

REVIEW

A patient-specific approach to develop an exclusion diet to manage food allergy in infants and children

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Email: carina.venter@childrenscolorado.org**Abstract**

Food allergy is becoming increasingly common in infants and young children. This article set out to explain the different factors that should be taken into account during an individualized allergy consultation: Foods to avoid and degree of avoidance, suitable alternatives, self-management skills, co- and cross-reactive allergens and novel allergens alongside the role of the industry in allergen avoidance, importance of nutritional aspects of the diet and the future directions that nutritional guidance make take. Allergy management advice should be individualized to provide a patient-specific approach. Changes in the management of food allergies have in particular occurred in nut, milk and egg allergies over the past few years. There has also been a progressive increase in our understanding of cross-reactivity between different foods and also food and aero-allergens. A patient-specific approach of allergen avoidance should consider factors relating to industry and the environment such as food and nutrition literacy, threshold levels, cross-contact/contamination and safe eating away from home. Increasing migration and travel has also led to exposure of unfamiliar foods. As understanding improves on individual allergens and threshold levels, food labels and food labelling laws are affected. Allergy specialist dietitians should also keep up to date with the latest information on nutrition, the gut microbiome and the immune system to incorporate nutrition strategies in a dietetic consultation using an evidence-based approach.

1 | INTRODUCTION

Food allergy is an increasing and challenging health problem in childhood¹ with allergen avoidance forming the cornerstone of management.² Advice regarding allergen avoidance will remain standard in the allergy-focused dietary consultation including food label terminology, hidden allergens in foods, suitable replacement foods and ensuring dietary adequacy. (see Table 1)³ However, good nutrition does not end with adequate growth and should include a focus on long-term nutrition for healthy eating and the prevention of diseases such as obesity, hypertension, cardiovascular diseases, renal diseases, osteoporosis, auto-immune and inflammatory conditions.

Staying abreast of advances in food allergy research can help the allergy specialist to provide guidance beyond standard advice taking

into account, for example different phenotypes⁴ and gender.⁵ A patient-specific approach (Figure 1) requires a clear understanding of diagnostic methods, cross-sensitization and coexisting allergies, tolerance development, growth status, nutrient deficiencies specific to the patient with food allergies, relevant food labelling laws, allergen threshold levels and nutritional factors/food components that could affect the gut microbiome and immune system. Ideally, no food should be removed from a child's diet without the involvement of a dietitian. Dietetic input has been shown to improve growth and nutritional biomarkers,^{6,7} and may help to minimize risks and provide options for better nutritional care. This review will focus on recent advances in food allergy in children and offers "food for thought" and practical suggestions to provide more patient-specific advice during a dietary consultation.

TABLE 1 Standard allergen avoidance advice provided by the allergy specialist dietitian adapted with permission from Venter and Meyer³

Sources	Other terms	Nutrients involved	Alternatives
Milk	Butter/many margarines or fat spreads, cheese, any mammalian milk (cow's/sheep/goat milk), evaporated/condensed milk, cream, ghee, yoghurt, ice creams, custard, dairy desserts and manufactured food using any milk-based ingredient	Casein, caseinates, curd, lactoglobulin, lactose, milk solids, whey, buttermilk, milk sugar, whey sugar, whey syrup sweetener	Vitamin A, vitamin D, riboflavin, pantothenic acid, cyanocobalamin, calcium, magnesium, phosphate
Egg	Egg white and yolk, cakes, biscuits, specialty breads, mayonnaise	Albumin, dried egg, egg powder, egg protein, frozen egg, globulin, lecithin (E322), livetin, ovalbumin, ovomucin, ovovitellin, pasteurized egg, vitellin	Riboflavin, biotin, protein, vitamin A, cyanocobalamin, vitamin D, vitamin E, pantothenic acid, selenium, iodine, folate
Wheat	Bread, breakfast cereals, pasta, cakes, biscuits, crackers, cold cooked meat, pies, batter, flour, semolina, couscous, bottled sauces and gravies	Bran, cereal filler, farina, starch, wheat, durum wheat, semolina, spelt, kamut, wheat bran, wheat gluten, wheat starch, wheat germ oil, hydrolysed wheat protein, triticale, bulgur wheat	Fibre, thiamine, riboflavin, niacin, calcium, iron, folate if fortified
Fish	All types of white and fatty fish, anchovy, (Worcester sauce), aspic, caviar, surimi, Caesar salad, Gentleman's Relish, Kedgeree, Caponata, fish sauce, paella, bouillabaisse, gumbo Some people may tolerate canned fish Fish oil capsules may cause reactions in highly sensitized individuals	All fish: protein, iodine Fish bones: calcium, phosphorus, fluoride Fatty fish: vitamins A and D, omega-3 fatty acids	Under 2 y: - Extensively hydrolysed (casein/whey) - Hydrolysed rice formulas - Amino acid based formulas Over 2 y—over the counter calcium enriched, milk-free alternative drinks may be considered: - Rice milk* - Soya milk, oat milk, chufa milk, potato milk, almond milk, coconut milk, pea milk- Other foods: - Milk-free versions of spreading fats/margarine, cheese, yoghurts, ice cream and cream

(Continues)

TABLE 1 (Continued)

