

Probiotics in practice

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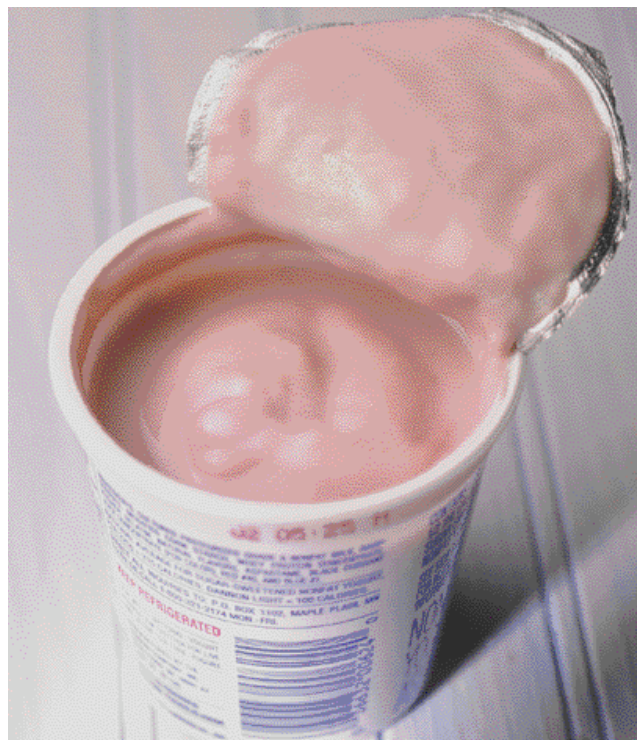
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Probiotics have become increasingly popular and are now credited with a wide range of benefits.

Probiotics are best defined as live viable micro-organisms that, when taken by mouth, exert beneficial effects on the host.¹ Requirements for an organism to act as a probiotic include acid stability and ability to colonise the intestine. Some of the most commonly used probiotics are organisms belonging to the lactobacilli group of lactase-producing bacteria, such as *Lactobacillus acidophilus*. Other organisms with probiotic effects include the bacteria *Bifidobacterium* and nonpathogenic *Escherichia coli*, and the yeast *Saccharomyces boulardii*. Probiotics are often used alone, but may be combined with prebiotics (inactive food components that assist in the growth of beneficial micro-organisms in the gut); the probiotic and prebiotic are then known as synbiotics.

The concept of probiotics was first developed by Metchnikov almost a century ago.¹ Only recently have we begun to understand how they work. A variety of mechanisms have been demonstrated, including antimicrobial activity (by the production of antimicrobial agents) and immunological and cytoprotective activities.² Further general mechanisms include competition for nutrients, inhibition of mucosal binding, alteration in production of mucins and immunomodulatory effects.^{3,4} An additional mechanism may be mucosal induction of nitric oxide: this locally active agent has antimicrobial effects but may also mediate immunoregulatory and cytoprotective activities.⁵

Probiotics have become increasingly popular in the community over the last decade or so because of their widespread acceptance and general lack of side effects, and they are now widely used. Almost a quarter of a group of children attending a general gastroenterology outpatient clinic at Sydney Children's Hospital, Randwick, had taken or were currently taking probiotics.⁶ The number of children using probiotics was even greater in a group of children with chronic inflammatory bowel disease: over half of these children were taking probiotics.⁷ Investigators have also shown that probiotics are often used by



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paediatric and adult populations with chronic diseases.^{8,9} Currently, however, good evidence only exists to support their use for a handful of medical conditions.

How they are used

Probiotics may be added to various food products or are available separately as capsules, tablets or powders. Dairy products containing probiotics are now available, such as some yoghurts (including drinking varieties), fermented milk drinks and cheeses. The probiotic may be the starter culture for these yoghurts and fermented milk drinks but is usually added to cheeses once they have been made. In addition, some brands of infant formula have probiotic agents added as supplements.

One rationale supporting the addition of probiotics to infant formula is that probiotics may increase bioavailability of nutrients in the milk source (e.g. calcium and magnesium) and may contribute to intestinal function by production of vitamins such as folic acid.¹⁰ Another rationale is that the probiotic agents may reduce permeability of the intestinal epithelium, thereby averting the presentation of large antigens to the immature immune system, which may help to prevent the development of immune mediated disease.¹¹ Furthermore, as most probiotics are lactase-producing, the addition of these to an infant formula may enhance digestion of lactose.

Of the large number of probiotic products available as capsules, tablets or powders, some may be free of milk proteins and

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others may have additional prebiotic components. The available products vary in terms of the type of micro-organism present, the number of different species in the product and the total number of organisms provided for each dose. Particular strains of organisms are used as probiotics. *L. acidophilus* is the most commonly available organism and has been assessed in most studies. Other available agents are *Bifidobacterium* species (e.g. *Bifidobacterium bifidus*) and other *Lactobacillus* species (e.g. *Lactobacillus rhamnosus* strain GG, named after its discoverers Drs Gorbach and Goldin and also known as *Lactobacillus* GG). Recommended doses for an adult are between one billion and ten billion organisms per day.

When they are used

Gastrointestinal conditions

Probiotics have been shown to have roles in the management of acute diarrhoeal illness, traveller's diarrhoea and antibiotic associated diarrhoea, and also in the management of inflammatory bowel disease.

