The custom clearance of prebiotics and probiotics in food allergy prevention.

Once upon a time...

If at the beginning of the last century allergy was considered a “white elephant”\(^1\), today it affects large strata of the population, peaking in the industrialized world but with an increasing incidence in emerging countries. After the increase in respiratory allergy in 1960-1990, there has been a remarkable increase in food allergy, which has now reached epidemic numbers\(^2\). Australian data indicate that more than 10% of 1-year-old infants in the 2010’s have challenge-proven IgE-mediated food allergy to one of the common allergenic foods of infancy, with sensitization reported at 8.9% for peanut, 16.5% for egg white, and 5.6% for cow's milk\(^3\). Given the epidemic rising of the disease, many ways of action hypothesized to prevent its development. The most followed are the following:

1) early administration of bacterial products (most studies are on probiotics)\(^4\)
2) early moisturizing in infants at risk for AD\(^4\)
3) administration of HA formulae
4) early exposure to allergenic foods (peanut and egg)
5) immunotherapy (IT) as primary intervention\(^4\).

In this article, we will review hypothesis (1).

Probiotics, prebiotics and food allergy prevention: clinical data

One of the theories used to explain the allergy outbreak is the hygiene hypothesis. It proposes that, due to modern public health practices, individuals living in the industrialized world experience a relative deficiency in immune stimulation by microbes, rendering them vulnerable to the development of allergic hypersensitivities and their associated diseases\(^2\). If the allergy epidemic, as other inflammatory diseases, are linked to ‘dysbiosis’, the addition of probiotics and/or prebiotics to the infants’ diet could prevent the development of allergy by restoring ‘eubiosis’\(^5\).

Probiotics (defined as live microorganisms able to confer a health benefit on the host) may exert their effects both systemically and locally. Systemic effects include enhancing of monocyte and IgA activity in enterocytes as well as in other tissues, like respiratory tract. Local effects may be a stimulation of immune, dendritic, and epithelial cells. The sum of these effects has as the ultimate goal of achieving tolerance\(^4\). Starting in early 2000’s, research has been targeted to evaluate if probiotic administration exert local and systemic immunological effects on the development of various aspects of allergic diseases. The first preventive study hypothesizing that probiotics can reduce allergy assessed infants born to 159 pregnant women with history of atopy in the foetus’ parents or siblings. At 2-4 week prenatally and for 6 months during lactation, mothers were given a placebo or *Lactobacillus GG* (LGG, 10,000 CFU daily). Non-breastfed infants were given the material directly orally. The infants were followed for several years. Among 132 children who completed the follow-up, AD incidence – but not food allergy incidence – in the probiotic group was one-half of that in the placebo group\(^6\).

These results paved the way to many studies with different probiotics and administration schedules. Their outcomes included AD, food allergy, pediatric asthma and allergic rhinitis. These pioneering studies raised great interest on the subject, providing conflicting results (reviewed in \(^7\)). New and more specific questions aroused, trying to determine the role (if any) of probiotic supplementation and the development of allergic diseases. Some of the issues: which probiotic should be used? At which dose? When should it be given? For how long? Have they a class effect?
Probiotics, prebiotics and food allergy prevention: metanalyses

These questions became soon too complicate to be answered univocally, and the growth of the literature allowed the metanalysis of data7,8,9. The metanalyses published up to 2014 concluded that probiotics may only obtain a modest reduction in AD and allergic sensitization, and guidelines indicated that they should not be used in the prevention of allergic diseases. In 2015, two metanalyses evaluated again the topic10,11. The first, targeted to evaluate the effect of probiotic supplementation during pregnancy and early infancy in prevention of atopic disease, localized 17 studies, reporting data from 4755 children (2381 in the probiotic group and 2374 in the control group). It confirmed that infants treated with probiotics had a significantly lower RR for eczema compared to controls (RR 0.78 [95% CI: 0.69–0.89], P = 0.0003). It indicated that mixtures of probiotics might be more effective than single strains (RR 0.54 [95% CI: 0.43–0.68]). No significant differences were found for asthma (RR 0.99 [95% CI: 0.77–1.27]), wheezing (RR 1.02 [95% CI: 0.89–1.17]) or rhinoconjunctivitis (RR 0.91 [95% CI: 0.67–1.23])10. The second, produced by our group to inform the World Allergy Organization GuideLines on Allergic Disease Prevention (GLAD-P), evaluated probiotics in two different forms: direct (probiotics given to infants as an oral supplement or in the context of milk formulae in non-breastfed infants) and indirect (probiotics given to mothers during breastfeeding or pregnancy). The assessed outcomes were eczema, asthma and/or wheezing, food allergy, allergic rhinitis, adverse effects, and severe adverse effects. Twenty-nine studies corresponded to the search criteria, but only nine gave direct evidences. Twenty assessed either pregnancy and infancy (8 studies), pregnancy and breastfeeding (4 studies), or pregnancy, breastfeeding and infancy together (eight studies). Even with a moderate-to-serious risk of bias, (i.e. randomization process and the number of patients lost to follow-up), the effects on the development of eczema resulted significant for all three interventions. The reduction of the risk of eczema in infants was:

