

ADVANCES IN THE DIETARY MANAGEMENT OF FOOD ALLERGY

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SUMMARY

Food allergies have increased in the past 20 years. Research into dietary management has also escalated, playing an integral role from diagnosis to management and, more recently, including tolerance induction and prevention. This overview article is aimed at reviewing recent advances in the dietary management of both Immunoglobulin E (IgE)-mediated and non-IgE-mediated food allergy, focusing on new research related to dietary elimination, food challenges, prevention in sensitised children through early introduction and tolerance induction through dietary manipulation of foods. The review concludes that the time for dietary elimination in non-IgE-mediated allergies and the type of elimination diet in EoE are now better understood and favour the SFED.

Key words: food allergy; dietary management; diagnostic elimination diet; food challenges; oral tolerance

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INTRODUCTION

Published data indicates that there has been an increase in the prevalence of food allergies in the past 20 years.¹ In fact, food allergy has been described as the 'second wave' of the allergy epidemic, the first being the increase in asthma, allergic rhinitis and inhalant sensitisation.² In some developed countries the prevalence of food allergy in infancy has reached 10 per cent and evidence is emerging that rates are also rapidly increasing in developing countries.^{1,3} In line with the increased prevalence, there has also been an escalation in research on dietary management, which plays an integral role from diagnosis (i.e. diagnostic elimination diet and food challenges) to management and, more recently, tolerance induction and prevention. Although many dietary interventions require further studies prior to their implementation into day-to-day practice, there have been some advances that may already be worth considering in the dietary management of the food-allergic child. This overview article is aimed at critically reviewing recent advances in the dietary management of both Immunoglobulin E (IgE)-mediated and non-IgE-mediated food allergy, focusing on new research related to dietary elimination (including diagnostic diets), food challenges, secondary prevention in sensitised children through early introduction and tolerance induction through dietary manipulation of foods.

DIAGNOSIS OF FOOD ALLERGY

The length of time required for a diagnostic dietary elimination diet for children with non-IgE-mediated gastrointestinal food allergies has long been debated. The recommended time for a diagnostic elimination diet has varied according to different publications, ranging from 2 to 4 weeks and some proposing 8–12 weeks, in particular, for eosinophilic oesophagitis (EoE). A recent study by Chebar-Lozinsky et al⁴ prospectively recruited a group of children with mixed non-IgE-mediated gastrointestinal allergies and assessed symptom improvements at four and eight weeks through a previously published symptoms questionnaire.^{5,6} In that study the vast majority of cases significantly improved after four weeks on the elimination diet; only 1.6% had improved further at the eight-week mark. It is, however, important to note that this study did not aim to establish histological improvements in children with EoE; this population may therefore require a longer time on the elimination diet before this is achieved.

- A four-week diagnostic elimination diet is sufficient for the majority of children with non-IgE-mediated gastrointestinal food allergies.
- The elimination diet should be guided by a suitably qualified dietician to ensure optimal elimination.

DIETARY ELIMINATION

An elimination diet forms the mainstay of dietetic management for both IgE- and non-IgE-mediated food allergy.⁷ Most notably, the greatest advances in dietary management have occurred in emerging food-allergic conditions, including EoE and Food Protein-induced Enterocolitis Syndrome (FPIES).^{8–11} In EoE, the treatment is focused on clinical and histological remission and the main options are based on dietary exclusions and/or topical steroids.¹² Three dietary approaches have been studied: the elemental diet (amino acid formula (AAF)), empiric elimination diet (EED) and directed elimination diet (DED). The elemental diet was the first dietary intervention studied in EoE and remains the most effective for clinical and histological remission, with improvement rates usually around 90%.^{13,14} However, the high cost, poor palatability and increased need for a nasogastric tube (45–85%) has led to alternative dietary approaches, including the empirical or directed approach, being introduced.^{14,15} It is, however, important that clinicians understand the effectiveness of these approaches. The most studied EED is the six foods elimination diet (SFED),^{14,15} which includes the avoidance of dairy, soya, egg, wheat, nuts and fish/shellfish. Studies have shown a clinical and histological remission rate around 70–80% and the most common food triggers identified by sequential food challenges have been cow's milk, wheat, egg and soya.^{10,14,15} Moreover, the majority of the patients responsive to SFED have just one to two causative food allergens, with nuts (6%) and seafood (0%) being the least likely causative foods.¹⁰ For this reason, a four foods elimination diet (FFED) (cow's milk, egg, soya and wheat) was developed and studied among patients with EoE. Molina-Infante et al¹⁶ studied the impact of FFED in adults with EoE and found an improvement rate of 54%. In paediatrics only one study has been performed with the FFED, has been published in abstract format, and has found a 74% remission rate.¹⁷ Kargawalla et al¹⁰ found that in 74% of children cow's milk was the main causative food, and in a retrospective study the same group found that 65% histological remission occurred if only cow's milk was removed.¹⁸ Similar results were found by Kruszewski et al,¹⁹ with a 64% histological remission on a cow's milk elimination diet only, but importantly the quality of life was better in those who were on the cow's milk elimination diet only compared to those on Fluticasone. Although the SFED remains the most successful described in the scientific literature, it is important to note that in the majority of children cow's milk will be the main culprit and nuts and seafood are rarely a problem in EoE. Wheat, according to a recent review, should also not be expanded to other gluten-containing foods (i.e. rye, oat and barley), as there is insufficient evidence at this stage and it would impose further unnecessary dietary elimination.²⁰

