

Prevention of allergic diseases*

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ABSTRACT

The prevalence of asthma and allergic diseases has increased in recent years, particularly in the industrialized world. Allergic disease begins to manifest in the first years of life. The disorder usually manifests initially in the form of food allergy and atopic dermatitis, followed in later stages by respiratory allergy with rhinitis and/or asthma. This has led to the adoption of preventive measures in those children with a high risk of atopy, based on the following considerations: 1) A family history of allergic diseases (asthma, eczema, and/or allergic rhinitis); 2) A personal history of atopy such as atopic dermatitis, particularly when associated to food allergy; and 3) The existence of allergic sensitization, particularly to pneumoallergens, of early or late onset, but persistent during childhood.

Prevention is established at three different levels: primary prevention, avoiding sensitization; secondary prevention, avoiding appearance of the disease; and tertiary prevention, avoiding the symptoms.

The present study discusses current knowledge of prevention and its efficacy, with mention of the importance of breastfeeding and the use of pre- and probiotics for securing adequate prevention.

Key words: Prevention in allergy. Primary prevention, Secondary prevention, Tertiary prevention.

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INTRODUCTION

The prevalence of asthma and allergic diseases has increased in recent years, particularly in the industrialized world - as evidenced by the ISAAC study¹.

Atopic disease develops in the first years of life, and other allergic processes can gradually manifest over time. The condition usually manifests initially in the form of food allergy and atopic dermatitis, followed in later stages by respiratory allergy with rhinitis and/or asthma. This has led to the adoption of preventive measures in those nursing infants at highest risk of developing atopy. However, these are very complex diseases involving the intervention of a broad range of etiopathogenic factors: environmental, genetic and epigenetic factors.

The first problem facing prevention is the definition of the newborn infant with a high risk of suffering atopy. With the purpose of joining criteria, such high risk cases can be defined as follows: 1) Infants with a family history of allergic diseases (asthma, eczema, and/or allergic rhinitis). The risk is greater if antecedents are found in both parents, or if the parents present the same phenotype as the child; 2) A personal history of atopy such as atopic dermatitis, particularly when associated to food allergy; and 3) The existence of allergic sensitization, particularly to pneumoallergens, of early or late onset, but persistent during childhood.

The present review analyzes the possible measures for the primary, secondary and tertiary prevention of allergic diseases and asthma, and whether they are truly effective.

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Possibilities of primary prevention

The studies conducted over the years reflect the great complexity involved in ensuring true primary prevention. Part of the problem is due to the importance of adequately defining what should be prevented: sensitization to a specific allergen or the tendency towards an IgE-dependent response in general.

It is generally assumed that the reduction of exposure to aeroallergens reduces sensitization, and thus the development of clinical symptoms. However, not all studies coincide on this point².

Lau et al³, in a multicenter study conducted during the nineties in Germany, showed that children with sustained sensitivity to pneumoallergens are more prone to develop asthma. As regards the primary prevention of this disease, the authors indicate that a reduction in the concentration of aeroallergens, particularly acarids, in the first months of life reduces the risk of future sensitization to pneumoallergens, but does not modify the evolution towards asthma. Therefore, according to these authors, allergic sensitization to pneumoallergens is clearly associated to asthma, but is not a sufficient causal factor for asthma development in children.

The European multicenter SPACE study (Study on the Prevention of Allergy in Children in Europe) has evaluated the efficacy of eliminating acarids (dust mites) in a large group of newborn infants at high risk of atopy⁴. According to this study, the reduction in acarid antigen load in the first months of life reduces allergic sensitization as well as allergic diseases in the first years of life. The prevalence of sensitization to acarids in the group of children subjected to prophylactic measures was 1.86 %, versus 5 % in the control group - though this protective effect against the symptoms of asthma or eczema disappears after two years.

