilus* NP 51 and *Propionibacterium freudenreichii* to feed for 7 days resulted in cattle being 57% less likely to shed *E coli* O157 in their feces than controls were ($P < .01$).[22] Although family physicians have no control over livestock practices, they should have some say in approaches to disease prevention and public health.

Inflammatory bowel disease and irritable bowel syndrome

A product called VSL#3 (Seaford Pharma, Toronto, Ont) containing more than 10^{10} viable bacteria (eight strains) in dried sachet form has level I evidence of effectiveness in ameliorating pouchitis and Crohn's disease.[23,24] In a recent randomized, placebo-controlled study, 36 patients with inflammation and infection in a rectal pouch, in whom remission was induced by 4 weeks of treatment with combined metronidazole and ciprofloxacin, were randomized to receive 6 g of VSL#3 or placebo once daily for 1 year or until relapse.[25] Seventeen patients (85%) taking VSL#3 were still in remission 1 year later, as was one patient (6%) taking placebo ($P < .0001$). The inflammatory bowel disease

questionnaire score remained high in the VSL#3 group ($P = .3$), but decreased in the placebo group ($P = .0005$).

Evidence is lacking for other strains, such as *L rhamnosus* GG. A 45-patient study failed to show that this probiotic prevented endoscopically observed recurrence of Crohn's disease or reduced severity of recurrent lesions.[26]

Evidence is also lacking for the efficacy of probiotics for irritable bowel syndrome (IBS). Twice-daily use of VSL#3 was not particularly effective in one study of gastrointestinal transit and symptoms.[27] *Lactobacillus plantarum* 299V was not shown to be effective in a double-blind, placebo-controlled, cross-over, 4-week trial in 12 previously untreated patients with IBS,[28] nor was *L rhamnosus* GG in another study of 25 patients.[29]

Urogenital infections

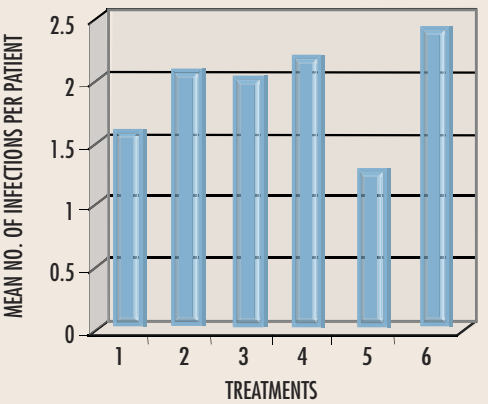
Family practitioners see many women with non–sexually transmitted urogenital infections (urinary tract infections [UTIs], bacterial vaginosis, yeast vaginitis, and group B streptococcal colonization). Unfortunately, there are no good treatments available in Canada. An Internet search (using the search terms "probiotics AND urinary OR vaginal") showed that women received misinformation about the cause and treatment of these ailments and were recommended unproven products. For example, **www.natren.com** incorrectly states that hygiene, bubble baths, and underwear are associated with increased risk of UTI.[30] The website recommends treatment of UTI with "2 capsules each of *L acidophilus* and *Bifidobacterium bifidum* (or 1 teaspoon each of powder), along with 1 teaspoon *L delbruekii* subsp. *bulgaricus* powder mixed in 6 to 8 ounces unchilled filtered water, twice daily, for 14 days." No known efficacy studies support this recommendation. Symptomatic UTIs require antibiotic therapy.

Other examples can be found at **www.uaslabs.com** (or in material published by the owner), **www.customprobiotics.com**, and **www.khadergroup.com** where statements lead readers to believe that the products are probiotics and are proven to be beneficial for urogenital infections. These statements cannot be confirmed by the literature.

Fermalac (Rosell-Lallemand, Montreal, Que) is advertised at the **www.only-in-canada.com** website where its lactobacilli content is referred to as "the Xena warrior princesses of the vagina," with a claim that it prevents yeast infections. The **www.berrytechnologies.ca** website claims that Fermalac will "stop recurrent bacterial or yeast infections from returning after an antibiotic or antifungal treatment." This product is supported by one peer-reviewed Czech study on prevention of colpitis (inflammation of the vagina) during pregnancy,[31] so the evidence is level II.

