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When and how to evaluate for immediate type food allergy in children with atopic dermatitis

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Atopic dermatitis (AD) typically develops in infancy and affects up to 20% of children in high-income countries (1). Immediate (IgE-mediated) food allergy (FA) affects around 3% of children (2). Children with AD are at higher risk of immediate-type FA (3, 4). Up to a third of children with moderate to severe AD have FA (3). A Danish population-based study, evaluating children from birth to 6 years, showed that 15% of all children with AD had concomitant FA and almost all children with FA had concomitant AD (4). In a recent review, the likelihood of food sensitization was reported to be 6 times higher in patients with AD compared to healthy controls at 3 months of age (5). Furthermore, up to 15% of subjects with AD had a positive oral food challenge (OFC) (5). A population-based study from Australia showed that one out of five infants with AD, mainly infants with early-onset AD (<3 months), were allergic to peanut, egg white, or sesame compared to one in 20 without AD (6), when evaluated by an oral food challenge at 12 months. Recent studies suggest that AD arises before FA and that increased severity of AD and chronicity further increase
the risk of FA (5). In a recent retrospective study, for each month duration of AD before proactive steroid treatment to manage the AD, the risk of IgE-mediated FA increased, with 50% of children allergic following 8 months of AD (7). A cardinal feature in AD is xerosis caused by the impaired skin barrier function including loss-of-function mutations in the filaggrin gene. These mutations have also been independently associated with FA, which confirms the genetic association between AD and FA. However, less than a third of AD patients bear this gene mutation and it is present also in patients without AD suggesting a role for other gene interactions. Indeed, a strong genotype-phenotype interaction was recently demonstrated in the LEAP cohort implicating the MALT1 pathway in the allergic immune pathogenesis of peanut allergy (8). The immunological interplay between AD and sensitization to food allergens via the cutaneous route due to the impaired skin barrier function is especially important, if it occurs in the absence of oral ingestion (9). This concept underpins the ‘dual allergen exposure’ hypothesis: allergic sensitization results from cutaneous exposure, and tolerance occurs as a result of oral exposure to food (9). Preventative emollient therapy from birth has not been shown to prevent the onset of AD or FA (10), results from studies assessing the influence of early topical steroid applications are underway (see clinicaltrials.gov). Randomized controlled trials that underpin the dual allergen exposure hypothesis have over the past five years led to several allergy societies, including the recent European Academy of Allergy and Clinical Immunology (EAACI) Task force for allergy prevention, updating their allergy prevention guidance (11). While the specifics of this advice may vary, all encourage parents to introduce one or more allergenic foods within the first year of life. Some of the guidance highlight increased risk factors for the development of FA, particularly AD, hence the importance of early diagnosis and management of AD and FA. As around 20% of children in the general population have AD and only around 3% of children have FA, an algorithm which directs the evaluation of infants and small children with AD for FA will prove useful for clinicians.

This algorithm (Figure 1) for evaluation for immediate FA in infants and children < 6 years of age is proposed by the Task Force on FA in children with AD of the EAACI. It is based on evidence as well as on expert opinion and reflects the consensus of the group. The diagnostic approach is restricted to immediate (IgE-mediated) FA.

The EAACI Food Allergy guideline details an approach for the diagnostic evaluation of immediate FA in children that includes clinical history, skin prick test (SPT) and/or specific IgE (including component-resolved diagnostics (CRD)) for evaluation of sensitization and an OFC to determine the clinical relevance of sensitization i.e. allergy (2) (Table 1). For all children a careful medical and dietary history is mandatory. The dietary history aims to identify the common food allergens that have already been eaten and tolerated as well as suspected triggers of allergic reactions. In addition, the history should establish which common food allergens for the patients have not yet been consumed. The allergic history aims to identify potential
immediate-onset reactions to foods including the timing and symptoms. If the child presents with a convincing history of immediate reactions to food allergen(s), testing should follow the recommendations for evaluation of FA (2), regardless of eczema severity. The OFC remains the gold standard for diagnosing FA which is undertaken to validate clinical suspicion unless decision points for the food in question are present e.g. size of positive SPT, level of specific IgE/CRD combined, rigour of the the clinical history. In the absence of a history of immediate-onset allergic reactions after repeat exposure of an age-appropriate portion of the food allergen in question, FA is excluded and testing is not indicated. If the child has moderate to severe AD which is characterized by a strongly itching eczema covering larger parts of the skin (SCORAD > 25, EASI > 7, POEM > 8) and more difficult to treat, and the food has not yet been ingested and unequivocally tolerated, testing for FA preceding first oral exposure is recommended for the most common food allergens given the strong association between AD and food allergy. The prevalence of specific food allergies may vary from country to country in Europe, with hen’s egg and cow’s milk generally being the most common food allergies, followed by peanut, tree nuts, sesame, fish, soy, and wheat. Testing should therefore be focused on those allergens that are relevant to the geographic location, whereas broad screening to multiple allergens is not recommended as children with AD infants have an increased risk of clinically irrelevant, transient sensitization (4).

