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ORIGINAL ARTICLE

Practical update guide - prevention of allergic diseases

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Abstract

The authors present in the form of questions and answers an update text on various allergic diseases of childhood.

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INTRODUCTION

The study of allergic diseases is a topic of interest to all society, in regard to both public health and everyday life aspects. It is estimated that more than a quarter of the Brazilian population has some type of allergy, especially among children and adolescents[1]. The progressive increase in the number of allergy patients leads to high costs to the economy because of hospital admissions and absenteeism from school and work. It is more difficult to measure the damage to quality of life and the risk to the optimal growth and development of atopic pediatric patients. All these factors have led to an intense search for effective preventive measures at primary and secondary levels[2].

Why have allergic diseases increased considerably in recent years?

One of the hypotheses studied to explain the progressive increase in the prevalence of allergic diseases in industrialized countries is the hygiene theory, which assumes that the effective control of infectious and parasitic diseases, increased hygiene care, and vaccination have left the immune system "unoccupied," with increased activation of Th2-lymphocyte clones, whose cytokine secretion stimulates IgE production and the accumulation of eosinophils, responsible for the IgE-mediated allergic response[3].

In recent years, the theory of developmental origins of health and disease (DOHaD), a line of study for chronic diseases, has highlighted the importance of epigenetic factors in the development of allergic diseases, particularly asthma and food allergies[4]. The phenotypic expression of allergic diseases appears to be regulated by the interaction between the genotype (genetic inheritance) and environmental factors-viruses, bacteria, environmental pollutants, maternal dietary factors-capable of acting on DNA methylation with chemical chromosomal modifications, histone modifications, and consequent change in gene transcription and phenotype[4-6].

With regard to the immune system, there is a decrease in the production of interferon-g, alteration of innate immunity, and regulatory T (Treg) cells (FOXP3 genes) with a predominant Th2 response. Some epigenetic factors are already well established, such as in utero smoke exposure and the development of allergic diseases[5-7].

Can allergic disease be effectively prevented from appearing (primary prevention)?

Primary prevention of allergy for all children should be the ideal goal. However, in this case, measures should promote health in a comprehensive way, be inexpensive, and target the general population[4]. This preventive objective at the level of the general population can be difficult to achieve. Costly measures and/or measures that are difficult to implement should be restricted to groups at a high risk for atopic disease while guaranteeing that there will be no detrimental impact on the child's full growth and development[2-4].

Possible strategies include early identification of children at higher risk of allergic diseases and focusing on the secondary prevention among those in the initial stages of the atopic march[8].

The recent medical literature seeks to find characteristics or biomarkers that detect those individuals at high risk of atopic diseases for the implementation of primary prevention measures. A child at high risk for developing an allergic disease is one who has at least one first-degree relative (father, mother, or sibling) with documented allergic disease (atopic dermatitis, allergic asthma, allergic rhinitis, or food allergy)[8].

Unfortunately, current clinical practice still focuses primarily on secondary prevention, provided it is in place as soon as the first signs and symptoms of the disease appear to allow the diagnosis to be established. This form of prevention can and has been used as an attempt to inhibit the atopic march, often present in young patients. It is important to note that atopy, because it is a genetic predisposition of the individual, cannot be modified at the current stage of knowledge. Allergies, however, can be inhibited or decreased provided that preventive measures are implemented at the primary, secondary, and tertiary levels, which are defined as follows:

a) **Primary Prevention:** the elimination of any risk factor or etiological agent before allergen sensitization (e.g., use of hydrolyzed infant formulas in the diet of high-risk infants to prevent food allergy and/or severe atopic dermatitis);
b) **Secondary Prevention:** it is carried out with the purpose of decreasing post-sensitization disease development; and
c) **Tertiary prevention:** it is aimed at decreasing symptoms after clinical manifestation of allergic disease.

