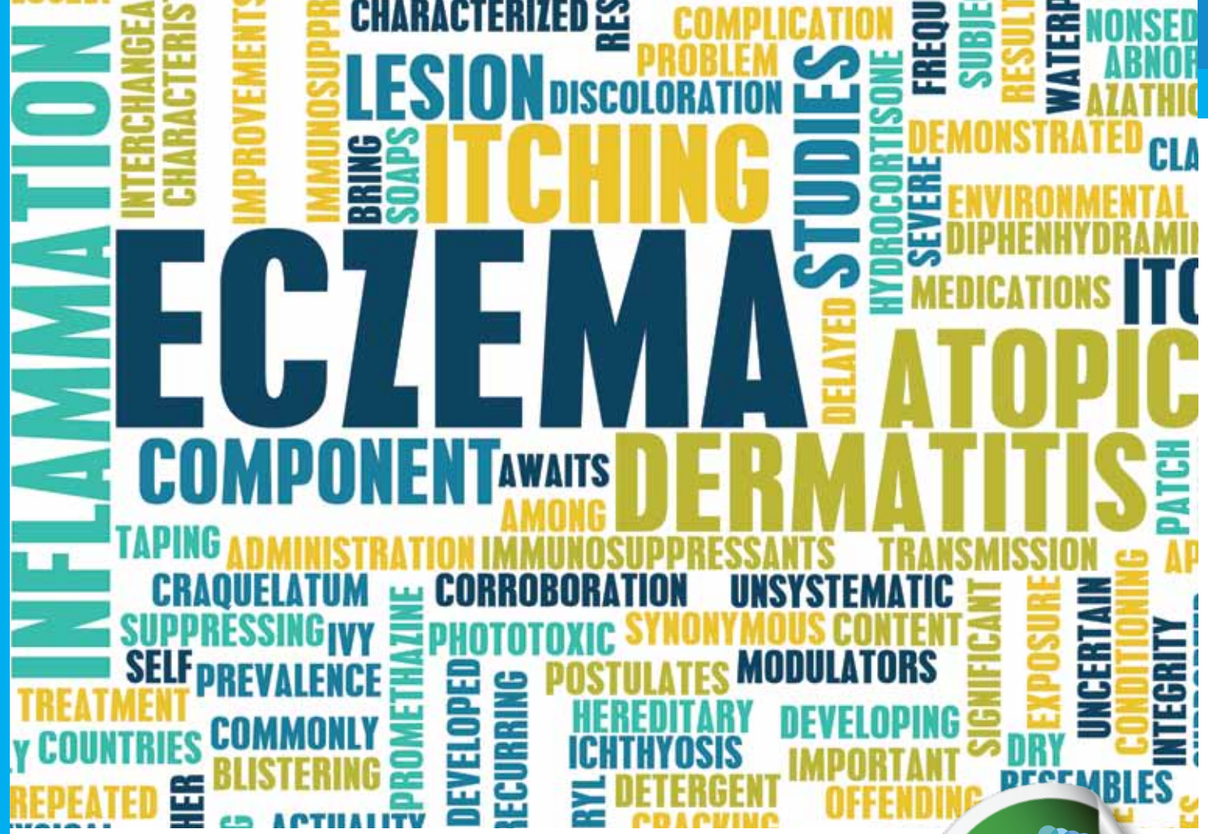

PROBIOTICS AND ALLERGIES

Dr Mayur Joshi reviews the growing evidence base for probiotic use in the prevention and management of allergic diseases.

LEARNING OUTCOMES

The aim of this CPD article is to improve understanding of how probiotics can be beneficial in preventing and managing allergic disease. Intended learning objectives are:

- **Learn about the importance of the bowel bacterial population in regulating the immune system and their role in the development of allergic disease.**
- **Improve understanding of the basic mechanisms of action of probiotics and how they can be used in allergic disease.**
- **Develop a basic understanding of the evidence base underpinning the use of probiotics in allergic disease.**

Allergic disease occurs as a result of hypersensitivity of the body's immune system to otherwise harmless stimuli (allergens). The presence of allergy is multifactorial, with hereditary components as important as environmental triggers in the development of disease. The Western world has seen an increase in the prevalence of allergic disease, with up to 20% of the population affected by some sort of allergy[1].

The 'hygiene hypothesis' states that the decreasing incidence of infections in Western countries and, more recently, in developing countries, is the origin of the increasing incidence of both autoimmune and allergic diseases. The decreased exposure to allergens in an increasingly sterile environment at a young age predicates to an inherent change in our innate immune system, leading to an increased prevalence of allergic disease in adulthood. This is related to antibiotic usage, vaccinations, improved hygiene, and consumption of almost sterile food, which reduces our contact with microbes[2].

