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Primary prevention of food allergy in 2021: Update and proposals of French-speaking pediatric allergists☆

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ABSTRACT

During the past years, there has been an alarming increase in cases of food allergy and anaphylaxis in ever-younger children. Often, these children have multiple food allergies and food sensitizations, involving allergens with high anaphylactic potential, such as peanuts and nuts, which have a major influence on their quality of life and future. After reviewing the current epidemiological data, we discuss the main causes of the increase in food allergies. We analyze data from studies on the skin barrier and its fundamental role in the development of sensitization and food allergies, data on the tolerogenic digestive tract applied in particular to hen eggs and peanuts, as well as data on the prevention of allergy to cow milk proteins. In light of these studies, we propose a practical guide of recommendations focused on infants and the introduction of cow milk, the management of eczema, and early and broad dietary diversification including high-risk food allergens, such as peanut and nuts while taking into account the food consumption habits of the family.

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Introduction

In recent years, in our practice as pediatric allergists, we have seen a worrisome increase in cases of food allergy (FA) and anaphylaxis in ever-younger children who have multiple food allergies and food sensitizations, involving allergens with high anaphylactic potential, such as peanuts and tree nuts. FAs greatly affects the quality of life (strict and imperative avoidance diet, emergency kit containing self-injectable adrenaline always available) and the future of these children (no spontaneous recovery, difficult allergy management).

Therefore, we would like to make proposals for primary prevention in young children by examining both the cutaneous aspect of prevention (role of atopic dermatitis) and the digestive impact of food tolerance, based on data from the literature. In addition, we also discuss the most appropriate practices to prevent cow's milk protein allergy (CMPA), due to the strong anaphylactic, an even lethal, risk of persistent forms of CMPA.

These recommendations should be integrated into the dietary and cultural habits of the child's family.

Epidemiology and context

Epidemiology

For several decades, the prevalence of allergic diseases has been increasing [1]. According to the World Health Organization (WHO),

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without preventive measures, 50% of the population will be affected by allergies by 2050. FAs, together with atopic dermatitis (AD), are the first manifestations of allergic march, preceding the onset of respiratory allergies such as asthma and rhinitis. Anaphylaxis is “an immediate systemic or generalized, severe, life-threatening hypersensitivity reaction.” It is the most severe form of immunoglobulin E (IgE)-mediated allergy, and is potentially lethal.

The most recent data from the French Elfe study, a cohort of more than 15,000 children born in 2011 and recruited from the general population, show a prevalence of FA at the age of 6 years of 6%, with 20% of multiple food allergies. In 2016, the prevalence of peanut allergy at 6 years of age was 0.85%, 0.5% for tree nut allergy and 3.5% for CMPA [2].

Furthermore, data from the Allergo-Vigilance Network [3], a non-exhaustive register of severe allergic reactions in France, Belgium, and Luxembourg, suggest that the allergens involved are quite similar to those described in other European countries and Anglo-Saxon countries. Thus, between 2002 and 2020, the allergens most often responsible for anaphylaxis in children under the age of 16 were peanut (24% of cases), cashew nut (13.7%), milk (cow milk and goat/ewe milk: 8.9%), hazelnut (4.3%), and hen egg (4.1%).

In Australia, the HealthNuts study provides robust data on the prevalence of FA confirmed by oral food challenge (OFC) at the age of 6 years in over 5000 children of the general population [4]. The study found that by the age of 1 year, 3% of children had peanut FA and the parent-reported prevalence of tree nut FA was 0.1%. At age 6, the prevalence of tree nut FA was 3.3%, of which 2.7% was cashew nut FA. More than one third of children who had an allergy to tree nut at 1 year of age had tree nut FA at the age of 6. Of the 147 peanut-allergic children at age 6, 45% had at least one FA to tree nut (36.7% to cashew).

The Pronuts study carried out in Switzerland, Spain, and the United Kingdom of 122 children under the age of 16 with at least one allergy to peanuts, tree nuts, or sesame reported a very high rate of multiple food allergies (60.7% of children). In addition, 55% of OFCs caused a moderate-to-severe reaction [5]. The most common allergens involved were peanut in the United Kingdom, cashew nut in Switzerland, and walnut in Spain. Age over 36 months was significantly associated with having multiple FAs, leading to the conclusion that primary prevention must be implemented very early.

In the United States, Gupta et al. conducted two surveys with children ($n = 38,408$) and adults ($n = 40,443$) to assess the prevalence of food allergies [6,7]. They estimated the prevalence of FA in children at 7.6%, with peanut (2.2%), milk (1.9%), shellfish (1.3%), and tree nut (1.2%) as the most common allergens. Nearly 40% of these children had multiple FAs; more than 40% had a severe allergic reaction. In adults, the prevalence of FA was estimated at 10.8% with the most common allergens being shellfish, milk, peanut, tree nut, and fish. More than 45.3% had multiple food allergies. More than 50% had at least one severe allergic reaction. From these two studies, it is noted that many food allergies in children continue in adulthood with a persistent high risk of anaphylaxis.