	Sources	Other terms	Nutrients involved	Alternatives
Shellfish	Crayfish, crab, lobster, shrimp, prawns		Similar nutrients to white fish Crab and mussels: good sources of omega 3 Selenium, zinc, iodine and copper	
Molluscs	Clams, mussels, oysters, octopus, squid, snails, scallop	Health food preparations such as green lipped mussel extract, oyster sauce	Varying amounts of protein (scallop), calcium (clam), zinc (oysters) and iron (clam)	
Peanut	Peanuts, expeller pressed peanut oil, peanut flour, peanut butter, peanut snacks, satay sauce May contain peanut: sprouts, confectionery, frozen desserts, Asian dishes (Indonesian, Malaysian, Thai and Chinese), trail mix, rice crackers, cereal bars, cookies, brownies, nut toppings on ice cream, vegetarian/vegan foods, breakfast cereals, pesto sauce may sometimes contain peanut	Arachis oil, hypogeia, peanut protein, groundnut, earth nut, monkey nut	Vitamin E, niacin, magnesium	
Tree nut	Similar foods as peanut	Hazelnut: filbert, cob nut	Depends on type of nut	
Almond, hazelnut, walnut, cashew nut, pecan nut, Brazil nut, pistachio nut, macadamia nut	Amaretto contains almond flavour Worcester sauce (walnuts) Korma sauce (almonds)	Macadamia: Queensland nut, candle nut Pecan: Hickory nut Please note: Nutmeg, coconut**, pine nut and palm nut are not classified as nuts		
Sesame seed	Sesame seeds, sesame oil, for example halva, tahini, hummus, seeded bread/rolls, gomashio, Asian foods using sesame oil, Greek, Iranian, Lebanese and Turkish food, Aqua libra		Protein, fats, vitamin E, calcium, potassium, phosphorus, vitamin B and iron. Avoidance has no significant effect on nutrition	
Celery/celeriac	Primary allergy: Celery and Celeriac in its raw, cooked, juiced, canned and dried (Celery spice) form Oral allergy syndrome: dried celery/celeriac may be tolerated		Fibre Avoidance has no significant effect on nutrition	
Mustard	Mustard Mustard seed Curry powder Pizza Sauces, marinades, dressings		Avoidance has no significant effect on nutrition	

(Continues)

TABLE 1 (Continued)

	Sources	Other terms	Nutrients involved	Alternatives
Soya	Soya sauce, soya products, meat substitutes, breads, vegetarian/vegan foods, processed meat, for example hot dogs, peanut butter, foods labelled as "diet" and "high-protein" or "low fat"	Soya beans Soya flour Soya protein / gum / starch Texturized (or hydrolysed) vegetable protein Soya flavouring Soya lecithin (E322)	Thiamin, riboflavin, pyridoxine, folate, calcium, phosphorus, magnesium, iron, zinc, protein, fibre	Cow's milk Rice milk* Oat milk Chufa milk Potato milk Almond milk Coconut milk Pea milk Meat, fish, poultry or other soya-free vegetarian alternatives
Lupin	Often used in mainland Europe in pastries, bread, pizza, and lupin seeds in seeded breads		Protein, fat, fibre, thiamin, riboflavin and vitamin E— Avoidance has no significant effect on nutrition	

*In some countries rice milk not allowed <4.5 y as a substitute for cow's milk due to high arsenic content

**Coconut is considered an allergen in the USA by the Food Allergen Labeling Consumer Protection Act (FALCPA).



FIGURE 1 Factors to take into account when developing a patient-specific exclusion diet. Figure 1 summarizes the factors that should be taken into account to ensure that a patient-specific advice is provided during the dietetic consultation

2 | CHALLENGES POSED BY INDIVIDUAL ALLERGENS

Although allergen avoidance remains standard for both immunoglobulin E (IgE) and non-IgE-mediated allergies, recent research highlights

areas where this advice needs to be modified to match novel data on sensitization vs tolerance⁸ as well as cross-reacting allergens (Box 1). For IgE-mediated allergy, it is possible to be sensitized, but not allergic and food sensitization should be evaluated in the context of the clinical history.⁹ In addition, a growing body of evidence indicates that for

sensitized but tolerant individuals, avoidance of the sensitized food may lead to loss of tolerance and development of allergy.⁸ Equally so, if previously allergic patients have demonstrated tolerance to an allergen, it should be consumed regularly.¹⁰ Unnecessary avoidance of foods increases the fiscal, emotional and nutritional burden of allergy.¹¹⁻¹³

The most striking advances in the management of food allergy in the past few years relate to nuts, lupin, milk, egg and foods cross-reacting with pollen or animal allergens.

3 | PEANUT AND TREE NUT ALLERGY

IgE-mediated peanut and tree nut allergies are common causes of anaphylaxis and often coexist, with up to 20%-30% of individuals

with peanut allergy also allergic to one or more tree nuts.^{4,14} Tree nut allergies are unevenly geographically distributed.^{15,16} Johnson et al showed that analysing data over a 10-year period, peanut and cashew nuts were more likely to cause anaphylaxis than hazelnuts. Cashew nut reactions increased over time compared to peanut and hazelnuts.¹⁷ The EuroPrevall study showed that not only does the prevalence to different tree nuts differ across Europe where, for example, hazelnut allergies are prevalent in most countries (with the exception of Spain and Greece), but the allergens leading to sensitization also differ between countries and between children and adults.¹⁵ Furthermore, Haroun-Diaz et al¹⁶ showed that differences in prevalence within countries also exist. Lipid transfer protein (LTP) sensitization and severe reactions to nuts were more common in southern Spain (Madrid) than in northern Spain (Asturias). This indicates that pollen sensitization, rather than food intake, may play a bigger role in different prevalence rates and sensitization patterns.

Previous recommendations advised peanut allergic individuals to avoid all tree nuts because of the likelihood of multiple tree nut allergies, and the high risk of cross-contact/contamination during processing. However, a study from the United Kingdom (UK)¹¹ indicated that about 30%-40% of peanut and tree nut allergic individuals are not sensitized to other tree nuts and tolerate these in their diets. In addition, a retrospective case series from the United States (USA) indicates that many individuals with a specific tree nut allergy pass oral food challenges to other tree nuts even when sensitized.¹⁸ Furthermore, development of tree nut allergy has been reported in sensitized, but tolerant individuals after exclusion from the diet.¹⁹ Recent British Society for Allergy and Clinical Immunology (BSACI) guidelines now recommend active inclusion of "non-allergic" nuts in diets of individuals with tree nut allergy, once tolerance has been ascertained,^{20,21} but it unclear to what extent families adhere to this advice.