There is level I evidence of the effectiveness of *L rhamnosus* GR-1 and *Lactobacillus reuteri* (formerly *fermentum*) B-54 and RC-14 in restoring vaginal lactobacilli and reducing infections in more than 50% of women after daily oral use and in

Figure 1. Mean number of breakthrough infections per year in women taking *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* B-54 compared with number of infections among those using various other treatments38-41: *Mean number of urinary tract infections was reduced from 6 per year with preventive treatment to less than 2.5 per year. The data suggest that weekly vaginal probiotic use compares with daily antibiotic treatment or twice-daily vaginal washes.*



1. Once-daily use of intravaginal *L rhamnosus* GR-1 and *L fermentum* B-54
2. Daily dose of 100 mg of trimethoprim-sufamethoxazole
3. Twice-daily dose of 1000 mg of methenamine hippurate
4. Twice daily use of povidone iodine
5. Daily dose of 50 mg of nitrofurantoin
6. Daily dose of 250 mg of cefaclor

79% of women after once-weekly vaginal use.[10,32-34] Results of 25 women's once-weekly vaginal use of *L rhamnosus* GR-1 and *L fermentum* B-54[33] compare favourably with results from various daily antibiotic regimens and twice-daily vaginal washes[35-37] for breakthrough UTI (**Figure 1**[38-41]).

In a study published in 1989, 15 women taking long-term daily prophylaxis with norfloxacin had no episodes of UTI.[42] Since then, escalating resistance to fluoroquinolones in some countries,[43,44] increased resistance to trimethoprim-sulfamethoxazol[45,46] (formerly recommended daily for up to 5 years[38]), decreasing rates of UTIs due to *E coli*,[46,47] and the adverse effects of antibiotics (reported as 28% for ciprofloxacin, 34% for nitrofurantoin, and 38% for trimethoprim-sulfamethoxazole in one study[48]) suggest that probiotics to prevent UTIs should be further studied.

Orally administered lactobacilli reach the vagina via the anus and the perineal and vulval skin, as do pathogens, irrespective of hygiene.[30] For reasons not yet understood, not all lactobacilli are able to colonize the vagina.[39-41,49]

Labeling and how to know what to recommend

Some products in Canada claim that they contain *Lactobacillus sporogenes*, an organism that does not exist.[50] Currently, Danone's Activia yogurt containing *B lactis* DN-173 010 for regularity, VSL#3's product for inflammatory bowel disease, and perhaps Rosell Lallemand's Fermalac vaginal suppositories for bacterial infections, are this country's only proven probiotics. Across the border, Culturelle containing *L rhamnosus* GG and Reuterin containing *L reuteri* SD2112 are reliable remedies for diarrhea in adults and children (**Table 1**[51]). Unless a probiotic product is manufactured under the best possible conditions and packaged extremely carefully, the contents could die steadily at room temperature.

Safety

The safety record of probiotics is remarkable considering that more than 20 billion doses are estimated to be used each year.[52] Nevertheless, there have been a few reports of bacteremia. One retrospective

Table 1. Products that Canadian patients might ask their physicians to comment on