- 9 per 100 (RR 0.72 [95%CI 0.60-0.86]) when given during pregnancy
- 16 per 100 (RR 0.58, [95%CI 0.47-0.72]) when given during breastfeeding
- 5 per 100 (RR 0.82, [95%CI 0.70-0.96]) when given during infancy.

No effect was found on other allergy outcomes. No specific strain reached the number of events allowing attributing a specific effect. This gave occasion for a comment contending the fact that, as clinicians must act on precise indications, they need data on individual probiotic strains, and clinicians should refrain from pooling data on different probiotics12. These authors did a metanalysis specifically on LGG, concurring in the conclusion that, even if it is the most-studied probiotic in allergy prevention, it is not possible to give a univocal indication for it13.

The GLAD-p recommendations

Based on this metanalysis13, the WAO guideline panel suggested recommendations for probiotics use in the context of allergy prevention. Infants “at high-risk for allergic disease”, defined as having a biological parent or sibling with existing or history of allergic rhinitis, asthma, eczema, and/or food allergy, would profit of a net benefit resulting primarily – but not exclusively – from prevention of eczema if probiotics are given in the following situations:

- pregnant women at high risk for allergy in their children
women who breastfeed infants at high risk of developing allergy
infants at high risk of developing allergies\textsuperscript{14}.

All recommendations are conditional, and thus non-mandatory.

The GLAD-p elaborated also recommendations for the use of prebiotics in allergy prevention. A specific metaanalysis on prebiotic use was not able to identify studies in pregnant and breastfeeding mothers in order to prevent allergy in their offspring. For infants, given the extant literature prebiotic supplementation was conditionally suggested in all not-exclusively breastfed infants, both at high and at low risk for developing allergy (low certainty of evidence)\textsuperscript{15}.

Conclusions

Waiting for the information from more powerful studies\textsuperscript{16}, the idea that supplemental probiotic bacteria can be used to manipulate allergy homeostatic mechanism is today more than a hypothesis. The effect of supplemented probiotic bacteria on the evolutionarily conserved homoeostatic mechanisms is only initially been addressed, and the question of the use of pro- and pre-biotics for allergy prevention is far from being completely elucidated\textsuperscript{7}. Non-systematic reviews casted doubts on the real effects of these approaches, and guidelines remained skeptical about the real opportunity to suggest the use of probiotics or prebiotics for allergy prevention\textsuperscript{9}. Despite this, the current information is enough to tell us that ‘something is there’. In this situation, we would expect more non-interventional studies on the microbiome of children prone to develop food allergy and/or AD vs. healthy children, and many more interventional studies. However, from 2015 to suggest the use of probiotics and/or prebiotics for the prevention of allergy in infants is no longer a scientific blasphemy.
1 Vaughan VT. Primer of allergy. Mosby, St Louis MO, 1939
4 Van Bever HC. Primary prevention of allergy: will it soon become a reality? Pediatric Allergy Immunol 2016;27:6-12
7 The WAO Special Committee on Food Allergy. Clinical Use of Probiotics for Paediatric Allergy -CUPPA- A WAO position paper, WAO Journal 2012; 5:148–67
12 Szajewska A. Recommendations on probiotics in allergy prevention should not be based on pooling data from different strains. J Allergy Clin Immunol. 2015; 136:1422-3