Primary Allergy Prevention-intervention opportunities-who, how, and when

It is not yet absolutely clear which primary prevention actions are effective, nor which is the ideal period for these measures should be initiated. Strong arguments suggest that sensitization to food allergens and even to inhalants may occur while still in utero, but preventive measures taken exclusively in the prenatal period have been ineffective in decreasing the prevalence of allergic diseases. Measures that have been shown to be effective in the prenatal period should continue to be implemented and extended for a period of extrauterine life, which casts doubt on the critical time at which the benefit is most likely to occur[5,6,9].

It is possible that a window of opportunity for immune modulation occurs during lymphoid development. This window should be used appropriately with persistent preventive measures during this critical period[5,6,9].

Primary prevention includes a comprehensive and transdisciplinary view of the health-disease process and is ideal. However, it covers an entire process that is very costly and difficult to implement in the everyday life of the general population. To improve the cost-benefit ratio of primary prevention, there is a strong argument in favor of the target population of prophylactic actions being a specific group.

Various prevention and intervention measures have been evaluated in terms of efficacy, such as reduction of exposure to household allergens, exclusion of pets, elimination of passive smoking, and dietary measures-exclusive breastfeeding and use of hydrolyzed infant formulas and probiotics.

It is important to emphasize that some of these measures, even if they are effective, will be indicated in secondary prevention. They will only be indicated in primary prevention for children at a high risk of developing allergic diseases. Relevant allergic disease prevention strategies described in the literature are reviewed and discussed in this guide.

Primary prevention of respiratory allergies-asthma and rhinitis

The prevalence of allergic diseases is increasing worldwide. However, genetic modifications in the population occur over a long span of time and are not sufficient to explain this increase. The major environmental and dietary changes in populations in recent decades have shifted the focus of primary preventions to interventions on modifiable factors in these two areas, including during the fetal period and early life[10,11].

Recent knowledge that the immune system may be influenced by environmental exposures and especially by the exposure to external microorganisms and to the human microbiota itself has provided new directions in the prevention of allergic diseases.

Few studies show significant evidence regarding the primary prevention of asthma and rhinitis. Below is a description of some aspects related to environmental factors, diet, and microbiota, and development or protection of asthma and rhinitis, always bearing in mind that these factors are not independent and can coexist in the modification of these allergic diseases.

Environmental factors and their relationship with Asthma and Rhinitis

Household allergens are of particular interest with regard to the origin and persistence of asthma and rhinitis because of exposure to them is constant and occurs from birth. The aeroallergens most closely involved in this relationship are those present in domestic dust *(Dermatophagoides pteronyssinus, Blomia tropicalis)*, animal hair (dogs and cats), cockroaches, and fungi. Sensitization to these allergens, in addition to early wheezing triggered by rhinovirus, is strongly related to the development of asthma and rhinitis, especially if it occurs before the age of 5 years[12-15].

The development of asthma and rhinitis is not only related to sensitization to aeroallergens, it also depends on other factors, including genetic predisposition and the possibility of mites stimulating innate immunity[16-18]. The risk of developing asthma and rhinitis can also be related to the levels of allergens to which the child is exposed, with very low or very high levels having a protective effect and intermediate levels causing allergy[19]; the causes of these differences are not known. Other potential sensitization routes are the following: via placenta, breast milk, and skin, which would explain atopic march when skin with atopic dermatitis (AD) facilitates the penetration of aeroallergens.

The presence of high concentrations of allergens from cockroaches and other animals such as rats are related to the higher prevalence and severity of early wheezing and persistence and severity of asthma in large towns and cities[20].

There is still controversy regarding furry animals (dogs and cats), despite several systematic reviews on the subject [21-23]. Some authors point out the lack of a relationship between early exposure to dogs and cats and the development of asthma,[22] and even some degree of protection against asthma during exposure to cats; the general evidence does not show an association between the risk of exposure to the allergens of these animals and the onset of asthma.

The relationship between exposure to fungi and the risk of developing asthma and rhinitis is also controversial, with some studies reporting a positive relationship when mold is smelled or seen and showing that the amount of beta-glucan in the environment may be an important protective or risk factor[24,25].

