Review Article

Childhood Food Allergy: A Singaporean Perspective

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Abstract

Food allergy is defined as reaction to a food which has an immunologic mechanism. Its prevalence is increasing in children globally and is therefore of increasing clinical importance. A useful clinical approach is to distinguish food allergic reactions by the timing of clinical reaction in relation to food exposure and classified as immediate (generally IgE-mediated) and delayed (generally non-IgE-mediated), with the exception of eczema and eosinophilic gastrointestinal disease, which, when associated with food allergy may be associated with either mechanism. This review is aimed at providing the clinician with a Singaporean perspective on the clinical approach and management of these disorders.

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Introduction

Food allergy is defined as reaction to a food which has an immunologic mechanism. If immunoglobulin E (IgE) is involved in the reaction, the term IgE-mediated food allergy is appropriate. All other reactions should be referred to as non-allergic food hypersensitivity.[1]

Food allergy is increasing throughout Asia and is reported to affect approximately 4% to 5% of Singaporean schoolchildren.[2] It is increasingly presenting as a clinical problem to paediatricians. This review is intended to examine the available information from a Singaporean perspective and to act as a guide to clinicians who care for children. The recommendations are based where possible, on the best available evidence, or if this is not available, on expert consensus. The review covers general principles applicable to both the immediate and delayed manifestations of food allergy.

Types of Food Allergy

As a practical approach to the evaluation of food allergy in a patient, 2 broad types of food allergy can be distinguished based on the timing of the clinical reaction in relation to the food exposure. Clinical features include immediate reactions occurring within minutes (usually up to 2 hours) of ingestion (e.g. anaphylaxis, angioedema, urticaria and vomiting), and delayed reactions that occur over hours to days. These delayed reactions commonly involve the gastrointestinal tract (e.g. food protein induced enteropathy, proctocolitis or eosinophilic oesophagitis) or skin (eczema).[3] Although other symptoms in children have implicated foods or food components in some cases (e.g. infant colic and cow's milk, hyperactivity and food colourings) the mechanisms are uncertain and these are not discussed further here. An algorithm showing the clinical approach to food allergy is shown in Figure 1.

An important feature of IgE-mediated food allergies in preschool aged children is that they may remit with time as tolerance to the offending food is attained. The possibility of tolerance development should be assessed regularly in particular by seeking a history of accidental exposures and by IgE-based testing [skin prick test (SPT), or Pharmacia ImmunoCAP® for immediate reactions] whenever appropriate. Patients are usually reviewed around 12 to 18 months of age to assess for tolerance. This may be confirmed by a formal food challenge which in most cases of IgE-mediated food allergy is conducted in hospital under medical supervision. If food specific IgE persists or the child reacts on accidental exposures, the allergist may

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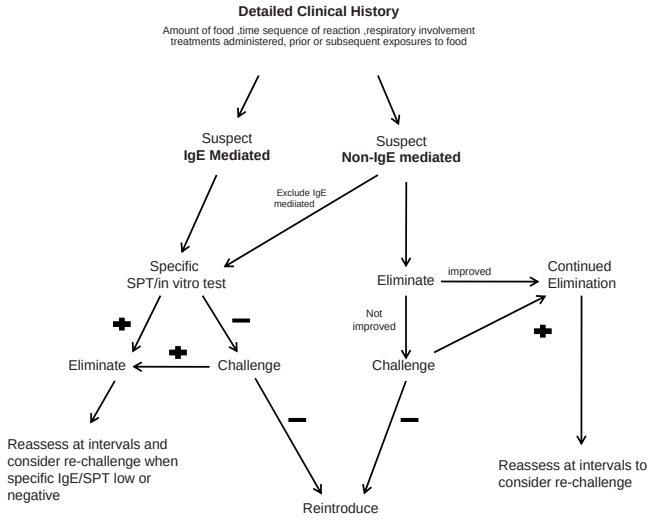

SPT: skin prick test; sIgE: allergen specific IgE

Fig. 1. Algorithm depicting a schematic clinical approach to food allergy.

wait until 4 to 5 years of age before considering a formal challenge or defer the food challenge. Depending on the food allergens, a significant proportion of children with IgE-mediated food allergies (20% to 80%) will still have their allergies when they are 5 years old, or older.[4]