Several studies have reported an increase in the incidence of anaphylaxis over the past 20–30 years. This increase in food anaphylaxis parallels the increase in FA. For example, in the United Kingdom, Turner et al. reported an incidence of hospitalizations for anaphylaxis ranging from 1 to 7 per 100,000 patients per year between 1992 and 2012 [8]. The European Anaphylaxis Registry reports that the most frequently reported foods in children younger than 18 years are in order of frequency: peanut, cow's milk, hen egg, cashew nut, and hazelnut [9].

Difficult management of FAs

For children allergic to one or more of these foods, the anaphylactic risk, if accidentally ingested, is significant. An emergency kit

containing self-injectable adrenaline should always be available to the child, and families should be educated on its use. Because of the anaphylactic risk and the need to maintain a dietary avoidance regimen on a permanent basis, FA has a negative impact on quality of life, hindering social life from early childhood onward. Birthday parties, holidays, and school canteens are often a source of anxiety for parents as well as for caregivers. Considering all these elements, the implementation of primary prevention strategies for FAs has become a public health issue today.

Thus, French epidemiological data do not yet reach the level of data from Anglo-Saxon countries. However, in clinical practice, pediatric allergists find the same clinical characteristics in their young patients with the emergence and worrisome increase of cases of multiple FAs at high anaphylactic risk (early sensitization, heralding FAs; frequent association of peanut allergy with tree nut allergies; alarming increase in cashew nut allergies).

In addition, the persistence of these allergies in adulthood with their risk of severe or even fatal anaphylaxis and the difficulty of managing them (strict avoidance, carrying a permanent emergency kit, etc.) encourages us to propose primary preventive measures to help avoid such pathologies that previously did not exist.

Understanding the reasons for the increase in FA toward better prevention

The reasons for the increase in FAs are numerous.

Besides the well-known causes, that is, the modern and Western way of life with decreased microbial exposure (the hygiene theory) and the globalization of food with exposure to new allergens, other hypotheses have been developed more recently (novel food, epigenetic modifications, genetics factors). Beside protective factors for FA, such as rural habitat and early varied diet, other risk factors for FA have been identified: atopic tendency in the family, early AD, birth by cesarean section, antibiotic therapy in the neonatal period, among others.

Hygiene hypothesis/importance of intestinal microbiota

Originally developed by Strachan in 1989, the hygiene theory states that the Western way of life limits microbial exposure and thus promotes dysbiosis (a state of imbalance in the microbial ecosystem) [10]. The evolution of our lifestyle has indeed led to a decrease in the diversity of microbial exposure in the perinatal period. Very early in life this diversity of microbial exposure plays a crucial role in the stimulation of the T1-type immune system. In the absence of stimulation of the T1 pathway there is stimulation of the T2 pathway, responsible for the development of allergic and autoimmune diseases [11]. The role of the microbiota in the immune system has been well demonstrated. Thus, axenic mice (germ-free) are unable to develop a state of tolerance to food allergens. This tolerance mechanism of the healthy microbiota is favored by the production of short-chain fatty acids, linked to the fermentation of dietary fibers and acting on the immune system, and in particular the stimulation of regulatory T cells [12]. It is understood that any state of dysbiosis is likely to modify the nature of the immune response, as can be seen at the epidemiological level: Certain factors influencing the microbiota are associated with an increased risk of FA (birth by cesarean section, taking antibiotics, low-fiber diet among others). In humans, studies have demonstrated differences in the microbial composition of the digestive tract between allergic and tolerant individuals, even if to date no study has been able to determine the ideal microbiota [13]. The microbiota builds up progressively in the first months of life, reaching an “adult” composition and variety at the age of 2 years. It seems that dysbiosis precedes the onset of FAs. Several studies have demonstrated an age-dependent association between microbiota abnormalities and the subsequent occurrence of food

sensitization [14]. Thus, FA could be prevented by avoiding over-prescription of antibiotics and anti-acids [15], since the prescription of broad-spectrum antibiotics interferes with the development of allergies in epidemiological studies, probably by altering and depleting the intestinal microbiota [16]. Cesarean section is also incriminated: The absence of passage through the vaginal route prevents contact with the vaginal flora and adequate colonization of the newborn's microbiota.

Thus, the perinatal period seems to be the window of opportunity for preventive interventions on the microbiota.

Dual-allergen exposure hypothesis

G. Lack's team has shown that food sensitization occurs through dermal exposure to the allergen favored by injured skin [17]. Sensitization via the cutaneous route is the result of skin barrier dysfunction. This can exist even before the development of clinical AD lesions, as suggested by the increase in insensible water loss observed even before the eczema and correlated with the onset of FA at the age of 2 [18]. It is also well demonstrated that when AD appears in the first 6 months of life, it is correlated with the subsequent development of FAs, with the high risk of being triggered earlier and with more severe skin conditions [19].

The amount of peanut present in the environment is associated with the development of peanut FA, especially since there is an alteration in the filaggrin gene (FLG). This exposure seems ubiquitous, not only indoors, but also outdoors.