Passing an oral food challenge is positively associated with the likelihood of continued ingestion of the nut.²² It is still unknown whether ingestion of tolerated tree nuts ameliorates development of tolerance to other tree nuts,²³ or whether it prevents development of allergy to the tolerated nut, but it does increase the quality of life of individuals and for vegetarians allows another protein source to be included in the diet.²⁴ It is, however, fair to say that the balance has shifted towards timely introduction of tolerated nuts with continued intake. For babies at high risk of development of peanut allergy (ie a history of egg allergy or severe atopic dermatitis), there are now guidelines on the early introduction of peanut,²⁵⁻²⁷ based on the outcomes of the LEAP study.²⁸ Early inclusion of common allergens into the weaning diet is now recommended in most feeding guidelines.²⁵⁻²⁷

4 | LUPIN AND LEGUMES

The legume family includes a number of main allergens (peanut, lupin and soya), each with characteristics of possible cross-reaction with other legumes, tree nuts and pollens.

Dried and boiled lupin (*lupini*) may be consumed whole as a traditional snack in some Mediterranean countries and lupin flour may be

BOX 1 Allergen avoidance

What we know

- Allergen avoidance is individualized, based on history, the allergen involved, testing results and oral food challenge outcome.
- Allergy to one food (eg cashew or salmon) within a species does not necessarily necessitate avoidance of ALL foods within the species (tree nuts or fish).
- Many children with IgE-mediated allergy to unheated hen's egg or unheated cow's milk may tolerate these ingredients in a baked form.
- Food allergies secondary to pollen are increasingly seen in paediatric allergy clinics.
- Shellfish allergic patients also react to certain insects.

Challenges

- Who/how/where do we challenge to baked cow's milk (BM) or baked hen's egg (BHE)?
- How should we educate families on inclusion of BM or BHE when tolerated?
- Providing practical advice on "traces/may contain" as threshold doses are not known for all foods.
- Dietary supplements and dietary manipulation practices that may impact on microbiome/immune system.
- Practical advice on lupin avoidance in countries where it is not considered a major allergen for food labelling and education on lupin cross-reactivity with other allergens.
- Dietary advice on food allergen avoidance secondary to pollen (eg soya, apple) in childhood.
- The emergence of insects as novel food with potential to cross-react in shellfish allergic children.

Important, but needs work

- Precautionary allergen labelling requires better definition and research to give reasonable and practical advice to patients.

added to improve the protein content of wheat flour or as a gluten-free alternative in baked goods.²⁹ In Denmark, 35% of peanut sensitized adults had challenge-proven allergy to lupin.³⁰ However, in children lupin allergy is very uncommon, both in the Netherlands³¹ and Italy.³² The rate of challenge-proven allergy to lupin is still unknown in other countries, including Australia and New Zealand where lupin has recently been declared a major allergen.³³

Lupin is considered a major allergen in the EU and UK despite a lack of clear prevalence data.³⁴ In the USA, lupin is not considered a major allergen but is also not typically a hidden ingredient so patients should easily be able to identify lupin on a product label if they are aware they are lupin allergic. Educating patients of this risk is therefore important (Box 2). In addition to its cross-sensitization with peanut (particularly Ara h1) and possible clinical allergy, lupin also cross-reacts with other legumes. Bahr et al³⁵ showed that in 6 subjects sensitized to lupin, 3 (50%) were also sensitized to peas, 3 (50%) to peanut and 5 (83%) to soya bean.

Legume allergy is complex to diagnose and manage.³⁶ Lupin, peanut and soya allergy are 3 of the main allergens encountered in the legume family but many other novel allergens in this family

are appearing (lentil, chickpea, green bean or pea) and these allergens, plus the effect of processing on their allergenicity need further investigation. Cousin et al³⁷ demonstrated that using cluster analysis, distinct cluster of possible cross-reactions between tree nut, peanut and legumes exist, with those suffering from eczema, showing the highest rates of cross-reactions between these 3 allergens.

A food allergy to any of the legumes therefore needs to be carefully investigated with a clear history of consumption and possible allergies to other legumes.

5 | SEEDS: SESAME AND MUSTARD AND OTHERS

Seeds are being used more often in the food chain, which increases the risk of reactions. The most commonly eaten seeds are sesame, sunflower seed, poppy seed, pumpkin seed, flaxseed and mustard seed.³⁸ Of these, sesame and mustard are included in the list of 14 major allergens in the EU, but not on the US FALCPA list, where sesame and mustard may be hidden ingredients on product labels.³⁹

BOX 2 Important points regarding the management of nut and lupin allergy

Nut avoidance strategies

- Due to the risk of cross-contact/contamination with peanut or other tree nuts, care should be taken when sourcing nuts for selective eating.
- Nut pastes may be contaminated with other nuts, and to reduce the risk of contamination it is advisable to purchase unshelled nuts to hull and process at home or pastes, which are processed in dedicated facilities with good allergen control processes if available.
- There is the option to contact companies and ask about nut contamination of specific nuts but this is time-consuming and may not be feasible in some countries.

Nut and Seed oils

- Cold pressed, expeller pressed, or extruded peanut oil must be avoided, but refined peanut oil is not considered an allergenic ingredient according to the Food Allergen Labeling and Consumer Protection Act (FALCPA) of 2004 (USA) and thus does not need to be avoided. However, it is not required to disclose on a product label if the peanut oil is refined or expeller pressed, hence consumers should proceed with caution.
- Sesame oil is never highly refined and should be avoided.⁴⁶
- The majority of tree nut oils are not safe, as they tend to be either cold pressed or expeller pressed.²³
- The decision about the use of peanut and nut oils should be country and nut specific because different terminology is used to describe the methods of processing, for example expeller pressed vs refined.

Lupin

- Lupin is considered a main allergen in the EU, Australia and New Zealand and is therefore easily identifiable on food labels in the EU and will be mandatory in Australasia from May 2018.
- Lupin is not considered a major allergen in the USA and most other countries outside of the EU and more detailed advice regarding label reading and foods that could contain lupin should be provided to those with lupin allergy.
- Those with peanut and other legume allergies should recognize lupin as a potential allergen and discuss with their physician.