Management of IgE-mediated Food Allergy

It is most important to determine if there are features of anaphylaxis. These include coughing, wheezing, severe distress, pallor, floppiness (in infants) and/or collapse. Over a 15-year period between 1990 and 2005, there have been 6 published series of food-related anaphylaxis in children from 4 different countries (UK, USA, Sweden and Germany) recording 31 deaths and 132 severe life-threatening reactions. The triggers of fatal reactions were peanut (48%), milk (17%) and egg (7%).[5] In Singaporean children, birds' nest is the most common cause of anaphylaxis.[6] Peanut allergy was the most common reason for provision of adrenaline (Table 1).[7] As anaphylaxis is a severe and potentially life-threatening allergic reaction that may be triggered by very small amounts of food allergen, strict avoidance of the relevant food is critical. Anaphylaxis has been defined as an acute-onset life-threatening multi-systemic illness that involves the skin and/or mucosal tissue and at least an involvement of one of the following: (i) respiratory compromise; (ii) reduced blood pressure (BP) or associated symptoms of end-organ dysfunction.[9]

For children with a convincing history of an immediate IgE-mediated allergic reaction without anaphylaxis (e.g. generalised urticaria, angioedema or acute vomiting, but without cardio-respiratory involvement) occurring within 1 to 2 hours of ingesting the food, the offending food should be strictly eliminated from the diet. Children with anaphylactic reactions to foods should be formally reviewed by a paediatrician with specialist expertise in food allergy, ideally within 6 to 8 weeks. A written anaphylaxis action plan and prescription of self-injectable adrenaline (for children who weigh over 10 kg), should be provided at the time of the acute episode, along with a demonstration of the correct use of this device. In addition, parents should be trained in anaphylaxis recognition and receive information on strict dietary avoidance.

Table 1. Causative Foods for Anaphylaxis and Epipen Prescriptions in Singaporean Children

Causes of anaphylaxis[8]	**Reasons for Epipen prescription[7]**
Bird's nest 27%	Peanut 41.9%
Crustacean seafood 24%	Shellfish allergy 28.5%
Egg and milk 11%	
Chinese herbs 7%	

Table 2. Positive Predictive (PPV) and Negative Predictive (NPV) Values of Food-specific IgE Concentration (in kU/L Using Pharmacia CAP-FEIA®) and PPV (Wheal diameter) for Skin Prick Test in Predicting Reactions in Children

Food allergen	**Food-specific IgE concentration (CAP-FEIA®)**		**Skin prick test**
	>95% PPV (kU_A/L)[11]	**>95% NPV (kU_A/L)[11]**	**>95% PPV (mm)[12]**
Egg	6	-	7
Milk	32	0.8	8
Peanut	15	<0.35	8
Fish	20	0.9	7
Soybean	65	2	-
Wheat	100	5	-

Diagnostic Tests

There are only limited diagnostic tests for the diagnosis of IgE-mediated food allergy. The standard techniques are SPT and *in-vitro* testing for specific IgE-antibodies.[10] These tests measure sensitisation to the allergen tested but do not necessarily mean that the child will develop symptoms on exposure to the food. Thus a negative result is an excellent negative predictor; however, a positive test may not necessarily indicate clinical allergy. The results of these tests therefore have to be interpreted with the clinical history. For those where the clinical history is not clear, for example in eczema, or when the child has never been exposed to the allergen, the level of the specific IgE may be used as a guide to possible clinical relevance (Table 2). It should be noted that the range of food allergens studied is limited to those listed in Table 2. These food-specific serum IgE levels have been established in western populations and its relevance in Asians has not been verified. However, it should be noted that high levels with a high positive predictive

value have been determined for a restricted range of food allergens.[9] Values below these thresholds do not necessary mean that there will be no clinical reaction; their positive predictive value is just less.

In situations where the allergen is labile, as in certain fruits and vegetables, testing with fresh fruit or vegetable, is a useful means to demonstrate sensitisation. Pollen allergy, which is uncommon in Singaporeans, may result in the oral allergy syndrome, which is a consequence of cross-reactivity allergens between pollen and fruit/vegetable allergens. In some case reports, it has been suggested that patients with dust mite allergy, which is highly prevalent in the tropics like Singapore, may also present with a different form of oral allergy syndrome due to IgE cross-reactivity between tropomyosin of dust mite allergens and shellfish proteins that share sequence and structural homologies.

Oral food challenges continue to be the gold standard in the diagnostic evaluation in both immediate and delayed food allergy reactions.