If immediate FA is confirmed, dietary guidance, elimination diet, and a bespoke emergency plan and appropriate medications e.g. adrenaline, are indicated. If FA is ruled out, it is important to consider the only established FA prevention strategy – the early introduction of the food allergen into the diet with ongoing regular consumption (12) and this approach is supported in the recent EAACI prevention Guideline update (11). This approach has been found to be effective for peanut and egg in countries with a high prevalence of these food allergies; changes to Australian infant feeding guidelines resulted in a 16% reduction in peanut allergy in the first year of life. The introduction of other common food allergens has not yet been validated. There is no evidence to support the early introduction other common allergens, and whilst the EAT Study investigated the effect of the introduction of milk, wheat, fish, and sesame at 4-6 months, there was no effect in the ITT analysis (13). The early introduction of food allergens in LEAP and EAT was not associated with adverse nutritional outcomes, and the duration of breastfeeding in these studies was not compromised. The evaluation of infants and young children with AD is recommended, but ideally should not delay introduction.

There are dangers to unnecessary dietary restrictions, such as nutritional risks and growth restriction, furthermore financial and psychosocial impacts. Hence elimination diets need to be justified and supervised (12). In light of successful prevention strategies, this algorithm offers an idealistic diagnostic approach to diagnose infants and young children within a high-risk population before the introduction of food. The
authors acknowledge that there is a debate as to the logistical and cost implications for testing all young infants with moderate to severe difficult-to-treat AD or with a convincing history of immediate reactions to food allergen(s) and that in some areas the number of test centers is insufficient and should be increased. The algorithm is intended to help the clinicians on when and how to evaluate children with AD for food allergy, and it is based on a combination of expert opinion and available literature. There are no safety or efficacy data for early introduction of common food allergens in the absence of allergy testing outside of the research setting. We therefore propose a novel algorithm to facilitate the safe and timeous evaluation for food allergy in high risk children. The algorithm includes a careful medical and dietary history of the infant/child prior to selecting the allergens to be tested is proposed. The history seeks to determine possible allergenic triggers for the patient as well as common food allergens that have been introduced in the diet. Testing will then aim to confirm suspected allergens as being clinically relevant especially if the history is equivocal as well as to allow for safe dietary expansion if other common allergens, relevant to the patient’s geographic location, have not yet been eaten. Specialists in dermatology, pediatrics and allergy/immunology have to work together on handling these children.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest to disclose in relation to this algorithm.

CONTRIBUTIONS

This algorithm for evaluation for immediate FA in children with AD was commissioned by EAACI, and undertaken by the Task Force on food allergy in children with atopic dermatitis. The Task force was initiated by CGM and BBW. It is based on evidence as well as on expert opinion. During the development of the algorithm, the consultation process included web-meetings in March, April, June and October 2020. Comments and suggestions were carefully considered and consented by the whole group. Drafting of the original manuscript: CGM, GdT. Reviewed and edited by all authors. All authors approved the final version.

References


### Table 1. Instruments for diagnosis and severity evaluation of atopic dermatitis and food allergy


<table>
<thead>
<tr>
<th>Severity (mild, moderate, severe)</th>
<th>SCORAD</th>
<th>EASI</th>
<th>POEM</th>
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<tr>
<th>Food allergy</th>
<th>Sensitization</th>
<th>Skin prick test (SPT)</th>
<th>Specific IgE (sIgE)</th>
<th>Component-resolved diagnosis (CRD)</th>
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- Muraro A, Werfel T, Hoffmann-Sommergruber K et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 2014; 69:1008-25
Infants, children < 6 years with atopic dermatitis (AD)

Mild AD
- Respond easily to treatment
- SCORAD ≤ 25, EASI ≤ 7, POEM ≤ 8

Moderate-severe AD
- More difficult to treat
- SCORAD > 25, EASI > 7, POEM > 8

No history of immediate reaction to food

History of immediate reactions to food

Persistent AD OR poor response to treatment

No history of immediate reaction to food, and some response on treatment but absence of regular uneventful consumption of certain foods

No history of immediate reaction to food, and some response on treatment and consume diet according to age including common potent allergens

No food allergy - normal diet according to age **

Dietary guidance
Elimination diet with suspected food(s)
Emergency plan
Adrenaline Autoinjector (depending on threshold)

Food allergy not likely - normal diet according to age **
(evaluation for food allergy if clinician suspects food allergy)

Food allergy not likely - normal diet according to age **
(evaluation for food allergy if clinician suspects food allergy)

Food allergy not likely - normal diet according to age **
(evaluation for food allergy if clinician suspects food allergy)

Evaluation for food allergy

Careful selection of food allergens for testing *

Skin prick test (SPT) and specific IgE (sIgE) +/- CRD.
Oral food challenge (OFC) - gold standard for the diagnosis and threshold. In cases, where decision points for the food in question and age group of the patient are available and case history is convincing, OFC may be omitted

Negative OFC or negative SPT and/or sIgE in case of no history of immediate reaction

Positive OFC or highly suggestive history together with availability of decision point for sIgE or SPT

Consider testing potent and common allergens in the area not introduced in the diet of the infant/small child

Food allergy not likely - normal diet according to age **
(evaluation for food allergy if clinician suspects food allergy)

Food allergy - normal diet according to age **
(evaluation for food allergy if clinician suspects food allergy)