Targeting the microbiome in paediatric disease of the intestine and beyond

Here we present the highlights from a recent Biostime Nutrition webinar with guest speaker Dr Ed Giles. Dr Giles is a consultant paediatric gastroenterologist at Monash Children's Hospital and Royal Children's Hospital. His research interests are in the field of mucosal immunology, particularly related to paediatrics and inflammatory bowel disease (IBD).

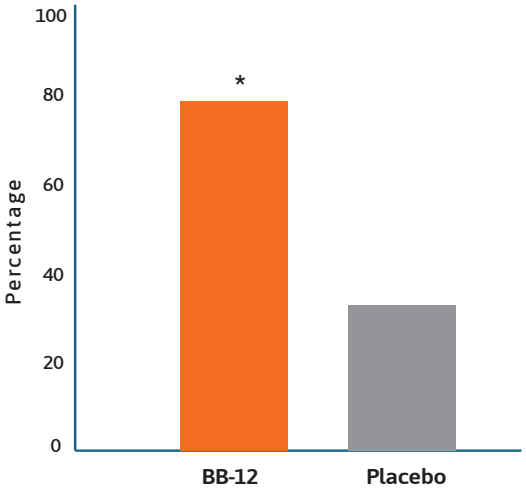
Humans have consumed live bacteria in foods for thousands of years.[1] Such foods, including yoghurt, kimchi, sauerkraut, and cheese, show widespread geographic and cultural consumption. The recent emergence of commercially available isolated live bacteria, probiotics, has led to an increase in live bacteria consumption, with rates doubling in the United states between 2002 and 2012.[1,2] Publications relating to the effect and/or modification by probiotics of the gut microbiome have risen exponentially in recent years.[3]

Although more research is required to clarify the most effective probiotics for any given disease or situation.[4] For example, health benefits shown for one strain may not occur with others, and there are even differences within species.[4] Here we discuss some aspects of the relationships between probiotics and health and disease.

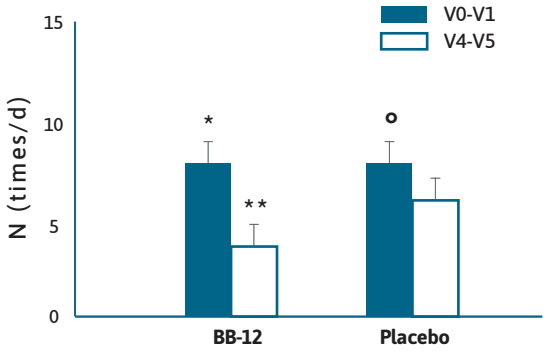
Dr Ed Giles received a speaker honorarium from Biostime® Nutrition.
This Summary was written by Professor Peter SW Davies, Honorary Professor of Childhood Nutrition, University of Queensland.
Professor Davies received a writing honorarium from Biostime® Nutrition.

Probiotics and colic

The work of Wessel and colleagues back in 1954, described colic as being associated with paroxysmal fussing in infancy.[5] Over 60 years later, the aetiology of colic remains unresolved and there are limited treatment options.[6] One treatment option that has been investigated in recent years is the role that probiotics may play in reducing fussiness and/or crying in infants with colic. This approach is based on the hypothesis that disturbances in the microbiota-gut-brain axis may be involved in the aetiology of the condition.[7,8] A randomised, double-blind placebo-controlled trial showed that, based on parental reports, the median crying time of infants given the probiotic *Lactobacillus reuteri DSM 17938*, reduced from 370 to 35 minutes a day, over a 3 week period.[9] The same probiotic was associated with less crying when compared to placebo (38 vs 71 minutes per day; p<0.01) in infants after 3 months.[10] This probiotic was also shown to have an economic impact, with an estimated mean saving per patient of ~US$120, with an additional US$140 for the community. Nevertheless, it is important to point out that not all the literature supports the use of *Lactobacillus reuteri* as an intervention for colic. In a Australian randomised, double-blind, placebo-controlled study, one month intervention with *Lactobacillus reuteri* did not show any benefit in breast fed and formula fed infants with colic.[11] Additonal research is reqiured, with a 2020 trial suggesting that *Bifidobacterium animalis subsp lactis BB-12* is effective in managing infant colic via the modulation of gut microbiota structure and function.[12]



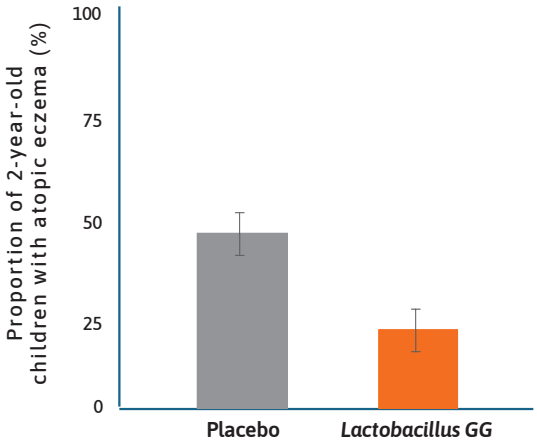
Rate of infants with ≥50% reduction of duration of crying after 28 days of treatment.[12]
* BB-12 vs placebo, p<0.0001.



Mean number of crying episodes during the week before treatment (V0-V1) and during the last week of treatment (V4-V5).[12]
* BB-12 V0-V1 vs BB-12 V4-V5, p<0.05.
** BB-12 V4-V5 vs placebo V4-V5, p<0.05.
° Placebo V0-V1 vs placebo V4-V5, p<0.05.