Brough et al. have demonstrated the presence of detectable peanut proteins in 100% of the English schools tested, making it difficult to reduce dermal exposure via air and hand transmission [20]. In France, eating habits are different and it is likely that there is much less peanut in the environment, whether school or domestic, except in families with regular consumption (cooking or appetizers). By contrast, early exposure to high-dose allergens via the digestive tract has been shown to be tolerogenic; the most emblematic study is the Learning Early About Peanut Allergy (LEAP) study for peanut [21].

Risk factors of FA

Genetics factors, epigenetic modifications

Genetic factors concern inheritance. Indeed, children with one allergic parent have twice the risk of having allergies, and those with two allergic parents have four to six times the risk of becoming allergic [22]. A large number of genes are involved in FA, including mutations in the FLG, SPINK5, and corneodesmosin genes [23]. Regarding gender, severe peanut allergy has been noted predominantly in girls. Interestingly, single or multiple FAs are more common in boys [24]. Moreover, ethnicity appears to be a risk factor. Thus, children of Asian or African origin, who have recently migrated to industrialized countries (Australia, North America, United Kingdom), would be more at risk of developing FA than children of Caucasian origin [1].

Epigenetic modifications by genomic adaptation to the environment are also involved in the development of allergic diseases, particularly in FAs. DNA methylation (CH₃ on CpG segments) has been proven in peanut allergy, and, therefore, a low degree of histone acetylation in the placenta would facilitate food sensitizations [25].

Other contributing factors

Vitamin D deficiency has been suggested to be a contributory factor. However, a recent meta-analysis by Yopez Nunuez et al. was inconclusive about the role of vitamin D [26]. Reduced consumption of long-chain polyunsaturated omega-3 fatty acids in comparison with the consumption of highly processed products also plays a role in the etiology of FA. However, there is insufficient evidence to suggest maternal supplementation during pregnancy or breastfeeding is a preventive measure. Similarly, there is insufficient evidence to

recommend pre- or probiotic supplementation in the diet of pregnant women and/or infants to prevent FA [1]. The role of highly processed foods – the rich Western diet of grilled meats, fats, and sugars – is also suggested via advanced glycation products (AGEs) and alarmins, and the role of obesity via chronic inflammation [27,28].

For which children should FA prevention be proposed?

Primary prevention aims at avoiding the outbreak of respiratory and/or food sensitization in a child at risk of atopic disease. Due to the major role of AD in the genesis of FA, it is necessary to remember the importance of its early and effective treatment, which is part of secondary prevention.

Atopy is the personal and/or familial tendency for sensitization toward and production of specific IgE in response to exposure to respiratory and/or food allergens.

Atopic risk is classically determined by the existence of at least one family record of atopy (parents, siblings). Approximately 30% of newborns have at least one family record of atopy, 5% have two and 60–65% have no family records. The risk of developing atopy is 10–15% in children with no atopic history, 30% if a first-degree family member has atopic manifestations, and approximately 60% in the case of both parents have atopy [24]. It is therefore obvious that if prevention is proposed only to children at risk of atopy determined by family history (10–12% of newborns), 10–12% of newborns without family history who will develop atopy will not be protected and 50% of children who will develop atopic disease will be ignored. Therefore, it is recommendable to propose preventive measures to all unborn children, regardless of family history of atopy [29]. Furthermore, studies should not be limited to the selection criteria of the LEAP (peanut) or PETIT (Two-Step Egg Introduction for the Prevention of Egg Allergy in High-Risk Infants with Eczema) studies that concern infants with very high atopic risk (severe AD and/or egg allergy) [30,31]. In addition, the results of the Enquiring about Tolerance (EAT) study, conducted with the general population, confirm the need to apply these early prevention measures to all infants, whether atopic or not [32].

The skin as a sensitizing pathway: acting on the skin barrier

The first year of life is a crucial for the outbreak of FA through alterations in the skin barrier. AD, which is mostly moderate to severe and has an early outbreak, especially before 3 months of age, is thus considered the main risk factor for FA in young children (30–50% risk) depending on the populations sampled. Specific mutations, such as those concerning the filaggrin (FLG), SPINK5, and corneodesmosin gene, also predispose infants to severe forms of AD with the occurrence of sensitization and FAs in older children [23]. Early and/or severe skin inflammation is more strongly associated with sensitization and FA than with late or less severe inflammation. Three types of preventive action are possible: act very early on the skin barrier via emollients and reduce skin aggressions; actively treat AD; limit the presence of allergens in the infant's environment. Thus, reducing both the severity and duration of AD could reduce the incidence of FA.

Skin barrier intervention: use of emollients?

The skin barrier in children with FA, whether or not associated with AD, is deficient (increased insensible water loss, FLG deficiency, and decreased long-chain lipids) [33]. Emollients reduce skin water loss and improve skin hydration. In 2015, Kelleher et al. showed that an increased measure of transepidermal water loss at 2 days and 2 months of life predicted the onset of AD at 1 year [18]. Neonatal use of emollients for at-risk neonates protected against AD at 6 and 12 months according to three other studies [34]. However, there was no

difference in IgE-mediated sensitization to food allergens either with or without the use of emollients. There was also no benefit in reducing exposure to irritating substances such as soaps, sodium laureth sulfate, shampoo, or household allergens in the frequency of onset and severity of eczema. Other studies, subsequently conducted in larger cohorts of infants at high atopic risk, did not find significant effects of emollient application on the prevention of AD or on the development of food or respiratory sensitization [34,35]. Preventive application of emollients to children at risk of atopy is, therefore, not recommended. However, these studies are difficult to compare since they vary in the nature of the emollients used, the methods of recruitment, the age of the infants, and the locations, frequency (daily or several times a day), and duration of application. Further studies will thus be needed to determine the impact of emollients on the prevention of AD and FA.

