DAILY PROBIOTICS – WHO DERIVES THE MOST BENEFIT?

Introduction

Regular use of probiotics (live micro-organisms that beneficially affect the host by improving microbial balance1) is on the increase worldwide; a recent epidemiological evaluation of probiotic usage in Canada and the USA has shown that 12% of these populations regularly consume probiotics.2,3 Usage by women predominates in the USA (15% of women and 8% of men).3

KEY MESSAGES

• In the USA and Canada, 8% of the population are regular users of probiotics
• New safety data on the daily use of probiotics are emerging as a result of the FDA and other regulatory agencies requiring data to substantiate health claims
• Specific population groups/subsets of patients derive more health benefit when treated with daily probiotics
• Recently available clinical trial data on the major groups of bacteria used as probiotics can help to guide evidence-based prescribing of these products.

Major micro-organisms considered to be probiotics

Lactic acid bacteria are the major group of bacteria suitable for use as probiotics. They are Gram-positive and catalase-negative, and produce lactic acid as the main end-product from the fermentation of carbohydrates. The most important genera are Lactobacillus and Bifidobacterium, which are used in both food products and nutraceuticals. Enterococcus is also an important lactic acid bacterium, which is often used in combination with either Lactobacillus or Bifidobacterium. Table 1 provides a list of species used and cited in clinical research.4

Essential probiotic properties

Probiotics need to be able to withstand the harsh gastric environment to reach the intestine and adhere to the mucosal and epithelial surfaces. In vitro tests are used to determine the following desirable properties:

1. Acid and bile tolerance, which is essential for oral administration
2. Adhesion to mucosal and epithelial surfaces to compete with and exclude pathogenic bacteria from the receptor
3. Production of antimicrobial activity against pathogenic bacteria (so that the probiotic can compete even more successfully with pathogenic bacteria)
4. Bile salt hydrolase activity
5. Resistance to certain antibiotics, so that the probiotic is able to restore the microbial balance and prevent antibiotic side-effects
6. Quantity of viable micro-organisms, although not precisely defined, should reach a minimum total of $10^8-10^9$ colony-forming units (CFUs). Viability should also be maintained under normal storage conditions.

Mechanisms of action

Probiotics have various mechanisms of action. These include the production of bacteriocins (antibacterial peptides) and short-chain fatty acids, lowering of gut pH, stimulation of mucosal barrier function and immunomodulation. There is considerable evidence that probiotics influence the acquired and innate immune response by inducing phagocytosis and IgA secretion, modifying helper T-cell response and the release of cytokines in a strain-specific manner.

Link between gastrointestinal flora and immune function

Probiotics maintain the balance of gastrointestinal microbiota, which helps to prevent invasion of the epithelium by pathogenic bacteria. The body’s immune system is associated with the intestinal epithelial barrier and its mucosal lining. Disruption of the healthy, indigenous microbiota by pathogens leads to a dysfunctional innate immune system and increases the risk of developing disease (Figure 1).

The increase in probiotic usage has been positively influenced by two independent meta-analyses that support the use of probiotics, both in food products and nutritional supplements, as a preventative measure against respiratory tract infections (RTIs). In particular, the Cochrane Collaborations Study showed that probiotic consumption reduced the incidence of RTIs by 47% and very significantly reduced the antibiotic prescription rate by 35%.

Vaginal probiotics are being developed and trialled to reduce bacterial vaginosis, a condition characterised microbiologically by replacement of the lactobacilli predominant in the vaginal microbiota.

Table 1. Micro-organisms considered to be probiotics

<table>
<thead>
<tr>
<th>Lactobacillus species</th>
<th>Bifidobacterium species</th>
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<tbody>
<tr>
<td>L. acidophilus</td>
<td>B. adolescentis</td>
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<tr>
<td>L. casei</td>
<td>B. animalis</td>
</tr>
<tr>
<td>L. crispatus</td>
<td>B. bifidum</td>
</tr>
<tr>
<td>L. gallinarum (Mainly used in veterinary medicine)</td>
<td>B. breve</td>
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<tr>
<td>L. gasseril</td>
<td>B. infantis</td>
</tr>
<tr>
<td>L. johnsonii</td>
<td>B. lactis (Recently reclassified as B. animalis subsp. lactis)</td>
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<tr>
<td>L. paracasei</td>
<td>B. longum</td>
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<tr>
<td>L. plantarum</td>
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<tr>
<td>L. reuteri</td>
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<tr>
<td>L. rhamnosus</td>
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For primary care practitioners, including pharmacists, recent double-blind randomised studies provide data on selecting patients who will benefit from daily probiotic use. The first aspect to consider is the safety of daily probiotic use, particularly in the young and the elderly.

Safety of daily probiotic use
The increase in the use of probiotics based on demonstrated benefit in a variety of diseases, including diarrhoea, necrotising enterocolitis and respiratory infections, has led to safety initiatives aimed at satisfying the FDA’s standards for the use of these agents as medicines. Validating health claims also requires more rigorous safety testing in today’s regulatory environment.

Two recent studies provide safety data that are likely to expand in the near future.8, 9 A recent Finnish study evaluated the adverse events associated with specific probiotics (L rhamnosus GG (LGG) alone or LGG in combination with L rhamnosus Lc705, Propionibacterium freudenreichii JS, B lactis BB12 or B breve 99) in almost 2000 people included in clinical trials conducted under the auspices of the University of Helsinki. The evaluation concluded that probiotic ingestion did not result in statistical differences in adverse events in either young or elderly subjects included in the study.

