

PRE- AND PROBIOTIC USE IN ALLERGY PREVENTION

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ABSTRACT

Manipulation of the intestinal flora through the use of pre- and probiotics is a therapeutic modality which addresses two candidate environmental factors thought to contribute to the increase in allergic diseases: hygiene and nutrition. Controlling the allergy epidemic may in part be accomplished by providing safe and nutritionally well-characterised live micro-organisms (probiotics), with the potential to improve the gut mucosal defence barrier, and to serve as a microbial stimulus for the human immune system.

Advances in biotechnology have enabled the safe and effective production of pre- and probiotics. This is a major medical development, and one which challenges the traditional approach of health care practitioners as we are now able to actively, and safely, 're-infect' our patients with micro-organisms. This follows an era where, since the discovery of penicillin, medical cures have largely been sought through bacterial elimination.

The rising incidence of allergic disorders, particularly among Western societies, has generated substantial research into the underlying reasons which may contribute to this trend.¹ As the increase in allergic disorders has occurred over a relatively short period of time, a genetic aetiology alone seems unlikely. Two general hypotheses have been proposed in an attempt to explain this well-documented trend.

1. New risk factors that were unknown several decades ago have become relevant in connection with nutrition, environmental exposure or lifestyle.
2. Protective factors that were related to a more traditional lifestyle in the past have been lost, which has led to a greater susceptibility for atopic diseases.

Immune deviation towards the 'pro-allergic' TH2-type cytokine response is known to occur early in life. Pre- and probiotics are potential modalities which may help us alter intestinal bacterial colonisation, and in so doing, manipulate two candidate environmental factors thought to underlie the recent increase in allergic diseases: hygiene and nutrition.² A probiotic is a live microbial food supplement that beneficially affects the host, by safely altering the intestinal microbial balance. An example of a probiotic is non-irradiated natural yoghurt, which may contain colonies of bifidobacteria and lactobacilli. A prebiotic is a non-digestible food ingredient, which affects the host by selectively targeting growth and/or activity of one or more bacterial colonies. Natural prebiotic substances, such as inulin and oligosaccharides, are found in foods such as onion, asparagus and artichoke.

Intestinal flora provide the human host with numerous beneficial properties, such as, aiding digestion, deconjugation of bile salts, synthesis of vitamins and neutralising potential carcinogenic substances. The microflora also form an important constituent of the gut mucosal defence barrier. The *Lactobacillus GG* strain ATCC 53103, (L-GG), a component of the normal intestinal flora, has been shown to facilitate gut mucosal defence through the following mechanisms: promotion of local antigen-specific immune responses (particularly in the IgA class), prevention of permeability defects, and by facilitating antigen absorption.² Intestinal microflora also serve as a major source of microbial stimulation of the immune system in early childhood.³ A recent study demonstrated that differences in the neonatal gut microflora precede the development of atopy, suggesting a crucial role in the balance of indigenous intestinal bacteria for the maturation of human immunity towards a non-atopic mode.⁴ The intestinal microflora are thought to enhance the development of TH1-type responses, and so a 'pro-allergic' TH2-type cytokine response may be suppressed.^{2,5,6} By modifying the intestinal flora through the use of probiotics, and thereby altering the intestinal milieu, the potential exists to attain prophylactic and/or therapeutic effects in atopy and other diseases.

A recent comparative study of Estonian and Swedish children demonstrated that there are indeed differences in the intestinal microflora between children from developing and developed countries. In the rural Estonian children, the typical microflora include more lactobacilli and fewer clostridia, which are associated with a lower prevalence of atopic disease.⁷ Only prospective intervention studies can demonstrate the relevance of these findings when examining the effect of adding probiotics to infant formulas. One such study from Finland was recently published.² The investigation was a randomised, double-blind comparison of two groups: infants with atopic dermatitis and challenge-proven cow's milk allergy who were fed either an extensively hydrolysed formula or an extensively hydrolysed formula containing *Lactobacillus GG*. A significant improvement in the clinical course of atopic eczema was observed in infants given *Lactobacillus GG*-supplemented formula, and in parallel, markers of intestinal inflammation, faecal alpha-1 antitrypsin and eosinophil cationic protein, were also decreased. Markers of systemic allergic inflammation as assessed in a subsequent, randomised and blinded study,³ were also significantly decreased. Similar results have been obtained in milk-hypersensitive adults.⁸

