The role of prebiotics in the prevention of allergies in infancy

Food allergy in childhood has been on the increase over the last decade, with the prevalence in the UK being between 6-8%. Several studies have focused on possible preventive measures and strategies: avoidance of food allergens during pregnancy, breastfeeding and weaning; and the addition of omega-3-fatty acids, antioxidants and pre- and probiotics. The gastrointestinal tract is one of the first lines of immunological defence and must be healthy to maintain an effective immune response. The concept of prebiotics, normally found in breast milk, has been introduced as a measure to improve gut health. Recent research has focussed on the use of prebiotics in the prevention of allergies in infancy.

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Key points

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1. Infants with low numbers of bifidobacteria have been shown to be more prone to infections and exhibit a reduced gut barrier against pathogenic bacteria.
2. The stimulation of bifidobacteria growth through the use of a prebiotic supplemented formula is associated with a reduction in the presence of pathogenic bacteria.
3. Studies have demonstrated that the incidence of atopic dermatitis during the first two years of life was significantly reduced in infants that received a formula with added prebiotic.

The past two decades have witnessed a steady increase in the burden of allergic disease in the UK. There are now approximately 12.5 million GP consultations per year in the UK which occur as a result of allergic disease, costing approximately £224 million[1]. There is also a general consensus that food allergy in particular has been on the increase, although this phenomenon is best described for peanut allergy. The brunt of food allergy is borne by children, with a prevalence in the UK of between 6-8%[2]. Several studies have focussed on possible preventive measures and strategies. These include the avoidance of food allergens during pregnancy, breastfeeding and weaning, and the addition of omega-3-fatty acids, antioxidants and pre-and probiotics to the diet[3-6].

The gastrointestinal tract is one of the first lines of immunological defence and must be healthy to maintain an effective immune response. The mucosal epithelium of the gastrointestinal tract is the largest surface of the infant's body where the interaction between the microflora and the immune system occurs. Hence, the newly-colonised gut flora is important for the development of the newborn's immune system[7,8]. It has therefore been suggested that the development of the infant's immune system may be favourably influenced through the colonisation of the infant's gut with 'good' bacteria[9]. Subsequently, a significant amount of research has looked at the impact of gut flora on diarrhoea, upper respiratory tract infections and also the prevention and treatment of allergies[10]. This review will focus on the current evidence available to support the use of prebiotics in the prevention and treatment of allergies.

Clinical manifestation of food allergies in childhood

Food allergies in childhood can induce different immune responses with variable clinical presentations. Reactions are classified as either IgE-mediated (immediate response), mixed IgE and cell mediated (immediate and/or delayed) or only cell mediated (intermediate – delayed reactions)[11]. Typical symptoms for each reaction are listed in **TABLE 1**.

Relationship between prebiotics and gut immunity

Breast milk remains the gold standard for infant nutrition. It is the main source of active and passive immunity in the vulnerable early months and years of life and is considered to be the most effective preventive means of reducing morbidity and mortality in children under five. Apart from containing optimal proportions of nutrients and immunomodulatory components, breast milk contains oligosaccharides – also known as prebiotics[9]. Prebiotics are defined as

> "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improve host health"[7].

Prebiotics should not be confused with

IgE mediated	
Gastrointestinal	Gastrointestinal anaphylaxis: symptoms include, vomiting, pain and/or diarrhoea
Cutaneous	Urticaria, angioedema, pruritus, morbilliform rashes and flushing
Respiratory	Acute rhino-conjunctivitis, wheezing, coughing and stridor
Generalised	Anaphylaxis
Mixed IgE and cell mediated	
Gastrointestinal	Eosinophilic oesophagitis, colitis and/or proctocolitis
Cutaneous	Atopic eczema
Respiratory	Asthma
Cell mediated	
Gastrointestinal	Food protein-induced enterocolitis, food protein-induced proctocolitis and food protein-induced enteropathy syndrome – which may present with a clinical picture of 'sepsis'
Cutaneous	CMP-induced contact dermatitis
Respiratory	Food-induced pulmonary haemosiderosis (Heiner syndrome) (rare) – pulmonary haemosiderosis or bleeding in the lower respiratory tract.

TABLE 1 Clinical symptoms of allergic reactions[12].