Reduce inflammation, treat AD early

All authors agree on the need to treat any AD early enough and actively in order to avoid skin sensitization to food allergens [36,37]. The application of an emollient, at least once a day in the case of moderate-to-severe AD over the body, in association with a dermocorticoid treatment makes it possible to decrease the severity of AD and to space out the outbreaks. Reducing the inflammation caused by AD will subsequently prevent sensitization and FA. This is illustrated by the findings of the HealthNuts study, where 50% of children with severe early-onset AD developed allergies to egg, peanut, or sesame by 12 months of age. There was also a direct correlation between food sensitization and Scoring Atopic Dermatitis (SCORAD) scores in children between 4 and 11 months of age. Moreover, it has been shown that delay in AD management increases the risk of FA with each passing month [36].

Thus, acting on the duration and severity of AD should reduce the impact of epicutaneous exposure to environmental dietary proteins and prevent sensitization and subsequent FA. In practice, the treatment of AD should be initiated early, adapted to each patient, and accompanied by treatment education and regular follow-up due to the families' frequent fears of using dermocorticoids. Active treatment of bacterial skin colonization by *Staphylococcus aureus* should be associated with AD treatment, since this microbe is recognized as one of the aggravating factors of atopic diseases [38].

Elimination of food allergens in the environment

A significant association has been demonstrated between home consumption of peanut, almond, or nut and sensitization to these allergens, correlated with AD and concomitant egg sensitization in children. In the households where these foods are not consumed, no children are sensitized [39]. It is therefore very important to advise parents to avoid contact of the infant's skin with dietary proteins, either indirectly when parents consume them, or by application of emollients containing dietary proteins (almond oil, coconut oil, shea butter among others) to prevent sensitization or aggravation of a pre-existing allergy [37].

Diet: induction of tolerance through the digestive tract

Unlike the skin, many studies show that the digestive tract is tolerogenic, preventing the development of FA. Although recommendations for food diversification have changed significantly over time, it seems that a window of opportunity exists at around 4–6 months of age to induce this food tolerance, especially foods with high allergenic potential and in infants at high atopic risk [40].

Dietary diversification

Early diversification

Several cohort studies including more than 20,000 infants have shown that the delayed introduction of different foods has no effect on allergy prevention and may even be responsible for eczema, asthma, allergic rhinitis or sensitization, or even FAs [41].

The Enquiring About Tolerance (EAT) study [30] sought to show in the general population whether the early introduction of six highly allergenic foods (CM, hen's egg, sesame, white fish, peanut, and wheat) from the age of 3 months, compared with the conventional introduction from 6 months onwards in breastfed infants, would protect against FA. The 1303 exclusively breastfed infants included were randomized to either the early food introduction group or the control group with exclusive breastfeeding up to 6 months of age. Milk in the form of yoghurt was the first food introduced; wheat was the last, with the other foods introduced in random order. Analysis of the intent-to-treat (ITT) group revealed no difference between the two groups in the prevalence of FA at 1 and 3 years of age. Adherence to the dietary protocol was difficult as only 32% of the participants in the early introduction group were able to adhere to the diet protocol (i.e., able to consume the six allergenic foods in the required amount and timing). However, in the per protocol (PP) analysis, the prevalence of food allergy was significantly lower in the early introduction group than in the standard introduction group (2.4% vs. 7.3%, $p = 0.01$), and more specifically for the prevalence of peanut allergy (0% vs. 2.5%, $p = 0.003$) and egg allergy (1.4% vs. 5.5%, $p = 0.009$). This effect was not found for other foods. The authors also showed that the consumption of at least 2 g of peanut protein or egg white per week was necessary to prevent allergy. These results, also obtained in the PP group, support the recommendation not to delay the introduction of allergenic foods and to introduce them as early as 4–6 months of age. It is interesting to note that this early diversification did not influence the continuation of breastfeeding.

Broad diversification

Just as the diversity of microbial exposure seems to be important in the development of the immune system of young children, the diversity of foods consumed during the first year of life also plays a significant role in the protection against allergic risk.

The European PASTURE cohort [42], which included 1133 families in the third trimester of pregnancy, studied protective factors for the occurrence of allergic diseases in rural populations, a population known to be at lower allergic risk. The analysis of children's diets in this cohort showed that diversity in the introduction of foods other than milk in the first year of life was inversely associated with AD after this first year, even when the inverse causality was taken into account (avoidance or delay of diversification in families at risk of allergies). The introduction of yogurt during the first year of life was also significantly associated with a lower risk of AD. Furthermore, a greater variety of foods introduced during the first year of life was significantly associated with protection against the occurrence of asthma (dose–response relationship), FA, and AD. The introduction of yogurt, butter, or other dairy products before the age of 1 year was associated with a decreased risk of asthma and FA at age 6. Hypotheses regarding the protective effect of early consumption of dairy products are multiple and include high omega-3 and butyrate content and a rich and diverse microbial composition [42].