The DED is centred on the removal of specific food allergens from the patients' diet based on a suggestive history of food sensitisation supported by positive results

of a skin-prick test and/or a patch test.²¹ Spergel et al²² found in their paediatric cohort an 89% and 72% symptom and histological improvement respectively; however, these data have not been reproduced by other centres and significant concerns exist regarding the reliability of the atopy patch test, which is not recommended for routine practice in the diagnosis of food allergy.^{23,24} In addition, Henderson et al¹⁴ found this method to lead to remission in only 65% of cases compared to 81% remission with the SFED.

FPIES is a non-IgE-mediated allergy that is characterised by profuse, repetitive and severe vomiting usually one to four hours after the ingestion of the offending allergen.²⁵ Caubet et al⁸ reported from the largest FPIES cohort to date that 65% of children reacted to one food only, 26% to two foods and 9% to three or more foods. Although there is agreement in studies that cow's milk is the most common liquid FPIES allergen, there is disagreement on the rate of soya allergy in children with FPIES. Studies performed in United States found that 30–50% of the children with FPIES react to both cow's milk and soya;^{8,11} however, other studies from Australia, Europe and Israel had significantly lower levels of soya FPIES,^{26–28} which is an important consideration, especially in resource-poor environments where soya may offer a cost-effective alternative to cow's milk.

FPIES through breast milk is reported in single cases only;²⁹ consequently, guidelines do not suggest routine avoidance of the culprit food in breastfeeding mothers.³⁰ In cases where breast milk is not available, the majority of guidelines recommend the use of a hypoallergenic formula [extensively hydrolysed or AAF] and an AAF in particular if growth faltering is involved;³⁰ however, it is clear from the data that in some children soya may be considered. Although avoidance of the offending allergen remains the cornerstone of liquid FPIES management, the difficulty often lies in the introduction of complementary foods, as almost one-third of children with liquid FPIES will also have solid FPIES. A joint publication of authors from Europe, Israel and the United States indicates the avoidance of grains, legumes and poultry until six months

- The elemental diet has the best efficacy in EoE, however, is difficult to implement.
- Although the SFED has to date the best efficacy, it is important to note that nuts and seafood are rare causative allergens in EoE, hence an FFED may offer a good alternative.
- Cow's milk protein is the most common cause of liquid FPIES but not all countries report a high level of soya FPIES – this will need to be established in each child.
- The pre-emptive elimination of foods beyond six months is not recommended in FPIES.

of age, but after this introduction should occur either as a hospital-based challenge or at home.⁹ Venter and Groetch have published a useful practical weaning guide for FPIES; however, this will need to be adjusted to every individual child depending on the culprit allergen.³¹ No current evidence supports the introduction of baked milk for children with cow's milk FPIES; however, if the child is already tolerating baked milk products without symptoms, these can be continued.

FOOD CHALLENGES

Although oral food challenges have been well established in IgE-mediated food allergies, practice has varied significantly between centres. This has been recognised by both the American Academy of Allergy Asthma and Immunology and the European Academy of Allergy and Clinical Immunology with the publication of the PRACTALL consensus report on food challenges in 2012.³² On the basis of an extensive literature review, a general challenge schedule comprising 3, 10, 30, 100, 300, 1 000 and 3 000 mg of food protein at intervals of at least 20 minutes was recommended. However, the authors do acknowledge that for low-protein foods (i.e. fruit and vegetables) other amounts will be required for challenges to deliver a reasonable amount of food and highlight the importance of considering the food matrix with food challenges.³²