Sesame and other seeds

- Sesame and mustard seeds are considered to be main allergens by the EU.
- Sesame allergy is prevalent in the Middle East and Israel but not as often encountered outside of these countries.
- The predicted value of SPT and specific IgE tests for sesame allergy is poor and data for other seeds are not currently available.

Sesame allergy is frequently encountered in the Middle East and Israel, but sesame allergy is infrequently encountered outside of these countries and Europe.⁴⁰ The diagnosis of sesame allergy is complicated by the poor predictive value of SPT and specific IgE and the difficulty in masking its distinct taste during food challenges. A large range of allergens in sesame have been defined, including (Ses i 1 and Ses i 2, 2S albumin; Ses i 3, 7S vicilin-type globulin, Ses i 4 and Ses i 5, oleosin; Ses i 6 and Ses i 7, a 11S globulin and Ses i profilin.^{41,42} Mustard is often present in commercial foods and allergic symptoms can vary from those typically encountered in pollen-food syndrome to anaphylaxis. The food allergens involved have not been clearly defined but possible candidates include LTPs (Art v 3, Sin a 3), profilins (Art v 4, Sin a 4) and Art v 60 kDa.⁴³

The field of seed allergy is constantly evolving, and novel seed allergens are being identified; for example, citrus seed in cashew allergic individuals has been reported⁴⁴ or allergy to spices if pollen sensitized.⁴⁵

6 | COW'S MILK AND EGG ALLERGIES

Cow's milk and egg allergies are indeed the 2 most common allergens in infancy.⁴⁷⁻⁵⁰ Differing phenotypes of cow's milk and egg allergies exist, with some phenotypes resolving earlier, some tolerating baked forms of the allergen, and some persisting into late adolescence and adulthood.⁵¹ A number of guideline papers have been published covering the management of cow's milk allergy,⁵²⁻⁵⁴ but the most interesting development in this field is the use of baked cow's milk (BM) and baked hen's egg (BHE);⁵⁵ ingredients tolerated by many children with IgE-mediated allergy to unheated egg or milk.⁵⁶⁻⁶¹ BM and BHE ingredients can easily be incorporated into the diet with good compliance and reassuring feedback⁶² while decreasing the stress of strict avoidance. However, much is still not known including how to challenge to baked milk and egg ingredients, the need for a wheat matrix in baked recipes, and if the inclusion of baked ingredients in the diet accelerates tolerance development.

There is debate as to how to go about determining tolerance to BM or BHE: home introduction or physician-supervised oral food challenge (OFC). The BSACI guideline for the diagnosis and management of cow's milk allergy (CMA) suggests gradual home introduction of BM in children who have had only mild symptoms on "noteworthy exposure" to milk (such as a mouthful) and no reaction in the past 6 months and (for those with IgE-mediated CMA) a significant reduction in sIgE/SPT.⁵⁴ Additionally, physician-supervised challenges are recommended to BM by BSACI if the patient has a history of severe symptoms, symptoms with trace ingestions, high sIgE without a history of milk ingestion, no significant reduction in SPT diameter or sIgE since diagnosis, poorly controlled asthma or use of regular preventive asthma treatment, or multiple or complex allergies.⁶³ There is considerable debate around the aforementioned, as Nowak-Węgrzyn et al⁶⁴ found that of the children who were reactive to BM on challenge, 35% experienced symptoms of anaphylaxis and 4% of those challenged to BHE received epinephrine.⁶⁵ Mehr et al⁶⁶ found that 4 factors were

predictive of BM intolerance: asthma requiring preventive treatment, IgE-mediated food allergic reactions to >3 foods and prior history of anaphylaxis to other foods. The Mount Sinai cohort indicated that those with lower serum egg white, ovomucoid and ovalbumin-specific IgE levels and lower ovomucoid and ovalbumin IgE/IgG4 ratios were more likely to tolerate baked egg.^{58,65} Nowak-Węgrzyn et al found BM tolerant subjects were more likely to have smaller CM SPT wheal diameters but also lower serum CM and casein-specific IgE levels and lower serum casein and beta-lactoglobulin IgE/IgG4 ratios. Component testing may therefore be beneficial; however, more data are needed to suggest diagnostic values.⁵⁶

Although many clinicians make the decision about OFC location on clinical experience,⁵⁵ introduction of BM or BHE at home may pose a risk, particularly with IgE-mediated allergy and some forms of non-IgE-mediated food allergy such as severe food protein-induced enterocolitis syndrome (FPIES).^{63,67} In the USA, a recent death associated with a physician-supervised baked milk challenge in a child with IgE-mediated cow's milk allergy highlights the risk.⁶⁸ Box 3 provides practical pointers relating to the dietary management of baked milk and baked hen's egg allergies.

Advice on introduction of gradually increasing amounts of baked and unheated milk has been published for use in children with mild, non-IgE-mediated food allergy (eg proctocolitis, atopic dermatitis, reflux and constipation) although no prospective studies have been performed to assess efficacy of these ladders.⁵⁵ Despite positive results from a small case series in children with FPIES⁶⁹ and a retrospective trial in adults with EoE, more studies are needed to determine tolerance of BM/BHE in FPIES and EoE.⁷⁰

Several non-randomized studies found that the inclusion of BM and BHE appears to hasten a more tolerant immune profile,^{58,71,72} but a recent RCT using BHE⁷¹ and systemic review (6 studies) focusing on BM and BHE did not find evidenced to confirm this hypothesis.⁷³ Further research comparing resolution rates of those ingesting and those avoiding baked ingredients in BM and BHE-tolerant participants is needed to determine the immunomodulatory impact of including BM and BHE in the diet. Although there are clear benefits in quality of life to allowing baked ingredients in the diet, liberalizing the diet to allow baked ingredients is not the same as including baked ingredients in the diet with the goal of improving time to tolerance of unheated ingredients. The latter may potentially result in parents feeling pressure to feed these items rather than freedom to allow them.