Egg allergy prevention

From the HealthNuts study, the feeding pattern of infants (duration of breastfeeding, age at introduction of solids) and the existence or not of an egg allergy were studied. The authors showed that late introduction of eggs was associated with an increased risk of egg allergy for introduction at 10–12 months of age and after 12 months.

These results were also obtained in children without atopic risk factors [43]. The meta-analysis of Ierodiakonou, comprising 1915 patients in five selected studies, concluded that early introduction of egg between 4 and 6 months of age was moderately to highly effective in reducing egg allergy [31,44]. Cooked egg, in small increasing doses seems to be the form of choice for early introduction, plain or given in cookie form [31].

Evidence for the prevention of peanut allergy

The Learning Early About Peanut Allergy (LEAP) study was the first randomized trial to demonstrate the effectiveness of early peanut introduction (between 4 and 11 months) in preventing peanut FA [28]. Thus, 640 children aged 4–11 months (median: 7.8 months) with severe eczema and/or egg allergy were randomized into two groups: consumption of peanut in high doses, 6 g of peanut protein per week or 24 g of peanut (i.e., about 5 teaspoons of peanut butter or the equivalent of 180 Curlys®, french peanut-based snack) or avoidance until the age of 5 years. Previous peanut sensitization was sought through skin prick tests (sPT) and specific IgE (sIgE); children with sPT findings greater than 4 mm were excluded from the intervention. The presence or absence of peanut allergy was determined at age 5 by either consumption of a single dose of 5 g of peanut protein in the absence of skin sensitization or by peanut OFC at the cumulative total dose of 9.4 g of peanut protein in the event of sensitization. Among the 530 children in the non-sensitized group, assessed at 60 months of age with OFC, 13.7% of the avoidance group and 1.9% of the consumption group were allergic to peanut, representing a relative risk reduction of 86%. Among the 98 children in the sensitized group (positive sPT but less than 4 mm), 35.3% of the avoidance group and 10.6% of the consumption group were allergic to peanut, representing a 70% relative risk reduction. The long-term follow-up study (LEAP-On) also showed that early induction of peanut tolerance still protected children from allergy, even after 1 year of peanut avoidance [45].

In addition, peanut consumption did not affect breastfeeding or the consumption of fruits and vegetables. There was neither nutritional impact in terms of caloric and protein intake nor in the consumption of calcium, zinc, iron, and vitamin D. Fat intake was higher in the peanut group but in the average range according to the child's age. There were also no differences between the two groups in terms of weight, height, BMI, and waist size despite the large amounts of peanuts administered weekly. Finally, the preventive effect of early peanut consumption found in the LEAP study is allergen-dependent, i.e., there is no preventive effect on other FAs or other atopic diseases. The meta-analysis of Ierodiakonou also validated, from the LEAP and EAT studies comprising 1550 patients, the moderate-to-high efficacy of early peanut introduction between 4 and 11 months of age in the prevention of peanut FA [44].

Recommendations of allergy societies

All learned societies now recommend the introduction of solid foods from at the age of 4–6 months in all infants, although the WHO still advocates exclusive breastfeeding during the first 6 months of life for its nutritional value and to prevent the risk of infection in developing countries.

The methods of introducing peanut and egg in at-risk populations are variable. Some learned societies (USA, Canada) recommend an allergological evaluation prior to the introduction of food (sPT or even sIgE) in children at high atopic risk; others (UK) consider that a prior assessment should not be carried out, even in very atopic infants. This could represent a missed opportunity by delaying (long delays in allergology consultations) the introduction of egg and/or peanut [45,46]. Moreover, the risk of allergic reaction in this

population is considered low as accidents in introduction have been limited to date.

There are currently no recommendations for the early introduction of tree nuts, due to the lack of available studies. However, because of the worrying increase of these allergies in young children in France, and in view of the results of the LEAP study, it seems logical and important to introduce them early in the child's diet. The administered dose should be comparable to those used in the LEAP and EAT study for peanut and egg, i.e., 2 g of protein per week per allergen, in families consuming them regularly.

Data on CMPA prevention

Cow milk protein allergy (CMPA) has some particularities compared to other food allergies. Its prevalence varies from 0.5 to 2% depending on the country [47]. This allergy disappears in most cases before the age of 5 years. However, there are persistent IgE-mediated forms, often severe, unfortunately sometimes lethal, which make their prevention challenging, as the quality of life of these children is quite impaired, and the anaphylactic risk is very high [47,48]. Cow milk (CM) is a ubiquitous allergen, often hidden, making it difficult to handle. It is the first allergen introduced to the infant, often at birth and well before diversification. Prevention measures must therefore be introduced earlier than those proposed for other food allergens (peanuts, nuts, eggs, among others).