Regarding the presence of animals in the home, a degree of controversy is found in the literature. According to some authors, animals in the home during the first years of life can induce a certain tolerance, and thus prevent sensitization and the appearance of asthma^{5,6}. However, other authors relate the presence of cats in the home to an increased risk of sensitization to these animals^{7,8}. The key consideration appears to be the degree of exposure to the dermal elements of the animal, inducing tolerance in the case of intense exposure since very early life, or sensitization in the case of sporadic or weak exposure.

Chan-Yeung et al^{9,10} conducted a study in Canada involving over 500 newborn infants at high risk of developing atopy, with avoidance in one group of infants of exposure to acarids, animals and tobacco

smoke, and administering partially hydrolyzed milk. The authors found that after two years wheezing decreased 90 % in the group subjected to prophylactic intervention versus the control group, with a 60 % lesser presence of asthma. After 7 years, the incidence of asthma was 12.9 % versus 25 % in the control children¹¹. In contrast, no statistically significant differences were observed in terms of the appearance of rhinitis and/or eczema, or in terms of sensitization to aeroallergens.

Very possibly, the fact of developing allergy or not is related to a greater or lesser concentration of endotoxins in the skin of domestic pets. In this sense it has been shown (hygiene hypothesis) that exposure to endotoxins of gramnegative bacteria induces a Th₁ immune response rather than a Th₂ mediated response in the host. Nevertheless, it is not easy to relate situations of greater or lesser exposure to microorganisms (number of siblings, nursery attendance, contact with animals, etc.) to a greater or lesser predisposition towards allergic diseases and to asthma.

Breastfeeding is undoubtedly one of the most important recommendations in primary prevention¹³⁻¹⁵, though in order to evaluate its efficacy, it is important first to define the corresponding breastfeeding cutoff point.

As has been shown by meta-analyses, breastfeeding during three months would be very beneficial for atopic dermatitis, particularly in children with a history of atopy, and would prevent the development of asthma between 2-5 years of age¹⁶. Not all studies reflect this particular beneficial effect of breastfeeding, though none question the overall benefits of the latter.

Regarding the efficacy of dietary modifications, Peat et al¹⁵ reported a reduction in wheezing among children fed a supplement rich in omega-3 fatty acids. This coincides with the observations of Rashd et al¹⁶, who combined acarid control measures with a hydrolyzed milk diet, and found a lesser incidence of nocturnal cough, wheezing, bronchial hyper-responsiveness and atopy after 8 years.

A very debated aspect is the possible efficacy (or lack of efficacy) in terms of atopy and asthma prevention of the diet in pregnant women. Diets particularly devoid of nuts are recommended for pregnant women by the American Academy of Pediatrics¹³, but not by the European societies¹⁴.

In contrast, there appears to be general agreement that when a child at risk of developing atopy requires a milk formula, a hydrolyzed formula rather than a partially hydrolyzed formula should be provided as primary prevention - though in this sense the findings of the different studies are contradictory¹⁷.

Secondary prevention. Is it effective?

In the last 30 years there has been genuine progress in our knowledge of the importance of avoiding aeroallergens, as a measure for preventing allergy and asthma. However, while the strategies of avoiding aeroallergens are increasingly clear, the same cannot be said of the timing of such strategies. Thus, as has been seen, the efficacy of primary prevention, i.e., the avoidance of atopic sensitization, remains to be established. In contrast, and in the light of the large recent studies on asthma reduction, there appear to be no doubts as to the efficacy of secondary prevention, destined to avoid symptoms in those patients that are already atopic. The reduction, as far as possible, of tolerogenic exposure is one of the key factors for the management of allergic diseases, together with pharmacological treatment and specific desensitization.

Many studies point to the appearance of asthma attacks in children sometimes requiring an emergency visit to hospital, in relation to high concentrations of pollen¹⁸, fungi such as *Alternaria*¹⁹, or acarids²⁰.