Diarrhoeal illness

Various probiotic agents have been shown to be useful in the prevention and treatment of acute viral enteritis in children.¹² These include *L. acidophilus*, *Lactobacillus* GG and *Lactobacillus reuteri*. They may help to prevent the acquisition of viral enteritis and lead to a more rapid resolution of symptoms. These agents may also be useful in the prevention or treatment of traveller's diarrhoea.¹³

Antibiotic associated diarrhoea is estimated to occur in up to 40% of individuals receiving oral antibiotics, especially broad spectrum antibiotics,^{4,14-16} and it may lead to significant morbidity, mortality and additional costs to health services. Probiotic agents, especially the lactobacilli and *S. boulardii*, have been shown to have both preventative and therapeutic roles in the management of this type of diarrhoea.

Two meta-analyses on the use of probiotic agents to prevent antibiotic associated diarrhoea concluded that probiotics have beneficial effects.^{17,18} D'Souza *et al* calculated from the combined results of nine studies that the use of probiotics reduced the chance of developing antibiotic associated diarrhoea by two-thirds.¹⁷

Probiotics are also helpful in managing recurrent antibiotic associated diarrhoea, which is commonly related to *Clostridium difficile* infection. Kimmey *et al* reported the use of *S. boulardii* for three months in an adult who had suffered six episodes of recurrent *C. difficile* colitis.¹⁹ Following the period of treatment, the patient had complete resolution of symptoms and no further recurrence over an extended follow up period. Subsequently, in a study of 168 adults with recurrent *C. difficile* infection treated with a regimen containing *S. boulardii*, the frequency of relapse of antibiotic associated diarrhoea fell from 50% to 16.7%.²⁰

Inflammatory bowel disease

Several human studies have shown that probiotic bacteria, as either single agents or combinations, may have benefits in inflammatory bowel disease (IBD), including in pouchitis, ulcerative colitis and Crohn's disease. Italian researchers showed that the use of VSL#3, a high potency probiotic containing eight bacterial strains, resulted in a substantially reduced frequency of relapse of pouchitis (relapse rate fell to 15%) when compared with placebo (relapse rate, 100%).²¹ These researchers have subsequently used the same probiotic as prophylaxis to successfully prevent the development of pouchitis in newly created pouches.²²

Probiotic agents such as *S. boulardii*, *E. coli* Nissle, *Lactobacillus* GG and VSL#3 have been used in patients with Crohn's disease in several open or blinded studies, with varying results.²³ An open label study of *Lactobacillus* GG in a small group of children demonstrated improvements in both the children's symptoms and a measure of intestinal barrier function.²⁴ Further studies are now required to define the optimal agent for each type of IBD so that these agents can be used rationally.

Allergic conditions

Atopic eczema, asthma and allergic rhinitis have all been recent targets of preventive strategies from birth by alteration of gut flora. A Finnish study showed a 50% reduction in the development of eczema in children at risk of eczema (i.e. with a strong family history) when mothers and babies were given *Lactobacillus* GG for six months.²⁵ Subsequently, a treatment study by the same investigators showed the benefit of an infant formula supplemented with probiotics in children with active atopic eczema.²⁶ While short term studies in asthma have not been as promising in the longer term, studies in this illness are ongoing.

Other conditions

Vaginal application and oral ingestion of probiotics have been shown in Canadian studies to have benefits in recurrent urogenital tract infections.^{27,28} Some preliminary results suggest that probiotics may have beneficial effects upon serum lipid levels and short term benefits upon hypertension, and may help in decreasing carcinogen levels, thereby reducing the risk of cancer.²⁹ These preliminary studies require confirmatory data to establish the precise benefits of probiotics for these varied conditions.

Their side effects

Probiotics have been shown to be very safe with minimal side effects. Abdominal bloating may be seen in the first few days after starting a new probiotic agent. This side effect is reported by up to 10% of individuals receiving the probiotic mix VSL#3, but is seen less often with single probiotic agents.

Bacteraemia is described in isolated case reports,³⁰ usually in the setting of severely immunocompromised patients.

Rarely, the use of lactic acid producing probiotic agents may lead to systemic metabolic events. In some patients, the systemic absorption of the unmetabolisable D-isomer of lactic acid leads to metabolic acidosis and related clinical effects such as encephalopathy. This syndrome, known as D-lactic acidosis, is seen almost exclusively in children with shortgut syndrome.³¹

A further consideration is the difficulty encountered in establishing consistent guidelines for evaluating and marketing probiotic agents. Many so-called probiotic agents have not been identified or assessed clinically, and have invalid claims made for them by manufacturers.

Precautions for their use

To help prevent the side effect of D-lactic acidosis, individuals with short bowel syndrome or bacterial overgrowth syndrome should limit their use of probiotics to those that contain bacteria producing only the L-isomer of lactic acid (e.g. *Lactobacillus GG*).

Some antibiotics may kill probiotic agents or diminish potency. However, several studies have shown continued benefit of probiotics even when given in combination with oral antibiotics. The use of nonbacterial probiotics, such as yeasts, obviates this potential downside.

It is generally thought that probiotics do not interact with medications.

Conclusions

Only a small number of the clinical roles ascribed to probiotic agents have been well validated scientifically. These include the management of antibiotic associated diarrhoea, acute infectious diarrhoea in children, traveller's diarrhoea and pouchitis. Several potential roles have been suggested, such as the prevention and treatment of allergic conditions and irritable bowel syndrome, but these roles are not yet supported with sound evidence. Furthermore, some of the benefits shown for probiotic agents are agent-specific (e.g. some probiotics work better for antibiotic associated diarrhoea than do others). Nonetheless, it is extremely likely that probiotics will play an increasingly important role in preventive health and the management of specific disease. **MT**

A list of references is available on request to the editorial office.

DECLARATION OF INTEREST: Drs Day and Lemberg are involved in clinical studies of the probiotic VSL#3 in children with inflammatory bowel disease. These studies have included the provision of probiotic agent by the manufacturer, VSL Pharma.

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