To date, there are no recommendations for primary prevention of CMPA. However, several questions arise: What type of milk should be used in the maternity ward to complement or replace breastfeeding (BF)? When should CM protein be introduced, and which milk formula should be chosen for strictly breastfed child? Does BF prevent CMPA? [48].

Several studies have shown that CM supplementation in the first few days of life (whole proteins) without subsequent continuation (strict BF) favored CMPA on subsequent re-exposure [48]. The use of a high hydrolysis or amino acid formula in this period reduces the risk of secondary CMPA [49]. Partially hydrolyzed milks, known as "hypoallergenic milks" (HA milks), do not have protective effects, not for the prevention of CMPA, other FAs, or respiratory allergic pathologies and are no longer recommended by the various learned societies [50].

Conversely, numerous observational studies have shown that early and daily introduction of whole CM proteins in the infant's diet, from the first days of life, favors tolerance to CM, at least for IgE-mediated allergies. Thus, Katz [51] studied the prevalence of IgE-mediated CMPA according to the BF mode, mixed or exclusive, in 13,019 newborns. Globally, the rate was found to be 0.5% at 2 years, but was much higher at 1.75% in infants who were exclusively breastfed up to 3 months, and only 0.05% in infants who had early and regular supplementation with CM. Sahikara [52] reported data from 374 egg-allergic children, of whom 171 children had IgE-mediated CMPA between 3 and 24 months. The risk of CMPA was 61.3% in those receiving exclusive BF and 14.7% in those breastfed with daily CM supplementation. Peters [53] showed in 5276 children followed up to 12 months of age that the introduction of CM before 3 months of age was associated with a decreased risk of CMPA.

BF should be encouraged for many reasons (nutritional, immunological, and psychological, among others), to which pediatricians fully adhere. However, the role of BF (exclusive or not) and its duration in protecting or promoting allergies has been debated for a long time. Exclusive BF, without being a promoting factor, is not a protective factor for CMPA, as shown by the study of CMPA cases reported to the French Allergo-Vigilance Network from 2002 to 2012 [54] as well as by other studies [55]. Indeed, most cases of anaphylaxis occurred at the time of weaning. CM proteins (bovine beta-lactoglobulin in particular) are thus present in breast milk and their protective or sensitizing role probably depends on the child, on the mother, and on

environmental factors that influence the composition of breast milk [55]. The small doses of CM proteins that pass through CM are probably not always tolerogenic.

As pediatric allergists, we are regularly called upon to care for children with severe and persistent allergies to CM, and for whom it is often very difficult to induce tolerance to CM. These children are at high risk of anaphylaxis and death. The last two deaths reported to the French Allergo-Vigilance Network were due to CM allergies owing to administration error. Thus, despite the absence to date of intervention studies comparable to the LEAP study for peanuts or PETIT for eggs, there seem to be sufficient observational arguments to propose, to children at risk of atopic disease, an early and regular introduction of CM, from the first days of life; this could be in the form of a first infant formula, whatever the child's mode of BF. Ierodakonou's meta-analysis [44], published in 2016, supports this approach. In the case of mixed or artificial BF, we therefore recommend introducing as soon as possible an infant formula based on non-hydrolyzed CM.

If exclusive BF is desired for infants at risk of atopic disease, the early introduction of CM, even before the implementation of food diversification, should be discussed with the family. The standard infant formula can be administered by spoon or syringe to preserve BF. In addition, it is fundamental to avoid the introduction of CM in these exclusively breastfed infants and to propose supplements instead, such as infant formula with advanced hydrolysis based on advanced hydrolysates of CM proteins or rice.

Prevention of FAs, proposals from French-speaking pediatric allergists

These proposals are summarized in Fig. 1.

Feeding at birth and in the first months: promoting breastfeeding

If exclusive BF is desired:

- Discuss with the family of infants at atopic risk the early introduction of CM (10 ml/day by teaspoon or syringe to preserve BF).
- Do not give first milk supplements while waiting for BF to be introduced. If necessary, use an advanced hydrolysate of CM protein or rice protein or even an amino acid formula.

If mixed feeding is desired:

- Introduce first milk daily, from the first weeks, as a complement to BF.
- Avoid unproven HA milks.

The skin

Active treatment of all infant AD with emollients and dermocorticoids should be initiated in order to restore the skin barrier, anti-