Pollutants outside and inside domestic environments are related to the health of exposed populations and the World Health Organization warns that 92% of the world's population lives in environments with levels of $PM_{2.5}$ (particulate matter with a diameter of < 2.5 microns) higher than the guideline value. The upper and lower airways are the most exposed areas and suffer undesirable consequences, including in lung development, already from its intrauterine formation. There is also an increase in the incidence of adolescent asthma and chronic obstructive pulmonary disease (COPD)[26,27] in adults. The smoke from tobacco is the number one pollutant of greatest potential for primary prevention. In the United States, an estimated 15 million children between the ages of 3 and 11 years are exposed to tobacco and at increased risk for allergic sensitization and asthma[28-30].

Factors related to Diet

Easy access to food and the ingestion of processed foods to the detriment of natural products has prompted the population to ingest smaller amounts of fiber, antioxidant products, and higher amounts of polyunsaturated fatty acids (omega-6), which has been related to the increase of inflammation-based diseases, including asthma.

A recent systematic review[31] showed evidence of the benefits of consuming fresh fruit and antioxidant vitamins (vitamin C and E) in the protection against asthma, especially during early childhood; further randomized, placebo-controlled studies are needed to confirm this evidence.

The limitations of many studies attempting to relate diet to the occurrence and/or prevention of asthma stem from the method used to collect dietary data, either using 24-h intake journals, food frequency questionnaires, or a complex combination of foods. Other aspects to be taken into account are the mother's diet during pregnancy, exclusive breastfeeding, and formula feeding. With regard to asthma and rhinitis, few studies show important evidence of their primary prevention.

Maternal Diet during Pregnancy

It remains controversial whether the type and amount of food consumed by a pregnant woman can influence the development of allergic diseases in her child. Protein, carbohydrate, and milk intake were negatively correlated with the onset of allergic diseases in high-risk infants. On the other hand, high intake of fats, vegetable oil, celery, citrus fruits, bell pepper, and nuts were associated with increased sensitization.

A systematic review and meta-analysis showed that a maternal diet rich in fruits and vegetables (as well as a Mediterranean style diet) prevents sensitization and development of asthma. However, because of the poor quality of the studies evaluated, no concrete recommendations can be made. No maternal diet is indisputably effective as a form of prevention of primary allergy in children. The pregnant woman's diet should be healthy and balanced, as it affects the baby's health. Restriction of food allergens is only justified if the mother is truly allergic to certain foods[32].

Breastfeeding

The impact of breastfeeding on allergy risk is difficult to establish because no randomized clinical trials have been conducted, for ethical reasons. As a gold standard for infant nutrition, human milk "per se" is not a "dietary intervention" for primary prevention of allergies; however, human breast milk is less allergenic than the standard cow milk formula.

Systematic reviews and meta-analyses on breastfeeding in the prevention of allergic diseases have shown conflicting results. Three systematic reviews have indicated that breastfeeding has preventive effects on asthma. The most recent systematic review included 117 studies (57 cohort, 47 cross-sectional, 13 case-control studies) on breastfeeding among children in the general population. The results suggest that exclusive breastfeeding for at least 3 months is associated with a reduction in the incidence of asthma in children aged 0-2 years, compared to exclusive breastfeeding for < 3 months**.** Exclusive breastfeeding for at least 3-6 months is recommended to prevent asthma (strong recommendation/evidence of moderate quality)[33,34].

In high-risk infants who cannot be breastfed, or when breast milk is not available, partially hydrolyzed whey formula or hydrolyzed casein formula are recommended for at least 6 months to prevent allergies (weak recommendation/evidence of moderate quality). In these cases, amino acid-based milk formulas, organic cow's milk formulas and nonbovine formulas such as soy formulas are not recommended for the prevention of allergic diseases (strong recommendation/evidence of low quality)[33,34].

Vitamin D

Observational studies and randomized trials have addressed the potential efficacy of vitamin D supplementation in preventing or treating a variety of disorders and adverse health situations. Emerging evidence indicates that vitamin D may play a role in the immune system. In particular, the active form of vitamin D, calcitriol, has been shown to modulate immune functioning in cell cultures and animal models. However, the understanding of the complex role of vitamin D in immune function remains limited.