PRODUCT AND SOURCE	PROBIOTIC CONTENT	RECOMMENDATION
Activia yogurt; Danone; Boucherville, Que	*Bifidobacterium lactis* DN-173 010	Recommended once or twice daily for regularity
VSL#3; Seaford Pharma; Toronto, Ont	Eight strains of lactobacilli, bifidobacteria, and streptococci	Recommended to maintain remission of inflammatory bowel disease
Culturelle; Con Agra Foods; Omaha, Neb or Valio; Helsinki, Finland	*Lactobacillus rhamnosus* GG in capsule form in United States or in various food forms in Europe	Recommended to treat and prevent diarrhea (adults and children). Use with oral rehydration
Reuterin; Biogaia; Raleigh, NC	*Lactobacillus reuteri* DSM 20016 in capsule form in United States or in various food forms in Europe and Japan	Recommended to treat and prevent diarrhea (adults and children). Use with oral rehydration
Fermalac Vaginal; Rosell Lallemand; Montreal, Que	Lactic acid bacterial strains	Only one publication on alleviating vaginal inflammation. Might benefit some patients, but more studies are needed
BioBest yogurt; Parmalat; Mississauga, Ont	Probiotic content and viable counts uncertain	Product not tested clinically; not a probiotic
Yoplait probiotic yogurt; Yoplait Canada; Longueuil, Que	Undesignated strain of *Bifidobacterium longum*	No way of knowing if it contains probiotic bacteria in amounts sufficient to confer health benefits
Lactobacillus acidophilus; Jamieson; Toronto, Ont	Labeled as containing an undesignated strain of *Lactobacillus acidophilus*	No clinical studies known for this product. Not a probiotic
Swiss Probiotics; Toronto, Ont	Various products have two or four strains of undesignated organisms	No clinical studies known for these products. Dubious viable counts according to Huff.[51] Not a probiotic
Yakult (product); Yakult (manufacturer); Japan	*Lactobacillus casei* Shirota, 65-mL drink imported by some food stores	Claims to enhance immunity; one study shows reduced recurrences of bladder cancer
Florastor; Biocodex; France	*Saccharomyces boulardii* LYO	Appears to help resolve diarrhea but not *Clostridium difficile*

analysis showed 89 cases of lactobacilli bacteremia, of which 11 might have been related to probiotic *L rhamnosus* GG use.[53] In 82% of these cases, patients had severe or fatal comorbidity.

Physicians are presented with a dilemma in giving seriously ill hospital patients (with pancreatitis or liver transplants and those undergoing abdominal surgery) probiotics. Studies show that such patients have benefited from daily intake of *L plantarum* 299.[54-56] They had fewer infectious complications of surgery. Animal studies showed less severe intra-abdominal infection with *Lactobacillus* R2LC treatment.[57] Some patients with short bowel syndrome[58] and leukemia[59] might be at risk of bacteremia from probiotics, yet *L reuteri* SD2112 has been safely taken by HIV and AIDS patients.[60] Probiotics are generally regarded as safe, but physicians should monitor their use in high-risk patients.[61]

Conclusion

The increasing availability of probiotic products makes it important that family physicians understand what to look for when making recommendations.[51] While products are available in Canada only for regularity, inflammatory bowel disease, and vaginal inflammation, patients gain access to products from other countries and seek advice about them from their local physicians. Examining the label for strain speciation and designation and shelf-life and learning about clinically proven strains of probiotics will help physicians feel comfortable recommending suitable probiotic supplements.

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Competing interests

Dr Reid *owns strains* Lactobacillus rhamnosus *GR-1 and* Lactobacillus reuteri *(formerly* fermentum*) B-54 and RC-14.*

EDITOR'S KEY POINTS

- Probiotics, live microorgansms that confer a benefit to the host when given in sufficient quantities, are becoming widely known. Patients increasingly choose to use probiotics and to ask their family physicians about them.
- A few specific probiotics have level I evidence of effectiveness, and they appear to be quite safe. They have been shown to be useful in preventing and treating diarrhea and urogenital infections.
- Unfortunately, most probiotics that have been proven effective are unavailable in Canada. They are sold in the United States and Europe. Family physicians recommending probiotics must be aware that only specific brands have proven effects and that packaging must be intact to preserve viability.

POINTS DE REPÈRE DU RÉDACTEUR

- Les probiotiques, des micro-organismes vivants qui en doses suffisantes ont des effets bénéfiques pour l'hôte, sont de plus en plus connus. Un nombre croissant de patients qui décident d'en prendre demandent l'avis de leur médecin de famille.
- L'efficacité de quelques probiotiques spécifiques repose sur des preuves de niveau I et leur usage semble plutôt sécuritaire. On a démontré qu'ils sont efficaces pour prévenir et traiter les diarrhées et les infections urogénitales.
- Malheureusement, la plupart des probiotiques d'efficacité prouvée ne sont pas disponibles au Canada. On peut les acheter aux États-Unis et en Europe. Le médecin de famille qui recommande des probiotiques doit savoir que seules certaines marques spécifiques se sont montrées efficaces et que l'empaquetage doit être intact pour préserver la viabilité du micro-organisme.

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