Despite this evidence supporting the therapeutic and prophylactic use of pre- and probiotics, numerous challenges remain. These include standardisation of products, and enforcing safe and ethical marketing. A recent review⁹ of 55 pre- and probiotic products sold in the European markets demonstrated that few of these contained adequate and/or viable quantities of the advertised bacterial strain. These products are generally marketed as 'food supplements' and therefore do not always comply with the stricter standards required to obtain authorisation from stringent Medical Councils. Probiotics must be capable of being prepared in a viable manner and on a large scale (e.g. for industrial purposes).

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es), and under storage the probiotic should remain viable and stable. Upon ingestion, the probiotic should be able to survive the hostile environment presented by the stomach and the existing intestinal microflora. Few studies characterise changes to the intestinal flora appropriately, as traditional culture techniques are inadequate, and require gas liquid chromatography and quantitative fluorescence *in situ* hybridisation (FISH) of bacterial cells, to accurately identify and quantify colonies. These expensive and labour-intensive techniques have shown that the stools of atopic children are more likely to have lower bifidobacteria:clostridia ratios than non-atopic children.³ At present there are insufficient longitudinal studies to confidently select the most appropriate bacterial strain.

Table I lists some of the pre- and probiotic products available in South Africa.

In summary, modification of the gut microflora forms a relatively new treatment modality for allergic disorders. Probiotics have succeeded in evoking research interest, but this is only because strict methodology has been applied in the validation of specific strains both *in vitro* and *in vivo*. Safety of these products has also been given top priority. Use of these novel products is likely to increase. It already appears 'fashionable' to join Rook and Stanford,¹⁰ who, in a recent review article in *Immunology Today*, pleaded, 'Give us this day our daily germs.' The challenges remain to firstly do no harm, and then to decide upon when to treat, with which bacteria and in which patients? Those who remain sceptical of the benefits of intestinal bacterial manipulation need only be reminded of the scepticism that initially



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Table I. Pre- and probiotic products available in South Africa

1. Biopro Reuteri. Contains *Lactobacillus reuteri*. Biopro. Tel 021-465-9372, Fax 021-465-9374
e-mail: info@biopro.co.za, www.reuteri.com
2. Infantiforte. Contains predominantly *Bifidobacterium infantis* (1 billion viable cells), indicated for infants 0-12 months. Kiddiforte chewable tablets, contain *Bifidobacterium longum*, *B. bifidum* and *Lactobacillus acidophilus*, one billion viable cells, indicated for children older than 1 year. Comibiforte contains *Bifidobacterium longum*, *B. bifidum* and *Lactobacillus acidophilus*, one billion viable cells. Sci-Pharm. Tel 011-652-4000, Fax 011-652-4577
3. Lactovita. Contains *Lactobacillus sporogenes* (6000 million spores per gram). Cipla Medro. Tel 021-914-0520, www.ciplamedro.co.za
4. *Bifidobacterium infantis*. Bio Care Supplements imported from Birmingham UK. Tel 0121-433-3727 Fax 0121-433-8705
5. Interflora. Contains 0.15 g lyophilised *Saccharomyces boulardii*. Marketed by Mer-National for Adcock Ingram Ltd. Tel 011-709-9300
6. Culturelle: Capsules and chew-tabs, containing a minimum of 100 million viable *Bifidobacterium longum* and *Lactobacillus rhamnosus* cells. Paediatric sachets, containing a minimum of 100 million viable *Bifidobacterium longum*, *Lactobacillus acidophilus* and *Streptococcus thermophilus* cells. Pharma Dynamics. Tel 021-701-6080, Fax 021-701-5898.
7. Many commercial infant formulas are now supplemented with LCPUFA and nucleotides, which possess prebiotic characteristics. Some formulas contain probiotics, e.g. Nestlé produce a formula supplemented with *Bifidobacterium* and *Lactobacillus*, NAN2BL.