In a phase 1 safety study typical of the regulatory process for new drugs, the safety of B animalis subsp. lactis (B lactis) strain was tested in 40 healthy participants and found to be safe and well-tolerated.9 This investigation will be followed by randomised clinical trials (RCTs) investigating the potential immunomodulatory effects of this probiotic in a variety of disease states.

Specific populations that benefit from regular probiotic use
While a RCT among free-living older adults was negative for benefit from three months use of probiotics,10 other RCTs have provided a clearer idea of which individuals in particular circumstances will benefit from daily probiotic supplementation.

Pregnant and lactating women
A RCT of high-dose probiotic supplementation in women during late pregnancy and lactation has shown that breast-milk cytokines and secretory IgA production in newborns are beneficially modified by therapy.11 This improves overall gastrointestinal function in infants of treated mothers with a reduction of colic symptoms.

Children on antibiotic therapy
A Cochrane analysis of available clinical trials suggests a positive outcome with regard to the reduction of antibiotic-associated diarrhoea with a number-needed-to-treat (NNT) of 10.12

Among the various probiotics evaluated, L rhamnosus or Saccharomyces boulardii at 5-40 billion CFUs/day may be appropriate given the modest NNT and the likelihood that adverse events are very rare. Although no serious adverse events from probiotic usage have been observed among otherwise healthy children, adverse events have been observed in severely debilitated or immune-compromised children with underlying risk factors, including central venous catheter use and disorders associated with bacterial/fungal translocation. Until further research has been conducted, probiotic use should be avoided in paediatric populations at risk for adverse events.
Adults on antibiotic therapy

In healthy adults, a randomised, double-blind placebo-controlled trial of two lactobacilli (L. helveticus (R0052) and L. rhamnosus R0011) taken for one week with the antibiotic and one week after completion, shows that supplementation significantly reduced the duration of diarrhoea-like symptoms.13

Diarrhoea related to antibiotic treatment is self-limiting, but there are specific circumstances when limiting the extent of the diarrhoea is important, particularly in patients who have had a number of sequential antibiotic treatments and in vulnerable elderly patients.

Patients on aspirin to reduce small bowel injuries

A very recent prospective randomised double-blind placebo-controlled trial showed that a lactobacillus (L. gasseri OLL2716 (LG)) given daily for six weeks reduces aspirin-induced small bowel injuries and mitigates gastrointestinal symptoms.14

Patients/people vulnerable to adverse effects of RTIs

In the elderly, upper RTIs can have severe implications. A RCT of healthy people aged 60-74 years, healthy and not living in retirement homes, showed that a Bacillus subtilis CU1 probiotic decreased the frequency of respiratory infections compared to placebo.15

Probiotic usage in vulnerable children/immunocompromised children is not recommended to prevent RTIs; however, Cochrane analysis has shown the value of probiotics in otherwise healthy children in reducing the occurrence of RTI’s.7

Athletes in training

Trained athletes benefit from probiotic usage as prolonged intense exercise is associated with the suppression of immune function and an increased risk of infections. A randomised, double-blind placebo-controlled trial conducted among Austrian athletes showed that a multi-species probiotic given for 12 weeks reduced exercise-induced drops in tryptophan levels and reduced the incidence of upper RTIs without enhancing athletic performance.16

Conclusion

Daily probiotic use can be beneficial, particularly to a subset of patients and can significantly improve immune status.

References

2. Ipsos Reid BioAccess Commercialization Centre Canadian Baseline Survey. www.agwest.sk.ca
bacterial breast milk cytokine profile and may have beneficial effects on neonatal gastrointestinal functional symptoms. A randomised clinical trial. Nutrients 2016; 8: 677.


PHARMACY COUNCIL REQUIREMENTS

In order to submit the CPD certificate to the South African Pharmacy Council, go to http://www.pharmcouncil.co.za/B_CPD_Record_Activities.asp

To record your CPD activity, you need to ensure that information is provided for each of the four steps in the CPD cycle: *Reflection on practice, Planning, Implementation* and *Evaluation or reflection on learning*.

We have provided information for these steps and questions you will be required to answer.

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<td><strong>STEP 1:</strong></td>
<td><strong>Reflection on practice</strong></td>
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<tr>
<td><strong>Question:</strong></td>
<td>Describe the learning need that you have identified to improve your knowledge and skill, and what you hope to achieve after addressing this learning need?</td>
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<td><strong>STEP 2:</strong></td>
<td><strong>Planning</strong></td>
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<td><strong>Question:</strong></td>
<td>Briefly describe the reasoning behind your planning selection. We suggest an answer for this module – &quot;Relevance to South African circumstances.&quot; This module was provided online with useful additional linked-in resources.</td>
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<td><strong>STEP 3:</strong></td>
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<td><strong>Question:</strong></td>
<td>Describe what you have learned.</td>
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<td><strong>STEP 4:</strong></td>
<td><strong>Evaluation or reflection on learning</strong></td>
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<tr>
<td><strong>Question:</strong></td>
<td>Describe, providing examples, how you have applied what you have learnt, including feedback on the impact of your learning and possible next step.</td>
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