Unconventional diagnostic methods are increasingly being made available by commercial groups. These include food specific IgG tests, cytotoxic food testing, ALCAT test, sublingual/intradermal provocation tests, applied kinesiology and electrodermal testing. These tests should not be used as they lack scientific rationale, standardisation, and reproducibility. Intradermal testing to food allergens is also not recommended as it has an unacceptably high false positive rate, and is associated with higher risks of systemic reactions, including fatal anaphylactic reactions.[13,14]

Specific IgE-mediated Food Allergies

Although allergy can occur to any food substance, there are only a few food allergies that are relatively common. The common food allergens in infancy are egg and cow's milk. Peanut and tree nut allergy is as common as 1% to 2% in Western populations and its increasing prevalence[15-17] is relatively uncommon in Singapore[18] and the Asian region.[19] Shellfish allergy tends to develop after infancy and in later childhood or adulthood.[1,12,20]

Egg

Egg white allergens include ovalbumin, ovomucoid, ovomucin, ovotransferrin and lysozyme.[21] There are also multiple allergenic proteins in egg yolk, with the most common being alpha-livitin. The reduction in allergenicity by heat or gastric digestion provides an explanation for those children who react to uncooked but not cooked egg,[22,23] and for subjects who react to egg after cutaneous contact but not after ingestion.[24] Children who are allergic to hen's eggs are not allergic to chicken.

Children are frequently found to be sensitised without having a previous history of egg ingestion.[25] The pattern of early life sensitisation to common allergens such as cow's milk and egg was also found in Singaporean children where sensitisation is more prevalent in children aged 1 year or younger than in older children.[26] In a study of 107 infants with atopic dermatitis and no known egg ingestion, 67% had evidence of IgE sensitivity to egg and positive reactions to an oral food challenge.[27]

Approximately two thirds of egg allergic children outgrow their egg allergy by 5 years of age.[25] Smaller SPT weal size, cutaneous reactions and lower specific IgE antibody levels are positive prognostic factors for the development of tolerance to egg. Subjects who are sensitised to the egg allergens which are resistant to gastrointestinal degradation appear to be less likely to outgrow their sensitivity.

There are several issues concerning immunisation in egg allergic children. Measles vaccines are produced in a culture of chick embryo fibroblasts. In the past, MMR vaccine for children with egg allergy has been controversial; however, now it is agreed that MMR vaccine is not contraindicated in egg allergy[28-30] and can be safely given in the normal manner. Vaccines have been caused by sensitisation to gelatin.[31]

A severe reaction to egg is a contraindication to influenza immunisation. Fatal anaphylaxis has also been documented in an egg allergic child following influenza immunisation. The influenza vaccine is derived from egg embryo fluid. An egg protein content of less than 1.2 mcg/mL of egg protein is proposed as an acceptable standard for influenza vaccine. Egg allergic children have been safely given influenza vaccine with a 2-dose injection protocol (1/10, followed 30 minutes later by 9/10 dose) with vaccines containing less than 1.2 μ/mL egg protein.[32] If influenza vaccine is to be given to an egg allergic child, it should be supervised by an allergist.

Crustaceans and Shellfish

In contrast to the low prevalence of peanut allergy in Singapore, crustacean shellfish appears to be an important cause of food allergy. In terms of severity, hospital-based studies on anaphylaxis show that crustacean shellfish are one of the most important food triggers in children in Singapore[8] and Thailand.[33] Interestingly, this phenomenon appears to be reversed in Western populations with less severe crustacean shellfish allergy in comparison to peanut allergy. Tropomysin is a major allergen in shrimp and shellfish allergy.[34] It is postulated that the high rates of crustacean shellfish allergy in Singapore and the Asian region could be due to cross reacting house dust mite allergens, which are highly potent inhalant allergens in Singapore and also contains tropomyosin. A study of shellfish allergic patients in Hong Kong found a high degree cross-reactivity between different species of shellfish and between shellfish and house dust mites.[35]

Peanut and Tree Nuts

Peanut allergy appears to be increasing in many societies. A population-based study of 3 year-olds in the UK found

the prevalence of sensitisation to peanuts increased from 1.3% to 3.2% in only 6 years between 1989 and 1995.[13] Its prevalence in Singapore is relatively low. A survey in preschool and secondary schoolchildren showed that the prevalence of peanut allergy is not more than 0.6%; however, peanut allergy was the most common reason for prescription of an adrenaline autoinjector (41.9% of prescriptions) in children in Singapore, although this included non-native children attending international schools.[7] Additionally, in a recent hospital-based study, peanut emerged as the most common food allergen triggering anaphylaxis.[36]

The allergenic component of the peanut is found in the protein (not the carbohydrate or fat). For this reason peanut oils are not allergenic unless they are contaminated with the protein. Eight peanut allergens have been identified and are termed Ara h 1 to Ara h 8. Most of these peanut allergens are members of the seed storage protein families. Peanuts belong to the plant family of legumes, which also includes soybeans, green beans and lentils. However, clinical cross-reactivity between peanut and other legumes is uncommon (less than 10% of cases).