To date, there is no direct evidence from clinical studies suggesting that vitamin D supplementation during pregnancy decreases the risk of children developing allergic diseases. Thus, the World Allergy Organization does not recommend vitamin D supplementation in pregnant women with the intention of preventing the development of allergic diseases in their children (very low certainty of evidence)[35].

Use of Probiotics

Several studies have been conducted using murine models to evaluate the efficacy of probiotics in the treatment and prevention of asthma and of hyperreactive airways. Blümer et al. evaluated the perinatal maternal administration of probiotics in mice[36].

The study showed that the ingestion of *Lactobacillus rhamnosus* GG (LGG) suppressed highly reactive airways and peribronchial inflammation in mouse offspring. In another murine model, Feleszko et al. found that the use of LGG or *Bifidobacterium lactis* (Bb12) significantly decreased pulmonary eosinophilia, airway reactivity, and allergen-specific IgE production[37]. In addition, administration of recombinant or wild-type *L. plantarum* effectively decreases airway eosinophilia following exposure to the allergen through aerosols. Moreover, coadministration of *L. plantarum* and *Lactococcus lactis* has been shown to decrease allergen-induced basophil degranulation in a murine grass sensitivity model.

A recent systematic review has demonstrated that probiotic supplementation during pregnancy and breastfeeding decreases childhood eczema risk. However, this level of evidence is weak, considering the inconsistency in the data and the lack of methodological standardization among the studies analyzed. Despite the promising results in murine models, current evidence does not confirm the reduction in

the risk of other allergies with probiotic supplementation, but neither does it disregard this possibility, suggesting that further studies are needed to contribute to this clarification[38-40].

Microbiota

The microbiome of the household environment is influenced by all the members of the household, their chores, and their presence. Evidence shows that certain populations have a low prevalence of asthma and that the presence of a large number of individuals in a household, living on farms, being exposed to endotoxins, and the presence of animals influence the appearance of allergies such as asthma and rhinitis.

Knowing precisely the types and quantity of microbes and how the gut and lung microbiota influence the innate and adaptive immune system in the early stages of life may be a strategy to prevent many allergic diseases[38-40].

Several factors promote dysbiosis that in turn promotes the loss of the protective effect of the normal lung microbiota, including the use of antibiotics, exposure to cigarette smoke, viral and bacterial infections, pollution, and treatment with corticosteroids. Evidence of the benefit of probiotics and prebiotics for the prevention or treatment of asthma and rhinitis is still scarce[38-40].

PRIMARY PREVENTION OF FOOD ALLERGY

In recent decades, food allergies (FA) have been a growing health problem, with a significant impact on pediatric health and family well-being. Recent data suggest that in addition to the increase in FA incidence and prevalence, we are also witnessing an increase in food allergy severity and a delay in the acquisition of tolerance to specific foods, with a consequent delay in the resolution of the associated clinical manifestations[41].

Among children aged < 1 year, 80% of FA cases are related to cow's milk proteins and manifest with various clinical symptoms, from nonspecific manifestations involving the skin, gastrointestinal system, or respiratory system to severe manifestations such as anaphylactic shock. Egg allergy is more prevalent in children with AD and is associated with increased risk for asthma. Other important foods involved in FA in Brazilian children are soybean and wheat, followed by peanuts, chestnuts, fish and crustaceans[42,43].

Among the concepts suggested in the atopic march theory, sensitization to food allergens precedes sensitization to aeroallergens, but it should be noted that in addition to predisposing genetic factors, environmental factors, and new lifestyle habits bear considerable weight in the development and clinical manifestation of allergic diseases. Therefore, it is vitally important to adopt preventive measures at the three levels: primary, secondary, and tertiary[44,45].