Clearly it is not appropriate to change current hygiene practices, so probiotics represent a useful way of exposing the body to microbes, thereby stimulating the immune system and improving responses to allergens.

FUNCTION OF GUT BACTERIA

Up to 1000 bacterial species inhabit the bowel, with concentrations increasing further down the intestinal tract[3]. In the most distal parts of the colon, the concentrations reach approximately 1011 cells/g of luminal contents[4]. In fact, there are approximately 10 times more microbial cells inhabiting the body than there are cells making up the human body itself,[5, 6,] with the mass of bacterial cells within the colon weighing up to 1.5kg[7], similar in weight to the liver. In addition, the collective genetic information of the gut microbiota (the microbiome), contains over 100 times the number of genes in the human genome, and as such this bacterial 'organ' has a multitude of functions that contribute to overall health[8]. Disruptions in the microbial population of the gut (or dysbiosis) can, therefore, have profound effects on health and disease.

The human gastrointestinal tract contains the largest mass of immune tissue in the body; in fact, Gut-Associated Lymphoid Tissue (GALT) is responsible for 60% of antibody secretion in the body[9]. The microflora of the gut has a complex relationship with the immune system and is able to exert local and systemic effects[10].

The gut bacterial population has a complex relationship with the GALT, through its interactions with specific immunomodulatory cells. These cells are able to influence the innate and adaptive immune response through up-regulation and down-regulation of specific cytokines, inflammatory markers and other immune cells[1]. In this way, they act as primers for the immune system and can therefore heighten or dampen allergic hypersensitivity reactions.

It is this complex relationship with the immune tissue in the gut that forms the basis for the use of probiotics in the prevention and management of certain allergic conditions.

TIMEOUT ACTIVITY A

It is important to note that the relationship between the bowel bacteria and the immune system starts with the Gut Associated Lymphoid Tissue. Not only that, it is extremely complex and has far-reaching effects on the immune system in general and not just within the bowel.

- **Think about the types of allergic disease that are common in childhood and compare the incidences with less-developed countries. See if there is a difference.**

PROBIOTICS

The accepted definition of a probiotic is live microorganisms that, when administered in adequate amounts, confers a health benefit on the host[11].

The beneficial effects of probiotics have been documented for over a century now, including the potential for probiotics to be used to boost and/or support the immune function and, in particular, their ability to help manage allergic disease. Research has increased greatly in recent decades and there is good evidence to suggest that probiotics can be used in the management of allergic disease.

MECHANISM OF ACTION

Multiple mechanisms of action of probiotics have been postulated and indeed identified as to how these living organisms produce their beneficial effects at a local and systemic level[12]. The overall concept is based on a redressing of any imbalance within the gut, displacing pathogenic bacteria with beneficial species. This also helps to increase microbial diversity and increase numbers of beneficial bacteria by helping to eliminate harmful bacteria.

The way they achieve this is through a number of mechanisms that have been summarised in the table below.

Modulation of Intestinal Ecosystem

↑ Beneficial bacteria

↓ Gut pH

Stimulation of gut peristalis

↓ Harmful substances

Modulation of Immune System

Stimulation of local & systemic systems

Enhanced defence response (↑ IgA, CD4+ & CD8+ T cells, NK cell activity, adjuvant effect)

DOWN REGULATION OF INFLAMMATORY & ALLERGIC RESPONSE

Improved colonisation resistance

↑ Competitive exclusion (e.g. for nutrients, adhesion sites)

↓ Harmful microbial species

↑ Epithelial cell mucin synthesis

Enhanced intestinal barrier function

Summary of main mechanisms of action of probiotic bacteria (adapted from Baker et al 2009)[13]

Not all probiotic strains will possess all of the above properties (and indeed this overview does not represent the full spectrum

of properties), but it serves to demonstrate the many ways in which they are able to displace pathogenic bacteria before exerting their local and systemic effects. In addition, it is thought that different strains of probiotic bacteria work together to exert a greater effect than a single strain, resulting in much improved clinical outcomes when using a multi-strain formulation[14]. This trend has been demonstrated right the way through scientific studies of probiotics; from laboratory studies to animal models and human clinical trials, the use of a multi-strain probiotic formulation has been shown to be advantageous[15].