Approximately 20% of preschool children who are allergic to peanuts will outgrow their allergy by the school years.[37] This is more likely if the level of peanut sensitisation is low. Because young children may grow out of the allergy, it is important to reassess such children when they start school (about 5 years of age).

Although tree nut allergy can occur in isolation, sensitisation and clinical allergy to tree nuts is common amongst children with peanut allergy. In the UK, 32% of peanut allergic children are sensitised to tree nuts and 21% reported clinical allergy.[38] The presence of peanut and multiple nut sensitisation is likely due to the cross-reactivity between vicillin allergens present in peanut (Ara h 1) and treenuts, walnut (Jug r 2), hazelnut (Cor a 11) and cashew nut (Ana o 1).[39]

There are recent studies examining the efficacy and safety of oral and injectable immunotherapy but these are still in progress and should be considered standard therapy.[40-42]

Fish

The fish from tropical waters consumed in Singapore are quite different from temperate fish. Consumption practices are also quite different. Fish is a weaning food for many children in Singapore. In a questionnaire survey conducted on Singaporean infants, up to 50% had consumed fish by the age of 6 months.[19] This contrasts with the Western diet, where fish is regarded as highly allergenic food**.** Fish allergy affects up to 3% of children in the Scandinavian population[43] and up until very recently, the American Academy of Pediatrics (AAP) had recommended that fish be avoided until the age of 3 years.[44] Based on a questionnaire survey, fish allergy amongst Singapore schoolchildren is less common than the Western world.[18]

Of the temperate fish, the major allergen of cod, Gad c 1, belonging to the protein family of parvalbumins has been the most extensively studied.[45] Parvalbumin constitutes the major cross-reactive fish allergen of other temperate fish. The evaluation of 4 species of tropical fish (threadfin, pomfret, Indian anchovy and tengiri) commonly consumed in Singapore and often used as weaning foods in infants have also shown that parvalbumin is the major allergen of these tropical fish.[46] These parvalbumins are cross-reactive with Gad c 1, which was also clinically evident as the majority of fish allergic children in this study had clinical reactions to more than 1 fish. Only 1 of the 10 children evaluated was mono-sensitised and could tolerate consuming other fish without a clinical reaction. Hence, the allergenicity of tropical fish is comparable with cod. Sera from fish allergic children in Japan demonstrated high IgE-binding activity to many fish species; however, there was low IgE-binding activity to a few species, e.g. halibut (Osteichthyes) and sharks (Chondrichthyes).[47] The reason(s) that fish allergy is not highly prevalent in tropical Asia despite high consumption and exposure in early life is not obvious, although it is tempting to postulate that paradoxically early large exposure rather than conventional strict avoidance has induced immune tolerance.[48]

Cow's Milk

Cow's milk contains a large number of potential allergens. Major allergens are caseins (alpha-, beta-, and kappa-casein) alpha-lactalbumin (ALA), beta-lactoglobulin (BLG) and bovine lactoferrin.

Only 40% to 80% of children with IgE-mediated cow's milk allergy will outgrow their allergy by 8 years of age, whereas with non-IgE-mediated cow's milk protein allergy, children will develop tolerance by 5 years of age.[49,50]

Management of IgE-mediated cow's milk allergy without anaphylaxis will generally involve formula replacement with an extensively hydrolysed formula (eHF) or a soy-based formula.[51] It is useful to confirm that the SPT and/or serum specific IgE are negative to soy before commencing the soy formula. In a Korean hospital-based population, 18% of cow's milk sensitised children were also sensitised to soy.[52] Mothers should be encouraged to continue breastfeeding and generally do not require dietary cow's milk protein restriction, unless the infant has residual manifestations, such as eczema, while being breastfed. For the rare infants who do not tolerate a soy or eHF formula or those with anaphylaxis, an amino acid-based formula (AAF) should be utilised. AAF contains no proteins or peptides so it is not possible to be allergic to such a formula.