7 | FOOD CROSS-REACTING WITH POLLEN OR ANIMAL ALLERGENS

7.1 | Allergies to fruits and vegetables

Allergies to fruit and vegetables can be triggered by pollen-food syndrome (PFS) (considered a secondary food allergy) and/or LTP syndrome (considered a primary IgE-mediated food allergy).⁷⁴ It is important to differentiate between these two presentations of fruit and vegetable allergies at the diagnostic stage as PFS is more likely to lead to milder symptoms and LTP syndrome can lead to severe

BOX 3 Practical pointers for introduction of baked cow's milk and baked egg, and inclusion of cross-reactive allergens

Baked egg and cow's milk

- Baking reduces allergenicity by destroying many conformational epitopes but has limited effect on the sequential epitopes.
- Most published reports suggest products should be baked for around 30 min at 180°C/350°F and the product must be "baked throughout and not wet or soggy in the middle".⁵⁷ The final cooking time will depend on the size of the finished product.
- Physician-supervised food challenges to products with standard amounts of BM/BHE enable guidance for the types of foods that may be introduced at home following the supervised challenge.

Pollen-food syndrome in childhood and soya allergy

- Pollen-food syndrome can occur early in childhood.^{79, 80}
- Most children with Gly m 4 sensitization will tolerate soya milk, but larger portions of soya milk or more concentrated forms of soya (soya protein isolates) consumed during birch pollen season may trigger more severe reactions.⁸⁶
- Highly processed and refined soya products, for example soya oil and soya lecithin (additive E476), are tolerated by most individuals with soya allergy.⁸³

Seafood

- Testing and potential food challenges to different species of fish (salmon, tuna, cod) may open the diet to a food with important nutritional value.
- Some people with fish allergies may tolerate canned/tinned fish.
- There is a high likelihood of reacting to cockroaches and mealworm with shellfish allergy. Shellfish allergic individuals should be aware of these novel foods.

symptoms, in some cases anaphylaxis.^{75,76} Dietary advice will also largely depend on the type of allergy, as the allergens leading to PFS are heat labile and those involved in LTP-allergies are not. Another important point to consider is that although children may be sensitized to LTP allergens, clinical manifestations of LTP allergy are not that often seen in children.

PFS is caused by cross-reactions between pollen allergens and allergens in plant foods, which occurs in some individuals with pollen allergies.⁷⁷ PFS is common in adolescents and adults with pollen allergy,⁷⁸ but also has been described in young children.⁷⁹⁻⁸¹ Regional variation in PFS occurs due to differences in pollen exposure. The main proteins of concern are profilin proteins including PR-10 and PR-14. Birch pollen (Bet v 1, from the PR-10 family) sensitive individuals may react to foods such as apple, celery, carrot and

hazelnut. An interesting development in this field is that individuals with birch pollen allergy may also develop soya allergy due to cross-reactivity of Bet v 1 with the soya allergen Gly m 4.⁸² Soya occurs widely in the food supply as soya isolate and soya flour; however, the levels of Gly m 4 in soya products vary with food processing.⁸² Highly refined soya oil and soya lecithin, other common soya ingredients, do not contain significant soya protein and are generally tolerated by those with soya allergy.⁸³

In Mediterranean countries reactivity to lipid transfer proteins (from the PR-14 family) is common, and foods implicated include apples, pears, peaches, apricots, plums and cherries.⁸⁴ Scala et al showed that 82% of non-specific lipid transfer protein (nsLTP)-positive participants from central Italy were sensitized to the plum LTP (Pru p 3) and 71% were sensitized to the walnut LTP (Jug r 3).⁸⁵

Depending on the specific allergens involved in fruit and vegetable allergy, milder or more severe symptoms may occur, which may affect the nutritional advice provided. Most children with Gly m 4 sensitization will tolerate soya milk, but larger portions of soya milk or more concentrated forms of soya (soya protein isolates) consumed during birch pollen season may trigger more severe reactions.⁸⁶

7.2 | Fish and shellfish allergy

Management of fish and shellfish allergies poses many questions to the practicing allergy dietitian. Nutritionally, fish is a rich source of protein and oily fish contributes essential long-chain polyunsaturated fatty acids to the diet. An individual with fish allergy is at high risk to reacting to other fish, but may tolerate some fish species.^{87,88} This is because, although the most common fish allergen is β parvalbumin, there are several fish allergens, and the predominant allergen varies between individual fish species.^{89,90} In addition, there is large regional variation in the predominant species of fish consumed,⁸⁹ and as skin prick testing reagents do not exist for all fish, food challenges to individual fish may be considered. More studies to inform clinical management are still required in this area.⁹⁰

Fish and shellfish allergies may coexist.⁹¹ However, clinical cross-reactivity between fish and shellfish is uncommon as the major allergen in shellfish is tropomyosin.⁹² There are high levels of clinical cross-reactivity between different species of shellfish,⁹² although some individuals may be allergic to crustacean and tolerate molluscs, and vice versa.⁹² Where allergy to both fish and shellfish does exist, this may be related to sensitization to the fish parasite *Anisakis Diphyllobothrium* rather to the seafood allergens.⁹³

The emergence of insects as foods within manufacturing or existing within certain cultures poses a problem for those with shellfish allergies.⁹⁴ Many children with shellfish allergy will also be sensitized to cockroaches, house-dust mite and mealworm (*tenebrio molitor*).⁹⁵ Although house-dust mite does not enter the food chain, both cockroaches and mealworm are becoming more recognized as protein source in foods. The high prevalence of cross-reactivity to insects in shellfish allergic patients has already been highlighted and needs to be taken into account with both travel to countries where insect consumption is common and in novel foods.⁹⁵

BOX 4 Multiple food allergies**Practical pointers for dealing with multiple food allergies**

- Ensure that children with multiple food allergies are reviewed regularly for growth (in particular height/length).
- Ensure that parents are give suitable nutritious alternatives that are free from multiple allergens.
- Consider targeted nutritional lab values in particular in children on few foods and amino acids based feed only.
- Perform a nutrient review to ensure sufficient macro and micronutrient intake and supplement with vitamins if required.