PROBIOTIC CHECK LIST

Probiotics

Do you know what you're getting?

CHARACTERISTICS OF SUPERIOR PROBIOTICS:

1. Are host specific and accurately identified. eg. Human origin
2. Contain at least 100 million organisms per strain per dose
3. Produce identified antimicrobial substances
4. Survive in the intestinal tract
5. Have documented safety data
6. Have clinically validated and documented health effects
7. Have documented shelf life stability and viability

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4. Reuteri survives acid and bile and adheres to the enterocytes
5. Reuteri is safe in all ages
6. Reuteri has proven efficacy in non-bloody infectious diarrhoea
7. Reuteri is stable at room temperature

surrounded the discovery of *Helicobacter pylori* from the stomach, and the claims that this organism served as the major cause of chronic gastritis and related mucosal ulceration.

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PRODUCT NEWS



PHARMACEUTICAL SECTOR

A DOUBLE BLIND RANDOMISED PLACEBO CONTROLLED TRIAL OF CETIRIZINE IN PREVENTING THE ONSET OF ASTHMA IN CHILDREN WITH ATOPIC DERMATITIS: 18 MONTHS' TREATMENT & 18 MONTHS' POST-TREATMENT FOLLOW-UP

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ABSTRACT

Background

As asthma is not a curable condition, the development of strategies for prevention of the disease has a high priority. Atopic dermatitis is a common precursor to the development of asthma and two studies have suggested that the use of an H1 receptor antagonist might reduce the development of asthma, at least in sub-groups with evidence of high IgE levels, whilst the treatment is being administered. However, no trial to date has conducted follow-up after the initial treatment has been stopped to establish whether the intervention has merely suppressed symptoms or truly prevented disease.

Objective

To establish whether the use of cetirizine compared with placebo for 18 months in infants with atopic dermatitis suppressed or truly delayed the onset of asthma, even after cessation of therapy.

Methods

Early treatment of the Atopic Child (ETAC) was a double-blind parallel group randomised trial of cetirizine 0.25 mgm/kg body weight twice daily, compared with placebo given to infants

between 1 and 2 years of age with atopic dermatitis. After 18 months of treatment follow-up has continued for a further 18 months. This paper reports the outcome over the full 3 years of follow-up and relates the outcomes to the allergic status based on IgE antibody measurements at recruitment.

Results

While there was no difference in cumulative prevalence of asthma active treatment and placebo in the intention-to-treat population ($p=0.7$), those infants with evidence of sensitivity to house dust mite and/or grass pollen and who were treated with cetirizine were significantly less likely to have developed asthma compared with placebo over 18 months of treatment ($p = 0.005$ and 0.002 respectively), and this effect was sustained for the grass pollen sensitised infants over the full 36 months ($p = 0.008$). In the house dust mite sensitised group, there was a gradual narrowing of the difference between active and placebo in terms of cumulative prevalence of asthma at the end of 36 months but no evidence of a rebound immediately after the treatment stopped ($p = 0.04$).

In the placebo population, there was a significantly higher risk of developing asthma in those sensitised at baseline to egg, [relative risk 1.4 (1.1 - 1.7)], house dust mite [RP 1.6 (1.3 - 1.9)], grass pollen [RR (1.4 - 2.1)], or cat [RR 1.5 (1.2 - 1.9)]. Early persistent sensitisation conferred a higher risk than transient or later sensitisation.

CONCLUSION

Cetirizine compared with placebo truly delays or, in some cases, perhaps prevents the development of asthma in a sub-group of infants with atopic dermatitis sensitised to grass pollen and, to a lesser extent, house dust mite. Further studies are required focusing specifically on sensitised groups to substantiate this finding. The study also highlights risk factors for asthma in infants with atopic dermatitis and indicated that early and persistent aeroallergen sensitisation confers a higher risk than later development of sensitivity.

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