Soy

Soy allergy affects less than 1% of the childhood population although up to 3% may show sensitisation.[53] Soy protein is commonly introduced into the diets of

Singaporean children in the first 2 years of life.[54] There are multiple allergens in soy (at least 16); however, there is uncertainty about which ones are important for clinical reactions.[55] Soy proteins are widely utilised in processed and manufactured foods. A variety of soy products have elicited allergic reactions, soybean sprouts, soy milk, yogurt, desserts, flakes, flour, tofu and meat substitutes. Soy is a legume as is peanut. However, cross-reactions between soy and peanut occur only in a minority of cases. A potential source of allergen in soybeans is soybean lecithin. Lecithins are important as emulsifiers and stabilisers for the food and pharmaceutical industries. However, the proteins present in soy lecithin and soy oil do not usually cross-react with those relevant to soybean allergy.

Severe reactions to soy are rare compared to reactions to peanut and tree nuts. In general, larger amounts of soy protein (10-50 mg) are required to trigger allergic reactions than with peanut.[56] A number of cases of soy allergy are non-IgE-mediated.

Wheat

There are a number of different clinically relevant allergens in wheat and sensitisation to these is associated with different patterns of clinical reactivity. Other cereals such as barley and rye may contain related allergens. Major wheat allergens are the albumins/globulins which are important in atopic eczema, the omega5-gliadins which can trigger the rare entity of wheat-dependent exercise-induced anaphylaxis or urticaria, and low-molecular-weight glutenin which can trigger anaphylaxis.[57] Some investigators have found that wheat allergy is more likely to persist into later childhood and adult life as compared with egg and cow's milk allergy.[58] Delaying exposure to wheat in infancy does not lessen and might even increase the development of wheat allergy.[59]

Although seemingly uncommon, anaphylaxis due to reaction to mite allergens in dust mite infested wheat flour has been described in the tropics and Singapore.[60] The diagnosis requires a high index of suspicion and could be mistakenly attributed to wheat allergy unless the ingested flour sample is examined microscopically for mites.

Bird's Nest

Allergy to edible bird's nest from swiftlets has been described in the Chinese population in Singapore, Malaysia and Hong Kong. It is the most common cause of anaphylaxis in Singapore children. This food allergen is unique to these regions as it is consumed mainly by ethnic Chinese. This food is a popular Chinese delicacy believed to have health benefits. A salivary protein with homology to the ovomucoid inhibitor has been identified as the major allergen.[61] The natural history of bird's nest allergy has not been described. Repeated exposure has resulted in recurrent anaphylaxis, and ultimately, most sufferers refrain from further exposure. There is no known cross reacting food allergen and hence avoidance of other foods is not necessary.

Cross Reactivity of Food Allergens

Clinical reactivity to food allergens is generally very specific. Consequently, therapeutic elimination diets should not be based on exclusion of food families but be based on individual foods proven to induce allergic symptoms. Furthermore, interpretation of IgE testing should be made with caution, as patients frequently have positive SPT or RAST test to related food families, but this often does not correlate with clinical reactivity. On the other hand, a limited number of food allergens may exhibit high cross-reactivity, eg. cow's milk and goat's milk, and these may have to be taken into consideration when prescribing an elimination diet. Table 3 illustrates general approximations of botanical or species allergen cross-reactivities of common food allergens.

Delayed (Non-IgE-mediated) Food Allergy Syndromes

With the exception of eczema, these syndromes are much less common than IgE-mediated food allergies. The diagnosis of non-IgE-mediated delayed food reactions poses particular diagnostic challenges as, apart from food elimination and re-challenge, no reliable diagnostic tests are available.[3] There are, however, well described entities affecting the gastrointestinal tract such as food protein-induced enterocolitis syndrome (FPIES), eosinophilic oesophagitis (EO), food protein-induced proctocolitis, allergic enteropathy and coeliac disease as summarised in Table 4. There is also a possibility of a clinical overlap with other food-associated disorders such as lactose malabsorption, coeliac disease or idiosyncratic reactions to foods. Management of delayed food allergy in breastfed infants (in particular those with eczema) may be further complicated by the possibility of exacerbation by food allergens in the breast milk.