Probiotics and allergy

It has long been suspected that there may be a role for probiotics in preventing allergy, notably atopic disease and eczema. One of the earliest studies was of *Lactobacillus GG* given prenatally to mothers with a family history of atopic disease and postnatally to their offspring for 6 months.[13] In this randomised placebo-controlled trial (RCT), the frequency of atopic eczema in the probiotic group was half that found in the placebo group (23% vs 46%) and relative risk of 0.51 (95% CI 0.32–0.84). Since then numerous studies have shown benefits to infants in terms of eczema prevention, using either single probiotics or a probiotic mix.[14–16] Although a recent publication by Wickens and colleagues suggested that maternal supplementation alone did not result in protection against eczema and that infant supplementation was important.[17]



Treatment effect of *Lactobacillus GG* on atopic disease.[13]

Probiotics and infections: Diarrhoea

A systematic review and meta-analysis in 2016 examined the efficacy of *Lactobacillus reuteri DSM 17938 (L. reuteri)* in the management of diarrhoeal disease in children.[18] Several studies showed that probiotics have both therapeutic and preventative effects in children with diarrhoeal diseases, however, there is a need to examine strain specific effects.[18] A total of eight RCTs were included and the authors concluded that the administration of *L. reuteri* reduced the duration of diarrhoea, however, in a preventative setting the findings were mixed, with one study showing benefits, and another showing less convincing evidence.

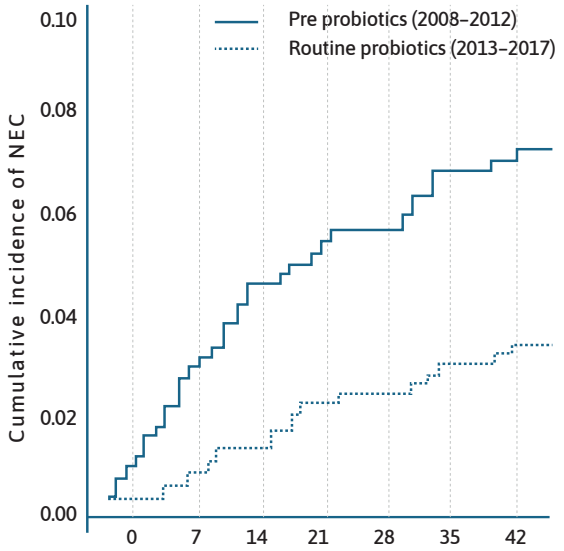
Studies that have evaluated the effects of probiotics on acute diarrhoea in children have produced contradictory findings. For example, a review of the potential benefits of *Saccharomyces boulardii* concluded this fungal probiotic reduced the mean duration of diarrhoea by ~20 hours.[19] Which contrasts with a 2020 RCT of children with acute gastroenteritis who were given *Lactobacillus rhamnosus, Lactobacillus helveticus* or placebo.[20] The authors concluded their data did not support routine probiotic administration in children with acute gastroenteritis. These conflicting results lend weight to the philosophy that "not all probiotics are equal". [18]

There is a well-established relationship between the effect of antibiotics on the existing microbiota, which can result in antibiotic-associated diarrhoea (AAD), and the administration of probiotics may help restore the gut microflora.[21] There was a recent Cochrane Database systematic review of 23 studies using probiotics in AAD, comprising nearly 4000 participants.[22] Different probiotic strains were used in these studies, but overall the incidence of AAD in the probiotic group was 8%, compared to 19% in the control group (RR 0.46; 95% CI 0.35-0.61). However, not all studies confirmed a beneficial effect. One study showed no effect of *Lactobacillus plantarum DSM 9848* (LP299V) on AAD, or the incidence of abdominal symptoms in a RCT in over 400 children aged 1–11 years.[23]

Probiotics in preterm infants

The use of probiotics in preterm infants is an area of burgeoning interest. There have been several RCTs, meta-analyses and systematic reviews that have shown that prophylactic probiotics prevent necrotising enterocolitis (NEC) in preterm infants.[24–26]

A meta-analysis published in 2017 of 25 RCTs, involving over 7000 neonates, revealed evidence supporting the use of multi-species probiotics to reduce the incidence of NEC (OR=0.36, 95% CI 0.24–0.53, p<0.00001).[27] This has led to the question why has this cost-effective practice of administering prophylactic probiotics not been universally adopted.[28]



Cumulative incidence of NEC from date of birth stratified by epoch.[29]

One reason may be that the evidence is still lacking relating to the optimal treatment strategy relating to both dose and strain of probiotic to use.[30] This is a rapidly evolving area of research, a recent position paper by the ESPGHAN Committee on Nutrition and ESPGHAN Working Group for Probiotics and Prebiotics, offered a measured, conditional recommendation, with low level of certainty. Providing that all safety issues are met, giving either *L. rhamnosus GG ATCC53103* or a combination of *B. infantis Bb-02, B. lactis Bb-12* and *Str. Thermophilus TH-4* could reduce rates of NEC.[31]

Probiotics in other conditions

In recent years, probiotics have been suggested as a treatment for many conditions including obesity[32], mastistis[33], respiratory infections[34–35] urinary tract infections[36] and more. While there is promise in these areas, at this stage there is insufficient data to make robust conclusions or recommendations, particularly realting to specific strains and dose to administer.[4,30]

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Clearly this is an exciting and expanding area, but much is still to be understood.[3,4]
As discussed and highlighted here the main benefits from probiotic administration at the moment seems to be in the prevention of atopy[13–17] and NEC in preterm infants.[24–26.]

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