There are no universal preventive measures. To be effective and feasible, they must target the at-risk population. Thus, the identification of this population is the first step to be taken. Children with one parent or both parents or siblings with allergies are considered at a high risk for atopy[44-46]. Interventions are suggested for these children during the fetal stage and in the first years of life, with nutrition in the first year of life being one of the pillars of primary prevention[44-46]. The following are some noteworthy current recommendations for the prevention of FA:

a) ***Maternal Diet during Pregnancy***-There are no recommendations for the restriction of potentially allergenic foods during pregnancy. The diet should be as healthy and nutritionally balanced as possible. Restrictive diets may even have deleterious effects on the nutritional status of the pregnant woman and the fetus;
b) ***Feeding during 0-6 months of age***-Human milk has several components that can be associated with mechanisms that protect against FA development, including modulation of the gut microbiota; this protection is definitely not guaranteed by any cow's milk-based formula. It also plays an important role in inducing oral tolerance. Therefore, the recommendation of exclusive breastfeeding up to the age of 6 months is still the consensus; and
c) ***If breastfeeding is absolutely impossible***-In the case of children at a high risk for allergic diseases, the indication is to use hydrolyzed cow's milk formulas that have shown preventive clinical efficacy against the onset of sensitization. Therefore, partially hydrolyzed formulas can be used as a primary prevention strategy. Extensively hydrolyzed formulas should be restricted for treatment. Soy-based formulas, formulas containing milk from other mammals, and amino acid formulas are not recommended for prevention.

The introduction of supplemental feeding should not occur before 4 months of age and should preferably occur after the sixth month of life. Both early and late introduction may increase FA risk. Although there are studies with recommendations to avoid egg whites until 24 months of age and peanuts until 36 months, the European Academy of Allergy and Clinical Immunology and the American Academy of Pediatrics currently recommend the introduction of solid foods at between the fourth and sixth months of life, in a gradual manner, to allow the detection of reactions to individual ingredients, a rule that applies even to foods considered "highly allergenic," which should neither be avoided nor offered too early, regardless of atopic heredity. This timely exposure is relevant for the development of oral tolerance[47,48].

Specific nutrients-food sources of omega 3 and vitamins A, E, C and selenium play an important role in the immune response and have been shown in several studies to offer protection against the development of FA. Vitamin D plays

an important role in the immune system, but recent studies are still inconclusive about its relevance in food sensitization[49].

Probiotics and prebiotics-these act by modifying the gut microbiota in a beneficial way, acting as protective factors against the risk of allergic sensitization in the long term. However, there is no evidence to prove the true benefit of their use in the primary prevention of FA. General measures such as encouraging vaginal births, contraindicating smoking, and avoiding the indiscriminate use of broad-spectrum antibiotics in the first year of life are also part of the set of recommendations[50].

Primary prevention of atopical dermatitis

AD is one of the most common childhood inflammatory skin diseases, and involves a complex interrelationship of genetic factors, changes in the skin barrier, and innate and adaptive immunity. Patients with AD suffer a considerable socioeconomic and quality of life impact[51]. There is widespread interest in primary prevention strategies, particularly in high-risk children.

Maternal diet (pregnant/breastfeeding)

The high prevalence of allergic diseases such as AD justifies the investigation of the potential immunomodulatory effect of nutritional factors provided through the maternal diet, during pregnancy and/or lactation, especially through fruits, vegetables, fatty acids, and fish[51,52].

The consumption of omega-3 polyunsaturated fatty acids (ω-3 LC-PUFAS) has been studied as a protective factor against the development of allergic diseases, because of their anti-inflammatory properties. Fish is a major natural source of ω-3 LC-PUFAS. A recent systematic review followed by a meta-analysis showed that fish ingestion in the first year of life decreased eczema risk but that it did not produce the same effect during pregnancy. In fact, the "effect of fish" on the outcome of allergic diseases remains controversial[51-52].

Breastfeeding

A systematic review involving 21 prospective cohort studies did not show strong evidence of the protective effect of exclusive breastfeeding in the first 3 months of life against the development of AD.

Early use of emollients

The altered skin barrier plays a key role in the pathophysiology of AD, either because of genetic disorders such as filaggrin deficiency and/or an abnormal immune system response to the environment with transcutaneous sensitization to allergens, identified in the first months of life but not at birth. This observation gave rise to several studies, according to the assumption that early skin hydration of genetically predisposed newborns is a primary preventive measure for AD[53-55].

