The use of probiotics and supplements in children

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Data on the use of probiotics and supplements in children are limited; however, a definite role has been shown for probiotics in gastrointestinal disease. Dietary supplements are important in treating deficiencies and insufficiencies when a child's nutritional status is impaired.

Understanding of the human gut microbiome has flourished in recent years. New methods of analysing bacteria have allowed the identification of species that were previously unrecognised due to limitations in culture methods. Colonisation of an infant's gastrointestinal tract evolves through the first years of life and is affected by gestational age, mode of delivery (i.e. vaginal or caesarean), breastfeeding, antibiotic use and diet.[1] The make up of the human microbiome and its function have been shown to vary with health and disease.[2]

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Probiotics are defined by the World Health Organization as 'live micro-organisms which when administered in adequate amounts confer a health benefit on the host'.[3] Sound research is limited to finite species and strains of 'micro-organisms', and the evidence for 'health benefit' is limited to a few specific indications. The relative safety of probiotics and the intuitive arguments for their use mean they can be marketed as potentially helpful for many conditions.

The use of dietary supplements, especially in children, is controversial. They are often self-prescribed, guided by family members, friends or nonprofessional advice found on the internet. Despite sparse literature, deleterious effects associated with their use have been documented. In 2009, the American Academy of Pediatrics recommended against multivitamins for children and adolescents who had a balanced diet because they may result in excessive intake of iron, zinc, copper, selenium, folic acid, vitamin A and vitamin C.[4] Thus, primary care physicians need to play a central role in discouraging patients from inappropriate use of supplements, and giving careful recommendations for their use.

Dietary supplements may help to meet nutritional requirements in people at risk of deficiency (e.g. in the population susceptible to vitamin D deficiency). In addition, much discussion has taken place to assess whether well-nourished people might benefit from high-dose micronutrient supplements (e.g. vitamin C, curcumin) in specific illnesses.

This article summarises current evidence and indications for using probiotics and supplements in children and presents practice points for GPs (Box).

Probiotics

Probiotics and antibiotic-associated diarrhoea

Antibiotic-associated diarrhoea (AAD) can occur during antibiotic exposure or up to eight weeks after exposure.[5] One

meta-analysis found a median incidence of AAD among children of 22%.[5]

Lactobacillus strains that have been shown to reduce the likelihood of developing AAD include *L. acidophilus, L. bulgaricus* and *L. rhamnosus* GG.[6] A meta-analysis of 22 randomised controlled trials found that only *L. rhamnosus* GG, a probiotic bacteria, and *Saccharomyces boulardii*, a yeast, were significantly effective in preventing and treating AAD in children.[5] Guidelines published recently by the European Society for Paediatric Gastroenterology Hepatology and Nutrition support the use of *L. rhamnosus* GG and *S. boulardii* for the prevention of AAD in children.[7]

AAD has multiple causative organisms without a single organism being implicated in many cases. However, *Clostridium difficile* is a well-described single-organism cause of ADD. Administration of *S. boulardii* has been shown to decrease the incidence of *C. difficile* infection in children treated with antibiotics and to be effective in treating *C. difficile* diarrhoea and recurrent AAD due to *C. difficile* infection.[1,5,6]

Over-the-counter high-potency probiotics containing hundreds of billions of bacteria have proven benefit for the above indications, as opposed to yoghurts, which have much smaller numbers of bacteria. There are, however, no data available on how long to treat with probiotics for this indication.

Probiotics in infectious gastroenteritis

Infectious diarrhoea in children can sometimes be severe, particularly in developing countries.[6] The *Lactobacillus* spp. *L. acidophilus, L. rhamnosus* GG and *L. reuteri* have been promoted as having benefit in preventing and treating acute viral enteritis in children.[6] Although there is some evidence to support the use of *S. boulardii, L. acidophilus, L. bulgaricus* and *L. rhamnosus* GG in the prevention of travellers' diarrhoea, there have been no studies to date evaluating their role among the paediatric population.[8]

The role for probiotics in the treatment of children with acute gastroenteritis is well documented. The greatest effect is noted in viral, watery diarrhoea, with a reduction in the duration of diarrhoea and hospitalisation of about 24 hours.[9] The use of *S. boulardii* CNCM I-745, *L. rhamnosus* GG and *L. reuteri* DSM 17938 for this particular indication is supported by evidence.[9,10]

Two recent randomised controlled trials provide some direction with regard to dosage and duration of therapy with probiotics for children with diarrhoea. One found that milk supplemented with *Bifidobacterium lactis* 14.5 x 10^6 CFU/ 100 mL daily for one week decreased the frequency and duration of diarrhoea and the length of hospital stay, and the other found that 250 mg twice daily of *S. boulardii* for five days reduced the duration of diarrhoea and of the hospital stay.[11,12]

Probiotic use in infants

Any interruption to the normal colonisation of an infant's gastrointestinal tract creates a dysbiosis that may predispose them to colic, necrotising enterocolitis (NEC) and the eventual development of immune-mediated diseases.[1] The role of probiotics in minimising these risks is becoming increasingly clear.

PRACTICE POINTS FOR GPS ON THE USE OF PROBIOTICS AND SUPPLEMENTS IN CHILDREN

- Use of high-potency probiotics reduces the likelihood of antibiotic-associated diarrhoea developing, including diarrhoea caused by *Clostridium difficile*.
- Use of probiotics reduces the duration and severity of viral gastroenteritis.
- Prophylactic use of probiotics may reduce the likelihood of necrotising enterocolitis in premature babies.
- Vitamin D deficiency is an emergent health issue among children in Australia. Children and adolescents presenting with at least one risk factor may benefit from having their 25-hydroxyvitamin D level measured.
- Regular vitamin C supplementation reduces the duration of the common cold.
- In children, zinc supplementation is associated with a reduction in duration of diarrhoeal disease.