8 | MULTIPLE FOOD ALLERGIES

The dietary management of infants and young children with multiple food allergies requires special attention as this increases the nutritional risk for deficiencies and parents will require significant practical support.⁹⁶ The true incidence of multiple food allergies (generally defined as having ≥ 3 food allergies) in children is unknown and more is known on multiple IgE-mediated allergies than non-IgE-mediated allergies. For IgE-mediated food allergy, Gupta et al⁹⁷ estimated that up to one-third of food allergic children in the USA had multiple food allergies. In the Australian HealthNuts cohort,⁴⁹ 12% of the children with challenge-proven food allergy to egg, sesame or shellfish were allergic to 2 or more of the allergens.

For children with multiple food allergies, it is essential that parents are supported with practical advice on multiple eliminations and food replacement. See Table 1 for alternatives and nutrients to consider. As the risk of growth and nutrient deficiencies is higher, it is important to monitor growth (in particular height/length growth) and advise parents on normal feeding to avoid feeding difficulties. In addition, assessment of nutrient intake should occur on a regular basis and vitamin and mineral supplementation prescribed as required. Carefully chosen targeted nutritional laboratory values may be helpful, in particular if children are on few foods and amino acid formula only⁹⁸ or a large number of foods are eliminated without supplementation with an amino acid formula or a vitamin/mineral supplement.⁹⁹ (See Box 4) A plan for rechallenge of foods that are excluded from the diet should be established.

9 | CHALLENGES POSED BY THE ENVIRONMENT AND INDUSTRY**9.1 | Increased immigration and travel**

Allergy clinics are reflective of culturally diverse populations and this must be considered when tailoring individual management plans. The Australian HealthNut study identified an increased risk of offspring of migrants developing allergies, particularly for Asian immigrants.¹⁰⁰ Recent immigrants from culturally and language diverse populations

may be unfamiliar with the local food supply and may lack basic literacy skills necessary to read and interpret allergen warnings on food labels.

Our global community has also become more mobile and the travelling food allergic consumer relies on clear and concise labelling information to make accurate and safe choices when purchasing food.¹⁰¹ Food allergen labelling for common food allergens is mandatory in most countries; however, consumers need to be aware that differences exist in terms of foods recognized as "major" allergens between countries and how these allergens are being labelled. Families should be educated about the labelling laws of other countries when travelling and reducing the risk of allergen cross-contact / contamination at home and when eating away from home.

9.2 | Precautionary allergen labelling and threshold levels

Precautionary allergen labelling ([PAL], eg "may contain traces") is present on many commercial food labels advising consumers that cross-contact/contamination with an allergen may have occurred during manufacturing. The use of such terms is confusing, as consumers and healthcare professionals try to apply a degree of risk based on the type of precautionary label used, for example "may contain" vs "manufactured in a facility," although these terms do not carry such a meaning.¹⁰² Additionally, the amount of allergen present may be none at all, to amounts well below the minimal threshold dose for many consumers, or significantly relevant especially for the most sensitive consumer¹⁰³ and strict avoidance can increase anxiety.¹⁰⁴ The use of PAL is voluntary and in most countries unregulated and does not follow industry best practice guidelines. Zagon et al¹⁰⁵ indicated that current instruments are indeed able to measure down to 2 ppm of peanut allergen. Of the 899 products, they sampled only 3 products contained peanut protein above 2 ppm and carried PAL statements. These factors clearly need to be considered when providing dietary counselling. "VITAL™" (Voluntary Incidental Trace Allergen Labeling) is a risk assessment tool that grades the level of risk of allergen contamination.¹⁰² The VITAL™ tool allows manufacturers to determine whether a food product should carry a PAL based on allergen concentration action levels, using the concentration of allergen likely to cause a reaction (eliciting dose; ED) in the most sensitive 1% of the allergic population (ED01).¹⁰⁶ Given our mobile world population and the use of imported foods, it would be ideal if this programme were adopted internationally; a concept currently being discussed. Box 5 summarizes practical pointers for dealing with challenges posed by the environment and industry.

10 | CHALLENGES POSED BY NUTRITIONAL ISSUES**10.1 | Growth**

The major allergens cow's milk, soya, egg and wheat contribute significantly to macronutrient and micronutrient intake in children (refer to Table 2). Nutritional assessment and regular dietetic follow-up are

therefore essential to ensure a balanced diet,⁶ in particular in light of both over- and undernutrition⁹⁹ being reported in this cohort of children.

Caregivers should be made aware of the importance of including nutritionally equivalent substitutes in the diet and nutrition literacy needs to be considered when providing this advice.¹⁰⁷ Growth monitoring is essential, as children with food allergies can have impaired growth, with height growth being affected in particular.¹⁰⁸ This may be secondary to higher energy needs (eg in children with severe eczema), as a result of malabsorption (ie diarrhoea) or as the result of overall inflammatory processes.¹⁰⁹ This issue is magnified for children with multiple food allergies where it may be challenging to find nutritionally matching “free-from” substitutes. On the other hand, excessive weight gain is now more frequently reported in children with food allergies, but poorly researched.^{10,82,99}

10.2 | Vitamin and mineral supplementation

It is well established that children on an elimination diet are at a higher risk of developing a vitamin or mineral deficiency.³ Many

authors have highlighted either insufficient dietary intake or actual deficiencies.^{12,110–113} Food allergic children are at risk of developing micronutrient deficiencies for a wide range of micronutrients, including iodine, calcium and vitamin D, which are particular problems relating to cow's milk allergy.^{12,110–116} If milk is excluded from the breastfeeding mothers' diet, nutrient intake in the maternal diet should be addressed as well.¹¹⁷ Inflammation and oxidative stress are considered main problems in patients with atopic dermatitis, and therefore, trace elements, vitamin E, magnesium, zinc and copper play a potential role.^{72,79}