What we have discussed above forms the basis for the theory that the composition of colonising bacteria is critical to the correct development of a balanced immune response. This is further supported by the fact that clinical studies that compared the gut microflora in children from countries with a low incidence of allergic disease to those from countries with a high incidence, have shown significant differences. A reduction in lactobacilli, bifidobacteria and enterococci, and higher numbers of Clostridia and Syaphylococcus aureus in infants that developed allergy has been demonstrated[16].

TIMEOUT ACTIVITY B

It is important to understand the large variety of potential modes of action of probiotic bacteria (as summarised above) and that individual strains will possess different combinations of properties. In addition they can work together to exert even more effects on a local and systemic level. Therefore, the take-home message is to appreciate the importance of multi-strain formulations when considering a probiotic.

• Look into and think about different probiotic formulations (yoghurt, milk drink, liquid form and capsules). What are the pros and cons of each formulation?

ATOPIC DERMATITIS

A randomised, double-blind, placebo-controlled study with 40 infants and children with mild to severe Atopic Dermatitis (AD) showed a significantly greater reduction in the Severity Scoring of Atopic Dermatitis (SCORAD) index than the placebo group. Both groups received optimal skin care treatment for AD, but the probiotic group showed an improvement in symptom severity[17].

A Korean population-based study showed that the administration of probiotics prenatally and post-natally significantly reduced the risk of developing AD in the first year of life[18]. This effect was particularly pronounced in those infants that were identified as high risk for the development of allergic disease.

An extensive meta-analysis of data available for the use of probiotic supplementation in the prevention of AD in children was performed in 2012[19]. They were able to show that the use of probiotics significantly reduced the occurrence of AD, particularly in children administered probiotics peri-natally. The evidence overwhelmingly supports the use of probiotics peri-natally to prevent the development of atopic dermatitis in later life[20, 21, 22].

ALLERGIC RHINITIS

A 2013 review paper demonstrated that probiotics have been shown to have a beneficial effect in the treatment and prevention of allergic rhinitis in both children and adults[23]. They also found that these improvements correlate to improvements in blood markers of inflammation and allergy. They found evidence to show that probiotics improved the nasal symptoms of allergic rhinitis.

These findings further backed up a study by Wassenger et al in 2011 that found that probiotics taken for a month actually reduced symptoms of nasal congestion and itching in allergic rhinitis sufferers[24]. In addition, they showed that the probiotics reduced specific immune markers, suggesting that there was a systemic effect.

The 2013 review suggested that the evidence points towards the use of probiotics in an ongoing fashion to confer a baseline protective effect, and they concluded that there is little or no evidence to show that taking probiotics in early life can actually prevent the development of allergic rhinitis later on.

ASTHMA

There is less promising evidence to show that the use of probiotics can help to treat or prevent asthma, or even reduce the severity of symptoms. This seems to be linked to the heterogeneity of the probiotics used as opposed to an inherent deficiency in the way in which probiotics may help.

A trial looking at the use of probiotics in patients with atopic dermatitis who had decreased pulmonary function and peak expiratory flow rates, found that the probiotics significantly improved asthma-like symptoms[25]. Another study found that probiotics improved clinical symptom scores for asthma and allergic rhinitis[26].

These two studies show that there is promise for the use of probiotics in asthma, but more clinical trial work needs to be done before their use can be fully-recommended as part of the management of asthma.

FOOD ALLERGY

Similarly, the evidence for the use of probiotics in the treatment or prevention of food allergies is contradictory, although very few studies have in fact been performed in this area. Castelazzi et al 2011 found several animal models suggesting there may be a role for probiotics in food allergy, but extensive further research is required in this area before any specific recommendations can be made[27].

CONCLUSION

As with most probiotic research, the evidence for the use of probiotics in allergic disease is dependent on a number of factors. These include the type of probiotic used, the dosing, the numbers

of strains within a mixture and the condition they are being applied to. There is clearly excellent evidence to show that there is a role for probiotics in atopic dermatitis and allergic rhinitis, but the evidence is not as strong in other conditions.

Importantly, probiotics have overwhelmingly been shown to be safe, so their use can be extensively investigated in the future. There is vast theoretical and technical evidence to support their use and the clinical evidence is growing. With this in mind, it is not outlandish to think that in the near future we may see probiotic products specifically developed for their use in allergic disease.

TIMEOUT ACTIVITY C

Think about the types of patients that you commonly deal with and what sorts of allergies they tend to present with. We have discussed a few conditions above, but there may be a role for probiotics in other allergic conditions that you may come across.

• Research the specific conditions and see whether there is any clinical evidence to suggest that probiotics may have a role.

As always, it is worth discussing with colleagues whether they recommend the use of probiotics. If they do, in what particular conditions are they recommending them? If not, are they aware of the evidence and would they consider it?

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