Nishioka et al²¹ have demonstrated that avoiding or reducing acarids in the home of the infant at risk of developing atopy (specifically atopic eczema), even when not yet sensitized to this allergen, reduces the appearance of asthma as well as the formation of specific IgE antibodies targeted to acarids. Moreover, in over half of the children that already presented symptoms of asthma, the exposure to under 2 µg/g of allergens reduced sensitization and improved the symptoms.

In this same sense, Boner et al, in a prospective study of 1756 asthmatic children with acarid allergy, reported lesser symptoms relapse, as well as improvement in bronchial hyper-responsiveness. In contrast, in those homes where no treatment was provided, the children persisted with the same symptoms²².

Despite these data, two meta-analyses reflect inefficacy in terms of the appearance of symptoms, on the part of those methods designed to reduce the concentration of acarids^{23,24}. In addition, these meta-analyses stress the defects in clinical studies of the efficacy of avoiding acarids in the homes of the patients: the difficulty of defining precise phenotypes, the use of non-homologated methods for the elimination of acarids, insufficient study times, etc. On the other hand, it should be pointed out that many of these studies have been conducted in adults.

While discrepancies also exist, some studies report that the presence in the home of cats or dogs in

the first years of life prevents the appearance of asthma at 12-13 years of age - though this only appears to occur in those children that do not have asthmatic parents²⁵. In any case it appears to be difficult to eliminate all animal allergens, even when using vacuum cleaners apparently suited to the effect.

Other domestic environmental factors also appear to play an important role in the appearance or worsening of asthma symptoms. In this sense, the relative risk of asthma attacks in children increases considerably when the parents smoke - thus also evidencing the relationship between the intensity of passive smoking and the prevalence of asthma^{26,27}.

Regarding other chemical contaminants, exposure to formaldehyde is a risk factor for asthma in children: for each 10 µg/m³ increment in formaldehyde content in the home of a child, the risk of asthma rises 3 %²⁸. Blay et al²⁹ have shown that exposure to 100 µg/ml of formaldehyde during 30 minutes aggravates the bronchial symptoms of asthmatic patients with allergy to acarids. Likewise, a certain dose-response relationship has been observed between asthma and exposure to NO₂ and SO₂.

Global intervention could possibly yield better results. Thus, recently Morgan et al³⁰, in a study of almost 1000 children with allergic asthma subjected to global preventive measures (education, water aspirators, air filtering units), observed a significant reduction in the levels of allergens corresponding to acarids, cockroaches and cats. In addition, the authors reported a reduction of almost 20 % in the symptoms, a lesser need for corticoid use, a 13 % reduction in visits to the emergency service, and a 20 % in school absenteeism. Furthermore, a correlation was observed between clinical improvement and the level of aeroallergen reduction. The authors therefore concluded that global intervention should be viewed as an important part of the treatment of allergic asthma in children sensitive to aeroallergens. Before any intervention is decided in this field, it is necessary to measure the presence of allergens in the environment of the child, and it must be taken into account that good aeroallergen elimination is not easy. In any case, when dealing with diseases such as allergy and allergic asthma, where environmental factors are so important, adequate environmental control is essential.

Tertiary prevention

The objective of tertiary prevention is to control the allergic disease, preventing (in the case of asthma) the exacerbations and reducing maintenance medication as far as possible.

Table I
Components of human milk that protect against or induce food allergy

Components	Inducers	Protectors
Antigens	Sensitizing allergens	Tolerance inducing allergens
Cytokines	IL-4 IL-5 IL-13	TGF- β Soluble CD14
Immunoglobulins		Secretory IgA Ovalbumin
Polyunsaturated Fatty acids	Arachidonic acid C22:an-6 C22:5n-6	Eicosapentaenoic acid Docosapentaenoic acid Docosatetraenoic acid Alpha-linoleic acid Polyunsaturated n-3 fatty acids
Chemokines	RANTES IL-8	
Eosinophil derivatives	Cationic protein	
Polyamines		Spermine Spermidine

(Zeiger RS. The role of breast-feeding in the development of allergies and asthma. *J Allergy Clin Immunol* 2005;115:1238-40)

It is known that exposure to the different allergens can trigger asthma attacks and exacerbate rhinitis and eczema in sensitized children. Different studies have reported the clinical benefits obtained by these patients on reducing or avoiding the allergens to which they are sensitive. Nevertheless, controversy also exists in this field. A number of large studies reflect the benefits of prevention, while others have obtained contradictory results^{31,32}.