Advances have also been made in food challenges for children with non-IgE-mediated gastrointestinal allergies. Nowak-Wegzyn et al³³ published their challenge guidelines for FPIES in 2009, which have since been internationally accepted as the standard challenge protocol for this allergy. These guidelines indicate that the challenge dose should be calculated based on gram of food protein per kilogram of body weight, with a usual dosing ranging between 0.15 g and 0.3 g protein/kg body weight and up to a maximum of 10 g. Dosages should be provided within 30–45 min intervals.³³ For children without FPIES, but other non-IgE-mediated cow's milk protein-related gastrointestinal food allergies, Venter et al³⁴ published a milk ladder approach for home reintroduction. This approach is based on the extent of milk heating and fermentation, which has an impact on both the conformational epitopes and the peptide length.^{35,36} Whether this approach can also be used for other common non-IgE mediated allergens (i.e. soya, egg, wheat) has been studied by Meyer et al and their findings are due to be published in 2016. It is crucial, however, that IgE-mediated allergy is ruled out prior to embarking on any home introduction of allergens.

- PRACTALL challenge guidelines should be used for IgE-mediated food allergy challenges.
- The dose for FPIES food challenges is based on protein/kg: 0.15–0.3 g protein/kg.
- The home challenge ladder for non-IgE-mediated

- IgE-mediated food allergies need to be excluded before embarking on home challenges.

EARLY INTRODUCTION

In 2015 Du Toit et al published their study on the early introduction of peanut protein in high-risk infants (LEAP study).^{37–39} Enrolment criteria included children between 4 and 11 months of age with egg allergy and/or eczema and the eligible cases were randomly assigned to either receiving 6 g of peanut protein per week or no peanut protein at all. The total reduction of peanut allergy at 60 months in the early introduction cohort was 86%. Within this cohort, there was sub-group of children who were already sensitised to peanut (defined as 1–4 mm skin-prick test size) and who had a prevalence of peanut allergy of 10.6% in the peanut consumption group versus 35.5% in the non-peanut consumption group. Subsequently international guidelines have been published, recommending the early introduction of peanuts following the protocol from this study in children who have eczema with/without egg allergy and also in those who have an SPT of 1–4 mm to peanut protein. According to these guidelines, the clinician may wish to perform an observed peanut challenge for those with evidence of a positive peanut SPT (1–4 mm) to determine whether they are clinically reactive before initiating at-home peanut introduction. It is at all times important that clinicians consider the safety of peanut protein introduction in the sensitised group.³⁹ We are awaiting the results of the PRONUT study (NCT01744990) for guidance on the early introduction of tree nuts.

- Early introduction of peanut protein is now recommended in children with eczema/egg allergy/SPT 1–4 mm of peanut protein.
- It is important to consider the safety of the peanut protein introduction in the sensitised cohort and therefore the clinician may wish to consider a supervised peanut challenge prior to at-home introduction.
- The peanut introduction protocol of the LEAP study is recommended.

TOLERANCE INDUCTION THROUGH PROBIOTICS

The involvement of the gut bacterial flora has long been recognised as a factor that may contribute to the development of food allergy.⁴⁰ Significant research has occurred in the domain of allergy prevention, but in recent years studies have also focused on using probiotics in tolerance induction in children allergic to cow's milk. Canani et al 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 (EHF) supplemented by *Lactobacillus rhamnosus* GG (LGG).^{41,42} Although several methodological concerns remain regarding these studies, including that all data

were produced by a single centre, no adverse events were reported, therefore EHF with LGG is already in use in many European countries. The addition of LGG is proving to be a novel approach to assisting tolerance induction; however, this requires further research.

- EHF with LGG is safe for children with food allergies to use, but further research is required to support its efficacy in tolerance induction.

CONCLUSION

Many advances have been made in the management of food allergy, from diagnosis to the induction of tolerance. The time for dietary elimination in non-IgE-mediated allergies and the type of elimination diet in EoE are now better understood and favour the SFED. However, there

is a drive towards eliminating fewer foods in children with EoE. Although further research is required with regard to the early introduction of other allergens in the cohort sensitised to food allergens, data from the LEAP study have indicated a clear benefit for early the introduction of peanuts in an already sensitised cohort.

Further data are required to confirm the impact of the addition of LGG to EHF, but this certainly opens up a new avenue for tolerance induction. The dietary management of food allergy is a fast-evolving area that requires clinicians to keep abreast of new research to ensure that children receive optimal clinical care.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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