Consumption of infant formula supplemented with *L. rhamnosus* GG and *Bifidobacterium breve* Bb12 increases the likelihood of colonisation of the gastrointestinal tract with these organisms, which have been shown to have specific effects on neonatal immune function.[1] Limited evidence also supports the use of formula enriched with *B. lactis, Bifidobacterium longum* and *L. rhamnosus* to reduce the risk of gastrointestinal infections in infants up to six months of age.[1] Two systematic reviews found a protective role for *L. reuteri* in the management of excessive crying among exclusively breastfed infants.[1]

One multicentre study demonstrated that a combination of *Bifidobacterium infantis* and *L. acidophilus* given with expressed breast milk reduced the incidence of NEC among preterm infants.[1] Enteral probiotic supplementation in extremely low birthweight infants has been shown to reduce the risk of NEC by almost

half and overall mortality by more than 25%.[1] The manufacturers of *L. reuteri* recommend 0.18 mL (100 million live active *L. reuteri* cells) daily for term neonates.[13] It bears noting that a prematurely born infant who had extremely low birthweight is no longer at high risk of NEC once their corrected gestational age is above 40 weeks.

A recent review has concluded that antenatal administration of probiotics to pregnant mothers in combination with postpartum use in their offspring reduced the risk of atopic sensitisation to any allergen (confirmed on skin-prick testing) and food hypersensitivity in high-risk children. Strains of lactobacillus and bifidobacterium were shown to be beneficial, although further research is needed to quantify more clearly the strains and amount and duration of treatment needed to achieve this effect, and to confirm that this effect persists.[14]

Supplements

Vitamin D supplements

Vitamin D reduces the prevalence of rickets in children and osteopenia in adults. With almost one-sixth (15%) of children from 12 to 17 years of age in Australasia being found to be vitamin D deficient (serum 25-hydroxyvitamin D [25(OH)D] <50 nmol/L), vitamin D status is a significant health issue.[15] The challenges related to this include identifying the populations at risk, preventing and treating vitamin D deficiency and identifying the population with an adequate vitamin D status who may benefit from supplementation.

The two sources of vitamin D are diet and sunlight, although it is difficult for pregnant and lactating mothers, breastfed babies and children to obtain adequate daily vitamin D from diet alone. The content of vitamin D in breast milk is 25 IU per litre and vitamin D intake via eggs, oily fish, butter and margarine is limited (50 to 100 IU per day). The dietary requirement for vitamin D in children in Australia is 200 to 400 IU per day.[16,17]

Maternal vitamin D deficiency and prolonged breastfeeding increase the risk of early vitamin D deficiency in infants. In addition, children and adolescents may benefit from having their 25(OH)D level measured if they present with at least one risk factor such as restricted sun exposure, dark skin colour or altered vitamin D metabolism (such as in obesity or with use of specific medications, e.g. antiepileptic drugs).[18] Measurement is also important during pregnancy, with trials suggesting that optimal maternal vitamin D status reduces the risk of preterm birth by 64% and low birthweight by 60%.[19] Therefore, if pregnant women are at risk of vitamin D deficiency they should be screened at the first antenatal visit.[18]

Vitamin C supplements

Further beneficial effects of vitamin C (ascorbic acid), aside from treating scurvy, were first highlighted by the Nobel laureate Linus Pauling in the 1970s. He postulated that vitamin C supplementation could alleviate or even prevent common colds; yet, after decades of research, its use for this purpose is still a controversial subject. A Cochrane review showed that regular supplementation with vitamin C (from 200 mg up to 2000 mg per day) in children reduced the duration, but not the incidence, of the common cold. The duration can be reduced by 14 to 18% depending on the dose.[20] However, no therapeutic trials have been conducted in children to examine the effects of vitamin C supplementation.

Zinc supplements

Zinc is essential for the development and growth of children. The prevalence of zinc deficiency in Australia is unknown; however, children, and especially those who adhere to a vegetarian or vegan diet, are more at risk. In randomised controlled trials in Bangladesh, India, Peru and South Africa, where zinc deficiency is presumed to be more prevalent, zinc supplementation in children reduced the incidence and prevalence of pneumonia by 13% and 41%, respectively.[21] In a Swiss study, zinc has been shown to reduce the frequency and duration of diarrhoea in children with gastrointestinal infections by several hours.[22] However, in the absence of malnourishment or a high risk of zinc deficiency, the systematic use of zinc supplementation in children with diarrhoea requires further study.

Curcumin supplements

Curcumin is a polyphenol from the turmeric plant (*Curcuma longa*) and has been used in Ayurvedic medicine for several decades. It has been demonstrated that curcumin modulates the activity of transcription factors (PPAR-γ, NF-κB), inhibits proinflammatory cytokines (e.g. TNF-α) and neutralises reactive oxidative stress.[23] Efforts are being made to establish its use in conditions such as inflammatory bowel disease, diabetes and asthma. Supplemental use of curcumin is limited by its low bioavailability, low solubility and poor pharmacokinetics.

Conclusion

Patients' and health professionals' interest in probiotics and supplements has grown quickly in the past few years. Although there is clearly a role for probiotics and dietary supplements in treating certain conditions, their use should preferably be guided by rigorous medical evidence in conjunction with conventional therapies.

Probiotics have been shown to be useful in some diseases such as AAD, viral gastroenteritis and NEC, yet their role in other diseases, such as travellers' diarrhoea, and in the prevention of atopic conditions is less clearly defined. Dietary supplements are important in treating deficiencies and insufficiencies when a child's nutritional status is impaired, although an optimal well-balanced diet is the best way to maintain sufficient intake of essential micronutrients. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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