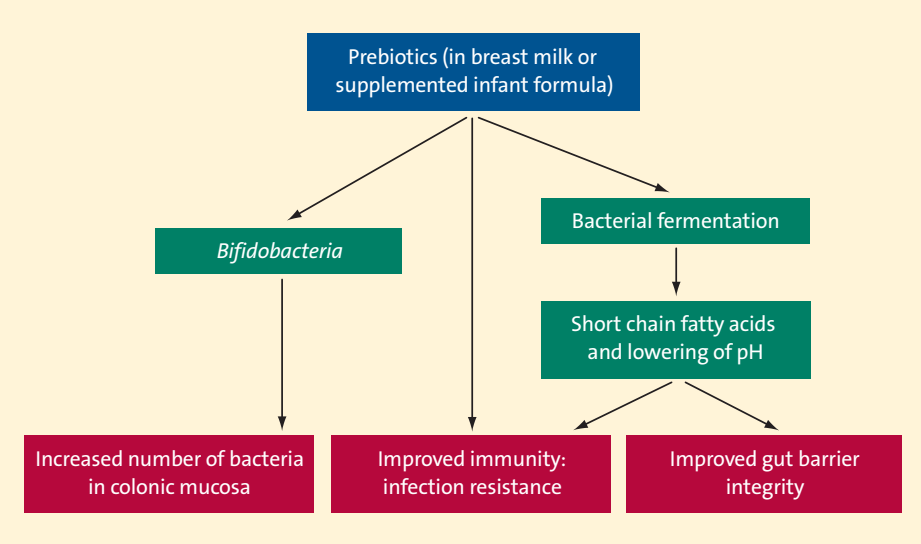

FIGURE 1 Proven effects of prebiotics (oligosaccharides) on the infants' immune system.

probiotics, which are dietary supplements containing potentially beneficial live bacteria or yeast.

Prebiotics are the third most abundant solid component in breast milk after lactose and lipids[9]. A considerable amount of human milk oligosaccharides reach the colon intact and have been found to specifically stimulate the growth of bifidobacteria, in addition to directly impacting on the immune system in the following way:

- by interacting with the intestinal epithelial cells, which stimulate the immune system[13].
- through the fermentation of the prebiotics to short chain fatty acids (e.g. acetate, butyrate, propionate), which are used as fuel for the colonocytes[14].
- by reducing the gut pH, which prevents an invasion of pathogenic bacteria[15].
- improving gut barrier function by increasing the number of good bacteria (e.g. bifidobacteria) on the colonic mucosa[10] (**FIGURE 1**).

Bifidobacteria and gut immunity

Gut bacteria can be divided into three broad categories – potentially harmful; beneficial; and those with apparently neutral or unknown effects. Beneficial gut flora are of specific interest to the development of the immune system and include lactic acid bacteria; lactobacilli, bifidobacteria and enterococcus[16]. These bacteria are found in the highest concentration in the large intestine (**TABLE 2**).

Both lactobacilli and bifidobacteria have been shown to enhance the infant's immunity by:

- Increasing the mucosal barrier function
- Participating in degradation of protein antigens
- Competing with pathogenic bacteria
- Promoting early immune system maturation[17].

It has been found that breastfed infants develop an intestinal flora in which bifidobacteria dominate. In contrast, formula-fed infants develop an intestinal flora comparable to that found later in life, with enterobacteriaceae, enterococci, bifidobacteria, bacteroides and *Clostridium difficile*[18,19]. Infants with low numbers of bifidobacteria have been shown to be more prone to infections and exhibit a reduced gut barrier against pathogenic bacteria[20]. Studies have also suggested that allergic children have lower counts of bifidobacteria, lactobacilli and enterococci and greater colonisation of pathogenic bacteria[9]. A gut predominantly colonised with bifodobacteria is therefore of benefit to the immune system of the infant.

Breast milk contains up to 1g/100mL of a unique mixture of oligosaccharides[18]. The structure of oligosaccharides in human milk is very complex and virtually resistant to digestion[21]. Certain infant formulas seek to mimic the mixture of oligosaccharides in breast milk. Currently most research has focussed on the addition of long chain fructo-oligosaccharides and galacto-oligosaccharides into infant formulas[22]. Boehm et al demonstrated that a 90:10 mixture of short chain galacto-oligosaccharides to long chain fructo-oligosaccharides (GOS/FOS), is effective in achieving a gut flora similar to that of breast fed infants[8,18]. This prebiotic mixture (0.8g/100 mL, Nutricia) has recently been introduced in selected term, preterm and hypoallergenic formulas (e.g. Cow & Gate as Prebiotic Care and Milupa Aptamil as Immunofortis). The stimulation of bifidobacteria growth through the use of a prebiotic-supplemented formula is also associated with a reduction in the presence of pathogenic bacteria, like *Staphylococcous aureus, Pseudomonas aeruginosa* and *Clostridium difficile* [23,24]. The incidence of diarrhoea, as well as recurrent upper respiratory tract infections, was also significantly lower in infants fed with prebiotic formula when compared to a standard formula without prebiotics[18,19].

Gastrointestinal Tract	Bacterial flora	Number of bacteria
Stomach	Streptococci Staphylococci Lactobacilli Some Fungi	$<10^3$ CFU/mL
Duodenum	Streptococci Staphylococci Lactobacilli	$<10^3 - 10^4$ CFU/mL
Ileum	Coliforms Bacteroides Bifidobacterium Clostridium	$<10^6 - 10^{10}$ CFU/mL
Colon	Bacteroides Bifidobacterium Clostridium Enterococci	$<10^6 - 10^{10}$ CFU/mL

TABLE 2 Gut flora species in the gastrointestinal tract.