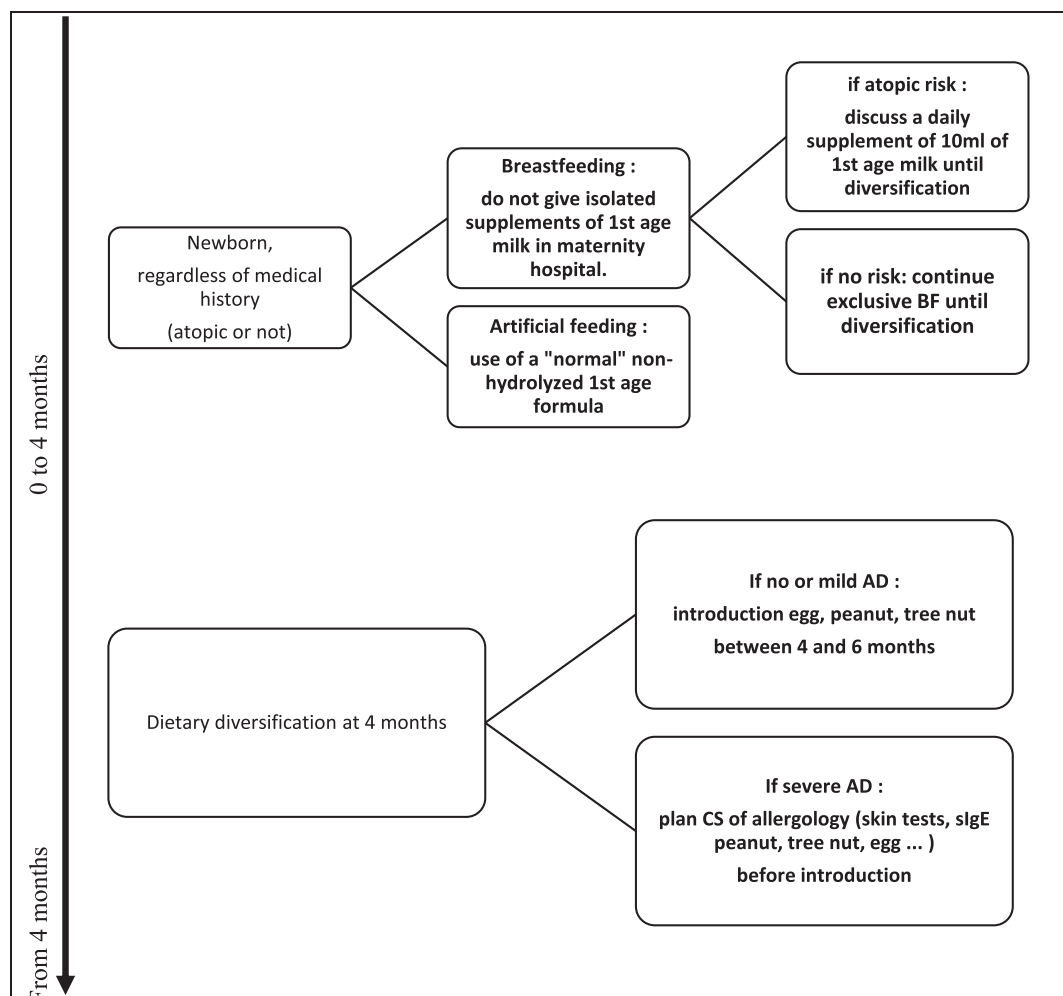


Fig. 1. Food allergy prevention in children: Advice summary BF: breastfeeding; AD: atopic dermatitis; CS: consultation.

staphylococcal treatment should be offered if there is secondary infection, and education on treatment should be promoted.

The application of emollients to newborns and infants as a preventive measure is still under discussion. Further studies are needed in this regard.

Cosmetics/emollients based on dietary proteins should not be used to avoid sensitization or even FAs.

Indirect contact via the infant's skin with peanuts and tree nuts (in France, appetizers are important for sensitization) should be limited as long as the child has not consumed any.

Food diversification starting at 4 months of age with early introduction of eggs, peanuts, and tree nuts

Early diversification is important for all children, whether atopic or not. It must be started between the ages of 4 and 6 months. Fruits and vegetables, eggs, meat, fish, milk and dairy products, including yoghurt, cereals, including bread, and also peanuts and tree nuts should be introduced.

Methods of introduction of egg, peanut, and tree nuts

In the absence of severe AD and/or FA, it is recommended that cookies containing egg, as well as peanut and tree nuts be introduced directly at home according to the protocol described below. It is not necessary to perform prick tests prior to introduction. Indeed, in the LEAP study, no at-risk child had a positive skin test before the age of 5 months.

If the child already has a severe AD and/or FA, we recommend that sPT should be performed in consultation with the following native foods: cooked egg white, crushed ladyfinger cookies, peanut, and nuts. In the case of difficult access to sPT, a specific IgE assay can be considered for allergens of interest: egg white, ovomucoid, peanut, hazelnut, cashew nut). If the sPT result (or sIgE if performed) is negative, the parents can start introduction at home. However, if the sPT result is positive, specific allergological management will be necessary to evaluate the allergic risk and propose a supervised introduction in hospital, an elimination diet, or tolerance induction.

The aim is to introduce 2 g per week of egg and peanut protein and, if possible, the tree nuts most often consumed by the family and entourage, according to the results of the EAT study. These recommendations must be simple to accept and will be even more easily followed in groups of children at high risk of developing an allergy. Nevertheless, it is very important to understand that once introduced into the diet, the allergen must be consumed regularly throughout childhood (necessary duration not known) to avoid the occurrence of an allergy. Indeed, the consumption of an allergen followed by a period of avoidance would lead to a greater risk of causing an allergy. This is why allergens introduced early must be foods that are usually consumed by the family.

Eggs. The working group of pediatric allergists and dietitians (Allergodiet) of the SFA, which has created these proposals and has no conflict of interest concerning the brands cited, proposes to use commercially available ladyfinger cookies: either Blédina® (“My 1st boudoir”) or Brossard® to start with.