Although deficiencies for a variety of micronutrients are documented, current guidelines mainly mention the importance of calcium and vitamin D in children with cow's milk allergy; however, little focus is given to practical suggestions of other vitamins and minerals.⁵³ Focus on nutritionally balanced food intake is important, but breastmilk adequacy, optimal hypoallergenic formula choice and/or multivitamin/mineral supplementation also need to be considered.¹¹⁰

10.3 | Developing and maintaining normal feeding skills

Eating is perceived to be a problem by 20% of parents of healthy toddlers, and the origin of feeding difficulties is thought to be multifactorial.¹¹⁸ In food allergic children, feeding difficulties are recognized to be a significant problem; however, the prevalence has mainly been established in non-IgE-mediated allergies ranging from 13.6% to 94%.^{110,119,120} In IgE-mediated food allergy, parents often report a “natural” avoidance of a specific food, which then often is confirmed on testing as an offending allergen. This phenomenon is well documented in food allergy animal models, which have shown increased anxiety on exposure to offending food allergens and specific allergen aversion.^{121,122} Children may therefore present with food avoidance, to foods to which they are allergic.

In 2016, a new practical approach to classification and management of feeding difficulties was published¹²³ and Levy et al¹²⁴ have suggested triggers for establish feeding difficulties. These tools provide useful guidance in the identification of feeding difficulties

BOX 5 Environment and industry

What we know

- Greater immigration and world travel raises issues regarding food avoidance and choosing suitable foods.
- Literacy skills and ability to read and understand food labels is a particular problem that allergy specialist dietitians must address.
- Precautionary allergen labelling (PAL) provides information that is not practical and poorly understood by most consumers.

Challenges

- How should safe threshold levels be set for all food allergens and how should this be conveyed?

Practical pointers

- Ask patients about country of origin and how long they have lived in the particular country.
- Ensure the caregiver can read and has an understanding of the relevant language and if not, advise on suitable allergen translation services.
- Discuss labelling laws of the particular country (eg “major allergens,” use of PAL) and that these vary between countries.
- Determine whether avoiding products with PAL is necessary and provide practical advice on risk.
- Those tolerating BM and BHE should not be advised to avoid products with PAL for milk or egg in baked goods although should be cautioned about unbaked milk or egg.

TABLE 2 Feeding difficulties as defined by Levy et al¹²⁴ linked to common presentations in food allergy

Triggers of feeding difficulties	Presentations specific to food allergy
Size	Faltering growth
Transitioning	Struggling with texture, commonly seen in infants with food allergy-related reflux ^{145,146}
Organic disease	IgE and/or non-IgE-mediated food allergies
Persecutory and/or mechanistic feeding	The loss of appetite is well documented in children with eosinophilic esophagitis ¹⁴⁷
Post-traumatic	Food aversion/avoidance following a severe reaction (eg FPIES)

BOX 6 Nutritional challenges and future directions**What we know**

- Allergen avoidance underpins management of food allergy.
- Growth should be closely monitored as both over- and undernutrition has been reported.
- Children with multiple food allergies are at a higher risk of macronutrient and micronutrient deficiencies and poor growth.
- In the absence of breastmilk, hypoallergenic formulas (in sufficient volume) have been shown to fill nutritional gaps and lead to good growth and nutritional status.
- Vitamin and mineral supplementation should be considered for both the infant and the breastfeeding mother on an elimination diet.
- Children with food allergy are at risk of developing feeding difficulties.
- Children with food allergies require timely and nutritionally appropriate complementary feeding that supports normal feeding skills and encourages a varied and healthy diet to promote long-term health.
- Food intake, the microbiome and the gut barrier are highly connected, and both the gut microbiome and gut barrier function are affected by food intake.
- A number of nutritional factors have been identified that affect the gut microbiome, gut barrier function and immune system.
- Western dietary patterns (high in saturated fat and low in fibre) negatively affect the microbiome in both human and animal studies.

Challenges

- Except for calcium and vitamin D, do children with food allergies require additional micronutrient supplementation?
- Does routine probiotic supplementation improve allergy outcomes?
- Does "healthy eating" affect allergy outcomes and how should "healthy eating" and "diet diversity" be defined in relation to allergy prevention and management.

(organic and behavioural red flag signs) and possible triggers in food allergy (Table 2).

An allergy specialist dietitian should have knowledge of oral-motor milestones and when these need to be achieved.¹²⁵ Assessment of the timely attainment of these oral-motor skills and taste exposures should be part of the dietitian's consultation from the onset of management.¹²⁶ Referral to a multidisciplinary feeding team may be required in more severe cases. Box 6 summarizes the practical points of management of nutritional issues in food allergic children.

11 | CHALLENGES AND OPPORTUNITIES POSED BY THE FUTURE OF NUTRITION SCIENCE

Knowledge regarding the role of the microbiome in the prevention and management of many diseases is expanding,¹²⁷ highlighting the fact that the microbiome plays an important role in maintaining the mucosal barrier and regulating the (local) immune system. In terms of food allergy, the microbiome has been highlighted in both prevention and management,¹²⁸ but dysbiosis may also play a role in the increased prevalence of other conditions (including obesity, auto-immune and inflammatory diseases).¹²⁹ Literature suggests that the microbiome of children, who develop food allergies, differs from those who do not. Evidence also suggests that the microbiome of children with and without food allergy¹³⁰ and food sensitization¹³⁰ differs in terms of alpha and beta-diversity and specific organism strains present. A recent study also indicates the microbial composition of those who develop tolerance, differed from those who did not.¹³¹

The gut microbiome plays an important role in ensuring not only a physical but also an immunological gut barrier, which is of particular relevance in food allergy. Recent review papers^{128,132,133} eloquently summarize that the human gut and its microbiome, the immune system, and dietary intake all influence and depend on each other. It is currently unclear whether dietary changes (other than allergen intake) targeting the microbiome and the immune system will affect food allergy outcomes in those with established food allergy. In other words, there is no direct evidence to support the use of specific nutritional factors to manipulate the gut (microbiome) and immune system to treat food allergy at this time.¹²⁸ There is some evidence that a more diverse diet may prevent allergic diseases,^{134,135} but its definition and usefulness in the management of food allergy are still unclear.