Eczema

Food allergy may exacerbate eczema. However, it is worthwhile noting that the majority with mild eczema are not triggered by food allergy. In a report from the US, about one third of children with eczema attending an allergy clinic had food allergy triggered eczema exacerbations proven

Table 3. Examples of Clinical Cross Reactivity among Food Allergens[62]

Food 1	Food 2	Cross reactivity	Percentage[62]
Fish	Other fish	Moderate to high	>50%
Peanut	Tree nuts	Moderate	≅35%
Peanut	Soy	Low	<10%
Cow's milk	Goat's milk	Very high	≅90%
Cow's milk	Beef	Low	≅10%
Hen's egg	Chicken	Very low	<1%

Table 4. Summary on Food-Protein Induced Gastrointestinal Disorders

	Onset of symptoms in relation to ingestion	Clinical manifestations/Physical examination	Expected age of clinical resolution	Investigations
Food protein-induced enterocolitis syndrome (FPIES)	2-4 hours	Profuse vomiting, diarrhoea, sudden onset of pallor and floppiness; hypovolaemic shock: responds dramatically to fluid resuscitation, adrenaline not required	Around 3 years old	History, no laboratory markers available
Eosinophic oesophagitis (EO)	days	Vomiting, refusal to feed, failure to thrive (FTT), oesophageal dysmotility, unresponsive to proton-pump inhibitors	Unknown	Endoscopy
Food protein-induced proctocolitis	hours/days	Rectal bleeding in a well infant, normal perineal inspection, well-thrived	12 months	Rectal biopsy
Allergic enteropathy	hours/days	Vomiting, diarrhoea, severe irritability, FTT, iron deficiency anaemia, protein losing enteropathy, receiving cow's milk in diet	Unknown	Small bowel biopsy
Coeliac disease	hours/days	Vomiting, chronic diarrhoea, abdominal distention, FTT	Life-long	Antibody testing HLA genetic typing Endoscopy

by food challenges.[63] The reactions may be IgE-mediated or non-IgE-mediated.[64] Eczema flares may occur over a variable period of time following ingestion of a food ranging from hours to days. Food-specific serum IgE testing is helpful in diagnosing IgE-mediated food allergy. There is no test for non-IgE-mediated food allergy in eczema apart from dietary elimination and rechallenge.[64] The duration of a trial of food elimination is a minimum of 2 to 4 weeks, and a clinical response would be expected within 2 weeks if the food is an exacerbating factor and the elimination is properly implemented. Infants with early onset (within the first 6 months) eczema of at least moderate severity have a high incidence of food allergies. If a food allergen is suspected to be exacerbating eczema, removal of the food should be accompanied by optimisation of eczema care which includes topical steroids, adequate emollient use and consideration for treatment of staphylococcal skin infections. In severe cases of eczema, it is often not possible to determine whether food is an exacerbating factor until the staphylococcal skin infection is controlled. Not all cases of eczema with a positive IgE on skin prick or RAST testing will improve following elimination of that food and many children with a positive IgE to a food will tolerate the food with no clinical problem.

Prevention of Food Allergy

Although it had been generally accepted that early introduction of food allergens can lead to an increase in allergic sensitisation to foods such as cow's milk, egg and peanuts, advice on allergen avoidance in the prevention of food allergy is still debatable. The previous recommendations by the AAP that solid foods be introduced later in life and to exclusively breastfeed until 6 months of age, especially in infants from allergic families, have recently been revised. Instead of delaying solids until 6 months of age, cow's milk until 1 year, egg until 2 years, and peanuts, tree nuts, and fish until 3 years,[65] the current 2008 guidelines are less dogmatic and have advised exclusive breastfeeding whenever possible in high-risk infants for the first 4 months[43] and such recommendations can also be seen in the Australian Society of Clinical Immunology and Allergy website: (http://www.allergy.org.au/images/stories/pospapers/ascia_infantfeedingadvice_oct08.pdf). There is modest evidence that atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolysed formulas, compared with cow milk formula, in early infancy. Extensively hydrolysed formulas may be more effective than partially hydrolysed in the prevention of atopic disease.[66]

Based on the 2008 AAP guidelines, weaning to semi-solids is recommended from 4 to 6 months of age. There is currently no convincing evidence that avoidance of allergenic foods after this age has a protective effect.[67] For example in a recent study on fish allergy, a low prevalence of fish allergy was found in Singaporean children, as compared to prevalence rates of fish allergy in Europe and the USA. This occurred despite very early introduction of fish in the infant's diet (50% by the 6th month of life) and a high consumption of fish in Singaporean children. These epidemiological data suggest that early introduction of fish and high intake of fish might protect against fish allergy, by inducing tolerance.

In conclusion, it is important that paediatricians be aware of the different types of food allergies, the limitations of the available tests and the appropriate management steps.

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