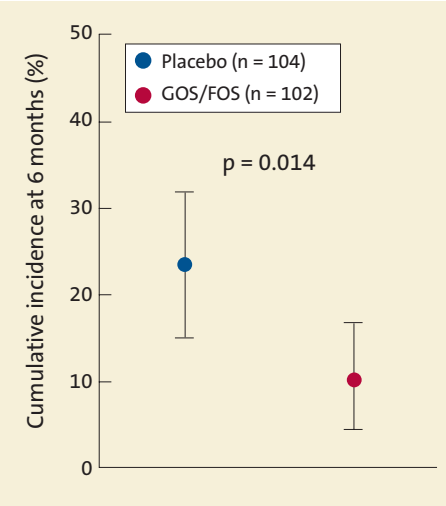

FIGURE 2 Cummulative incidence of atopic dermatitis at six months of age in the group fed a formula with prebiotics, compared with a placebo group[33].

Preterm infant formula feeding is commonly associated with hard stools, delayed gastrointestinal transport and constipation. Supplementing preterm infant formulas with the oligosaccharide mixture resulted in a reduced stool viscosity and accelerated gastrointestinal transport[21]. Studies have also attempted to establish the use of prebiotics in preventing necrotising enterocolitis, a serious bacterial infection in the intestine affecting about 10% of neonates[25]. Initial studies look promising and might provide more potential applications for prebiotics in the preterm in future.

The use of prebiotics in childhood allergy

Significant differences in the composition of the intestinal flora between allergic and non-allergic infants have been found very early in life, before the development of any clinical manifestation of allergies[26,27]. A low prevalence of bifidobacteria was found in the allergic infant, whereas the counts of pathogenic bacteria like *Staphylococcus aureus, Enterobacteria* and *Clostridium difficile* were higher[17]. Experimental studies indicate that bifidobacteria induce T-helper cell 1 (TH1) and T-regulatory cell type cytokines like γ-inteferon (IFN-γ), interleukin-12 and interleukin-10[9]. It has been shown that the expression of allergic disease results from an imbalance between the activation and suppression of TH1 and T-helper cell 2 (TH2) responses. It is thought that TH1 activation has a positive (preventative) effect on the development of allergies[28].

The premature or low birthweight infant has an immature gastrointestinal tract with an increased permeability and often raised levels of pathogenic bacteria in the gastrointestinal tract[29]. It was therefore thought that premature infants were more prone to allergies. However, Liem et al[30] has found that prematurity and low birth weight are not associated with a change in risk for development of food allergy in childhood. Furthermore, this research suggests the possibility that introduction of highly allergenic foods early in life, such as peanuts, might actually prevent the development of allergy.

Extensively hydrolysed formulas have been used for treating cows milk protein allergy for almost 60 years[31] and more recently have been introduced for the prevention of allergies with variable success[5,32]. The modification of extensively hydrolysed formulas with the addition of prebiotics therefore has the potential to further reduce the incidence of allergies by modifying the gut flora[9]. Research was performed by Moro et al in 2006, in a double blind randomised controlled study providing atopic infants within the first two weeks of life with an extensively hydrolysed whey formula, with or without prebiotics[33]. Infants continued on this formula until six months of age. This study demonstrated that the incidence of atopic dermatitis (AD) during the first six months of life was significantly reduced at six months of age in the group receiving the prebiotic mixture[17,33] (**FIGURE 2**). Other studies have found similar results[9,17].

Many have questioned whether this preventative effect seen at six months of age, would persist beyond one year of age. Recently, results for the two year follow-up study were presented. It was found that the cumulative incidence of AD during the follow-up period was 25% in the placebo and 12.1% in the intervention group ($p<0.05$). In addition the incidence of bronchial symptoms and acute allergic cutaneous reactions was 17.6% and 11.8% in the placebo group versus 6.3% and 0.0% in the intervention group[34]. During the follow-up period, the total number of episodes of infections, respiratory infections, otitis media and diarrhoea were also lower in the GOS/FOS group[34]. In addition the infant formula containing the GOS/FOS mixture lead to a microbiota with higher levels of faecal bifidobacteria

FIGURE 2 An infant with severe atopic dermatitis. *Photo courtesy of the National Eczema Society.*

and higher levels of faecal sIgA , suggesting an effect on mucosal immunity[35]. This is compelling data in that it shows for the first time that this preventative effect is extended beyond infancy in atopic children.

Conclusion

The infant's gut flora plays a pivotal role in the development and maintenance of a healthy immune system[26]. Breast milk is rich in prebiotics which are capable of positively influencing the growth of specific gut flora. Research has enabled the development of a unique prebiotic mixture, which mimics that of breast milk. Studies have suggested that this prebiotic mixture has a positive effect on the prevention of AD, cutaneous reactions and bronchial symptoms[24,33]. In the absence of breast milk, the use of an extensively hydrolysed formula with prebiotics seems to benefit atopic infants by favourably modulating the bacterial flora and thereby reducing the incidence of allergies.

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