The theoretical goal would be to give 2 g of egg protein per week until the introduction of hard-boiled egg during diversification. However, this amount of protein with cookies for very young children is difficult to obtain and we prefer to offer lower amounts at the beginning but more feasible for families.

In practice: one Blédina® cookie contains 1.3 g of egg (or 0.16 g of white and yellow egg protein) and no milk and one Brossard® cookie contains 1.7 g of egg (or 0.22 g of white and yellow egg protein) and milk. Both contain wheat. The Brossard® cookie is the favorite choice because the quantity of egg is closer to the recommendations, except for children with milk allergies who can only consume the Blédina®

cookie. In the case of allergy to CM proteins, the Peptijunior milk-free cookie (1.8 g of egg per cookie) can also be used. Between 4 and 5 months of age, a Brossard® cookie (0.22 g of protein) or a Blédina® cookie (0.16 g of protein) per day crushed and mixed with the compote (between 1.5 and 1.2 g of protein per week) can be introduced. From 5 to 6 months, parents can start using a hard-boiled egg and gradually increase the quantities (see **Appendix 1** on the reintroduction of the egg).

Peanut and tree nuts. For early introduction of both peanut and tree nuts, purees (butter or mash) are easy to use. These purees may contain a single allergen, but to make this early introduction easier we recommend the use of a mash blend containing both tree nuts and peanut at the same time. The “Hazelnut, Cashew and Peanut” mash from the La Vie Claire brand is currently recommended. A total of 28 g of this puree per week provides 8.4 g of peanut (2.18 g of protein), 9.8 g of roasted hazelnut (1.66 g of protein), and 9.8 g of cashew nut (1.76 g of protein). The child must consume one teaspoon of this mixture five times a week to have approximately 2 g of protein per week per meal. It can be suggested to introduce the mixture during consultations and to keep the child in the waiting room (pediatrician, general practitioner, or allergist) for 30 min after the intake.

Peanut only. In the case of sensitization/allergy to tree nuts or because of parents' reluctance to introduce peanut and tree nut at the same time, it can be suggested that peanut alone should be introduced initially and similarly during consultation. The peanut to be used should be in the form of pure peanut butter Léa Nature Jardin Bio® (100%) that is readily available in supermarkets (or other products of equivalent composition: Perl'Amande® or Jean Hervé® in organic stores). Plastic teaspoons can be used with the spoon partly filled: 4 Ml = 2 g peanut butter (0.5 g protein).

The peanut butter is to be mixed with compote or vegetable mash, as explained below. For the first intake, half a plastic teaspoon of peanut butter should be given. In the absence of a reaction, it is recommended to continue home administration of a small plastic teaspoon of peanut butter, 4 times a week from the age of 5 months (this is equal to 2 g of peanut protein per week).

Practical tips for parents on how to prepare the mix: Begin by homogenizing the peanut/tree nut dough with a large spoon so that the fat (oil) mixes with the solid part and thus smooth dough is obtained. Then, in a ramekin-type container, put the desired quantity (e.g., 1 teaspoon) of the peanut/tree nuts paste in the ramekin, add a tablespoon of compote, and mix well until the compote is perfectly mixed with the peanut/tree nuts paste. Finally, incorporate the mixture into the rest of the compote. Avoid giving the peanut paste directly with a spoon to the baby because it is very pasty and it could be difficult to swallow.

Conclusion

The first months of an infant's life are the key moment to implement FA prevention, by focusing on the importance of the intestinal microbiota, by preventing skin sensitization (limiting exposure to allergens, effective treatment of any AD), and by inducing digestive tolerance through broad and early food diversification.

It is therefore essential to provide all families and early childhood professionals (general practitioners, pediatricians, nurseries, day care centers, etc.) with basic prevention advice on both CM allergy (maternity wards) and peanut and nut allergy in order to contain this “epidemic” of FAs in young children.

Thus, families will be warned to avoid cosmetics based on dietary proteins, to wash their hands before touching an infant if peanut and/or tree nuts is consumed or used in the family kitchen, and to introduce allergens early and widely in the child's diet, according to their consumption habits.

Declaration of Competing Interest

None.

Appendix 1: Advice for the reintroduction of cooked eggs

Between 5 and 6 months: pure egg as hard-boiled egg (a hard-boiled egg is an egg that is cooked for 9 min from boiling) can be started. The white and yolk should then be blended and mixed with puree at noon, starting with 5 g of hard-boiled egg twice a week for 1 month (one rounded plastic teaspoon) or 1.3 g of protein per week. Cookies in the form of ladyfinger cookies or equivalent should be continued together throughout the progression of pure-egg intake.

- Between 6 and 8 months: 10 g of hard-boiled egg twice a week (two teaspoons) or 2.6 g of protein per week.
- Between 9 and 12 months: 20 g of hard-boiled egg twice a week (four teaspoons) or 5.2 g of protein per week.
- It is essential that eggs be given twice a week, adapting the quantity to the child's age (30 g for children aged 2–3 years, 40 g for ages 3–4 years, 50 g for ages 4–5 years, etc.).

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