The early use of emollient is defined as daily use, from the first 3 weeks of life. This practice was associated with a 50% relative risk reduction in the development of AD in high-risk children in a multicenter, randomized study with the inclusion of 124 neonates[54].

Another Japanese study evaluated the daily application of a moisturizer in 116 children at a high risk of developing AD, from the neonatal period up to 32 weeks of life, and the authors reported a reduction in the relative risk of AD in the first 8 months when compared to the controls (no daily moisturizer)[55].

Early skin hydration as a strategy for the primary prevention of AD is very promising because moisturizers are easy to apply, have few adverse effects, and appear to have a protective effect at least in the first months of life in at-risk children. However, few studies on this subject have been conducted, a small number of children have been followed up, and there has been no evaluation of this protective effect in the long term.

Probiotics/Prebiotics

Probiotics have been used in the prevention of allergic diseases, including AD. In a significant number of studies, the effectiveness of probiotic use in the prevention of AD has been evidenced, and different mechanisms have been proposed for their action. Some suggest that probiotics act in primary prevention through their immunomodulatory and anti-inflammatory actions on dendritic cells and production of Th2 cells[56].

The use of a mixture of probiotics appears to be more effective than the use of an isolated strain; moreover, they are more effective when administration is started in the prenatal period in combination with breastfeeding. The microbiome that the infant presents before supplement administration appears to be a determining factor in the response to probiotic prevention. The administration of Lactobacilli in the last trimester of pregnancy and during the breastfeeding period has been shown to be effective in the primary prevention of AD in high-risk infants[56,57].

Recent evidence suggests a relationship between the use of prebiotics and prevention of allergic diseases; however, there are no definitive recommendations because of the limited number of studies and the lack of conclusive evidence to date[56-58]. There is scope for further research with prebiotics in terms of prevention, effect on the microbiome and immune system, and consequent optimization of their use in the primary prevention of AD.

Vitamin D

Despite studies showing the importance of vitamin D in the modulation of various immunological mechanisms, there are no clinical studies suggesting that vitamin D supplementation promotes the primary prevention of allergic

diseases. A recent systematic review of randomized and non-randomized studies conducted by Nuñez et al. concluded that further studies are required before the use of vitamin D can be considered for the prevention of allergic diseases[59].

Exposure to household allergens

In the pathogenesis of AD, the presence of endogenous and exogenous protease inhibitors is responsible for maintaining permeability homeostasis in the skin barrier. Exogenous proteases derived from environmental allergens such as mites, cockroach allergens, and even from staphylococci present in the skin of patients with AD affect this balance, either because of their direct proteolytic actions or to the activation of protease receptors present mainly in keratinocytes, thus facilitating the penetration of environmental allergens (mites and foods). There are no studies of primary prevention in AD with the effective reduction of environmental allergens. This leaves measures of secondary prevention and the use of allergen-specific immunotherapy to decrease AD exacerbations, whose results are still controversial[57-60].

OUTLOOK

Lifestyle and early exposure from conception and early life are determining factors for the prevention of allergies. It is in this window of opportunity that the new preventive paradigms are likely to be found. However, effective prevention of allergic diseases such as asthma, AD, allergic rhinitis is not yet synchronized with the scientific advances of the 21st century[61]. One possibility is the future prospect of epigenetic manipulation with interference in DNA methylation. Studies to that end have demonstrated advances in a rapid, widespread, and precise manner, which will allow a better understanding of this gene-environment interaction[62].

The elucidation of the gene-environment interaction will open several perspectives on prevention, with special emphasis on effective dietary manipulation. Despite promising research on probiotic biotherapeutics, including microencapsulation, further research is needed to determine whether they really are successful strategies for preventing allergies[63]. It appears that a natural and ancestral diet rich in polyphenols existing in fruits and vegetables can be extremely beneficial at the cellular level, protecting against allergic diseases[64].

Likewise, children with high genetic susceptibility may benefit from specific prophylactic immunotherapy as primary prevention[65]. A more comprehensive and detailed analysis of the complex gene-environment interactions involved in the development of allergic diseases will in the future provide personalized and truly effective allergy prevention.

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