The measures cited in relation to secondary prevention, regarding the reduction of acarids in the environment, are able to reduce the concentration of dust mites - though these are costly interventions, and their actual efficacy in real life has been questioned.

A recent meta-analysis of 49 studies comprising 2733 patients reports that preventive measures are ineffective and should not be recommended in asthmatic and allergic patients²⁴. In contrast, another study published by Morgan et al²⁵ and involving 937 children with asthma from different areas in the United States, subjected to global preventive treatment, revealed that the proportion of symptoms-free days exceeded 50 % in those cases where allergen concentration (acarids and cockroaches) was effec-

tively reduced. A reduction in the number of visits to the emergency service was also recorded.

Regarding the tertiary prevention of rhinitis, a number of studies have analyzed the efficacy of dust mite covers. Scant benefits were recorded, however, and certainly no statistically significant differences were noted³³⁻³⁵ despite the fact that all the studies document a reduction in allergen levels.

Similar results apply to those studies made to evaluate the efficacy of allergen avoidance strategies (e.g., against acarids) in relation to atopic dermatitis. In children with eczema and sensitization to acarids, it has been shown that despite the reduction of allergen levels in the environment, clinical improvement is not significant with respect to the control group³⁶.

Role of infant diet in the development of asthma and atopy

The discussion of the effect of breastfeeding in terms of its capacity or not to protect against allergic diseases and asthma is conditioned by the complex interactions occurring among the components of human milk and the immune system in the intestine of the infant. Different components of human milk behave as protectors against the posterior appearance of allergy in the child, while others to the contrary could exert a facilitating effect³⁷ (table I).

There is no doubt that breastfeeding is ideal for the child from the nutritional, psychological and immunological perspectives. However, after many years of research in this field, the beneficial effect of breast milk in terms of the prevention of allergic sensitization or the appearance of asthma remains unclear. It seems that exclusive breastfeeding, at least during four months, prevents atopic dermatitis and wheezing in infants. However, it is not clear whether it can prevent the appearance of asthma over the long term. According to our experience³⁸, asthmatic children that have been breastfed for at least four months show better respiratory function and require less maintenance treatment for their asthma.

It therefore seems that the advisability of breastfeeding should be stressed particularly in children at high risk of developing atopy, as well as in the case of asthma antecedents in the mother^{39,40}.

On the other hand, it does not seem advisable for breastfeeding mothers to follow too strict a diet in relation to different types of foods, though in the past diets devoid of different foods including egg, fish, nuts, etc., were recommended. In this context, it may suffice to eliminate some dietary elements such

as nuts, which have a high sensitizing potential in infants.

The use of highly or partially hydrolyzed infant formulas has also been the subject of debate. The former appear advisable in children with a high risk of atopy, and in children with allergy to cow milk proteins, while the use of partially hydrolyzed formulas continues to be questioned - despite their lesser cost and superior organoleptic properties.

In recent years, attention has been drawn to the benefits of immune modulation in the prevention of atopy. In this sense, studies have been made of the effects of administering probiotics or lactobacilli, i.e., non-pathogenic microorganisms that prevent intestinal colonization by pathogens, particularly as a result of their capacity to stimulate Th1 responses. A certain reduction has been reported in the appearance of dermatitis, with lesser levels of specific IgE antibodies against foods, in children born of mothers that consumed probiotics during one month before delivery and during lactation⁴¹. There have also been reports of increased TGF- β_2 levels in breast milk⁴². Despite these observations, however, much research is still needed to determine the true efficacy of probiotics in preventing allergic diseases.

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