11.1 | Probiotics for the treatment of food allergy

Probiotics have mainly received attention in the past for playing a possible role in allergy prevention, with several recent guideline papers providing evidence-based opinions on the use of probiotics for this purpose.^{50,136} However, the use of supplemental probiotics as part of treatment in children who are already food allergic is relatively novel.

Tolerance induction using probiotics has been explored in particular for cow's milk protein allergy in recent years. Canani et al^{137,138} have published several articles on the acquisition of tolerance in children with both IgE- and non-IgE-mediated cows' milk protein allergy, using an extensively hydrolysed formula supplemented with *Lactobacillus rhamnosus* GG (LGG). Although several methodological concerns remain regarding these studies, including that all data were produced by a single centre, no adverse events were reported; therefore, this extensively hydrolysed casein formula with LGG is already in use in many countries. In a recent mouse model study, the mechanism of tolerance induction was investigated, comparing the

extensively hydrolysed casein formula with and without LGG. This study found that the addition of LGG significantly enhanced the impact of the extensively hydrolysed formula on IL-4, IL-5, IL-13 and anti- β lactoglobulin IgE production, and clinical symptoms were also reduced with the LGG. Although the use of probiotics, in conjunction with an extensively hydrolysed formula, offers potentially a new way of CM tolerance induction, to date no official guidelines suggest the routine use of probiotics, by itself or in combination with a hypoallergenic formula to induce tolerance.¹³⁹

Outside of the use of probiotics as a component of infant formula, to the knowledge of the authors only one further randomized controlled study has recently been published for treatment of food allergy where the probiotic strain, *Lactobacillus Reuteri* GG, was used in combination with peanuts for peanut oral desensitization. The study outcomes indicated that 82.1% in the active arm developed sustained unresponsiveness. While the peanut intake no doubt had a role in development tolerance, the probiotic possibly enhanced the effect via its effect on T-regulatory cell functioning.¹⁴⁰

12 | THE FUTURE OF NUTRITIONAL MANAGEMENT

Nutritional support in food allergy is constantly evolving, and one of the areas for future dietetic management is the role of the gut microbiome. Data have indicated that an intact gut barrier, mediated by a "tolerogenic" microbiota, also reduced allergen absorption in a mouse model.¹⁴¹ Furthermore, it is known that the gut barrier is also disrupted in children with eczema.¹⁴² The microbiome in itself affects the mucus production, maintenance of tight junctions, cytokine production, selective stimulation of dominant lipopolysaccharide variants, T cells and B cell function (affecting IgA secretion).^{143,144}

More recent studies (mostly on animal models) have indicated that the gut microbiome produces both useful and harmful metabolites from dietary substances which affect the immune response and most likely allergy outcomes¹³³ and that allergic inflammation in turn can affect the gut microbiome (Table 3). Increased dietary diversity in young children has been shown to have an allergy preventative effect, thought to be related to its impact on the gut microbiota and its metabolite.¹³⁵ Most of the data (Table 3) have been derived from animal studies, and we should be cautious about implementing more complex dietary regimes when many children with food allergies have food aversive behaviour and getting them to eat anything can be a challenge; especially while adhering to their individual allergen avoidance advice. Easier dietary strategies such as supplementation with probiotics may become options as data emerge.

These data do not yet exist in children with food allergy, but it is an appealing prospect to target and perhaps promote the gut microbiome with the potential of correcting potential barrier-related defects and promoting immune tolerance through dietary interventions. Many of these factors are affected by food and nutrient intake as summarized in Table 3.

13 | CONCLUSION

The nutritional management of food allergy requires the allergy specialist dietitian to fully understand the standard management principles of food allergies: allergen avoidance, suitable substitutes and meeting nutrient needs. The importance of an individualized assessment and follow-up plan is a crucial part of patient management this should be established on the basis of the age of the child and on the growth pattern. However, to truly individualize an allergy-focused dietetic consultation, factors such as individual tolerance levels, co-sensitization, cross-reacting allergens, coexisting allergies, label reading nuances and social factors such as travelling need to be taken into account. Importantly, allergy specialist dietitians need to be aware of the rapidly evolving association between nutrition, the microbiome and immune system to incorporate novel nutrition findings in standard dietetic practice when the time is ready.

TABLE 3 Nutritional factors possibly affecting the gut barrier function, inflammatory processes and the microbiome

Positive	Negative
Nutritional factors affecting the gut barrier	
Omega 6 fatty acids ^{a,148}	Western diet: high in saturated/trans fat and protein; low in fibre ^{a,151-155}
Fibre ^{a,149,150}	Advanced glycosylated end products (AGEs) ^{a,156-158}
	Emulsifiers ^{a,159}
Nutritional factors affecting inflammatory processes	
Fermented foods ¹⁶⁰	AGEs ^{a,b,156}
Vitamin A and B9 ^{a,161,162}	Emulsifiers ^{a,159}
Omega-3 fatty acids ^{a,163}	
Amino acids ^{a,164}	
Fibre ^{a,149,150}	
Nutritional factors affecting the microbiome	
Overall diet—could be positive or negative ^{128,133}	Western diet ^{a,151-155}
Increased diet diversity ^{134,135,165}	AGEs ^{a,b,156-158}
Fermented foods ¹⁶⁰	Emulsifiers ^{a,159}
Amino acids ^{a,164}	Phthalates ^{171,172}
Prebiotics ¹⁶⁶	
Polyphenols ^{167,168}	
Probiotics ¹³⁸	
Uncooked foods ^{169,170}	

^aMainly based on animal studies.

^bAGE content of foods may be affected by sugar content, grilled or roasted meats, fats, highly processed foods, fruit juice,¹⁷³ high-fructose corn syrup^{173, 174} and fizzy drinks.¹⁷³ This can be counteracted by steaming, boiling, slow-cooking and using acids when cooking.¹⁷⁵

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