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Position paper

Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA^{2}LEN

Food allergy and atopic eczema (AE) may occur in the same patient. Besides typical immediate types of allergic reactions (i.e. noneczematous reactions) which are observed in patients suffering from AE, it is clear that foods, such as cow's milk and hen's eggs, can directly provoke flares of AE, particularly in sensitized infants. In general, inhaled allergens and pollen-related foods are of greater importance in older children, adolescents and adults. Clinical studies have revealed that more than 50% of affected children with AE that can be exacerbated by certain foods will react with a worsening of skin eczema either alone or in addition to immediate symptoms. Adolescents and adults may also react to foods, but reactions to 'classical' food allergens, such as hen's eggs and cow's milk, are not as common as in childhood. Some patients with AE do react to pollen-associated foods. Food-induced eczema should not be neglected by the allergologist: On the one hand, food can be a relevant trigger factor of persistent moderate-to-severe AE; on the other hand, unnecessary diets which are not based on a proper diagnosis may lead to malnutrition and additional psychological stress on patients suffering from AE. Eczematous reactions to food can only be diagnosed by a thorough diagnostic procedure, taking into account the patient's history, the degree of sensitization and the clinical relevance of the sensitization. The latter has often to be proven by oral food challenges. Upon oral food challenge it is most important to evaluate the status of the skin with an established score (e.g. SCORAD, EASI) after 24 h and later because otherwise worsening of eczema will be missed.

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Food has been discussed as a trigger factor of atopic eczema (AE; atopic dermatitis) for many years. Many patients suppose that allergic reactions to foods cause – at least in part – eczema. During the course of the disease, a majority of the patients try elimination diets (1) which can cause malnutrition and emotional stress especially in children. Most clinicians and investigators believe that nutritional allergens may, indeed, be important trigger factors for AE in infancy because immediate-type food allergy is frequently observed (Table 1). In large series of studies, it was shown that approximately one-third of all children with severe AE also suffer from IgE-mediated food allergy (2–6). A problem in the most published clinical evaluations of food allergy in AE is that eczema which usually worsens on the day after the oral food challenge or even later was not scored systematically before and the day after oral food challenges (OFC).

In studies with limited numbers of selected patients, it was shown that severe eczema may be worsened by foods in adulthood as well (7–8). This is particularly true for 'pollen-associated' foods. Up to now, only one study investigated unselected adolescent or adult patients and reported about a low-frequency of food allergy in AE in this age group (9).

The aim of this position paper of the EAACI/GA^{2}LEN was to point out the role of food allergens for eczematous reactions in AE and to propose a diagnostic algorithm for the elucidation of such late reactions to foods. In that sense, this position paper extends the EAACI guideline on food allergy (10) and a position paper of the EAACI which proposes a standardization of food challenges in patients suffering from immediate reactions to foods (11). The paper also refers to a current EAACI position paper on the role of the 'atopy patch test (APT)' (12).

Abbreviations: AE, atopic eczema; APT, atopy patch test; DBPCFC, double blind placebo controlled food challenge; OFC, oral food challenge; SPT, skin prick test.

Clinical pattern of reactions to foods in AE

Food challenges can cause three different pattern of clinical reactions to foods (Fig. 1):

Table 1. Prevalence of food allergy in children with eczema (food allergy proved by double blind placebo-controlled food challenge)

Authors	Year	*n*	Food allergy (%)
Sampson and McCaskill (28)	1985	113	56
Burks et al. (29)	1988	46	33
Sampson (30)	1992	320	63
Eigenmann (2)*	1998	63	37
Burks et al. (31)	1998	165	39
Niggemann et al. (15)	1999	107	51
Eigenmann and Calza (32)*	2000	74	34
Breuer et al. (16)	2004	64	46

*unselected children with AE

1. Noneczematous reactions. The clinical symptoms include cutaneous symptoms such as pruritus, urticaria and rashes and/ or noncutaneous gastrointestinal or respiratory symptoms or even anaphylaxis.
2. Isolated eczematous reactions, e.g. flare-up after hours to days
3. A combination of noneczematous and eczematous reactions.

The main focus of this paper is on eczematous reactions to food (and not on e.g. gastrointestinal symptoms).

The role of eczematous reactions to foods in AE

Eczematous reactions can appear isolated or associated with preceding other symptoms. In some previous publications, those reactions were defined as late (i.e. by time) or delayed (i.e. by mechanism) reactions (13). In isolated eczematous reactions, it is often difficult to relate the clinical reaction to a relevant trigger factor which started to cause the reaction many hours before. Therefore, the identification of trigger factors of eczema in AE is usually more difficult than the elucidation of the cause of immediate symptoms in food allergy.

The evaluation of the type of clinical reaction upon OFC in children with AE showed that 25% of clinical reactions appear after 2 h or later following OFC (14, 15). When evaluated after 16 h or later more than 10% of the children who reacted to oral food challenge with milk, egg, wheat or soy developed isolated eczematous reactions after double blind placebo controlled food challenge (DBPCFC) (6, 16). More than 40% of the children who reacted to OFC showed a 'combined' eczematous and noneczematous reaction. The observed rate of eczematous reactions which followed immediate reactions is probably too low, since some children have to be treated with corticosteroids due to the immediate reaction. On the other hand, some of the preceding immediate reactions prior to the deterioration of eczema are mild so that the patients and/or the parents are sometimes not aware of them.

Eczematous reactions to foods may also appear among adolescents and adults. This has been shown in a few patients who reacted to cow's milk (8) and a cohort who reacted to foods cross-reactive to birch pollen (7). A recent study from unselected populations indicates that pollen sensitization is frequent in adult AE patients but the prevalence of inducible eczema through pollen-associated foods is rather low (9). Foods, cross-reactive to pollen, may also be clinically important for children with AE (17).

In addition to frequently suspected 'classical' food proteins food additives and biogenic amines may cause the worsening of AE. Until now it is believed that these reactions are non-IgE dependent hypersensitivity reactions (18). Of note, sugar, which is often suspected as a trigger factor of AE by patients or parents, does not play a role for AE due to results of a well-controlled study (19).

Diagnosis of food allergy in AE patients: general aspects

There is no single parameter which can prove the clinical relevance of a sensitizing food in patients with AE. A stepwise procedure addressing individual factors is recommended.

In patients suffering from AE and in addition from immediate reactions to foods the responsible food can often be identified by taking a careful history, performing skin prick tests (SPT) and/or determining food-specific IgE *in vitro*. Since specific IgE, prick tests and the history sometimes do not correlate with clinical observations, food challenges are necessary to show the clinical relevance of the findings. The placebo-controlled, double-blinded oral food challenge is the gold standard in the diagnostic procedure of food-associated reactions (11, 20).

Identification of noneczematous reactions to foods in AE

The diagnostic work-up for the identification of noneczematous reactions in AE patients is not discussed in this

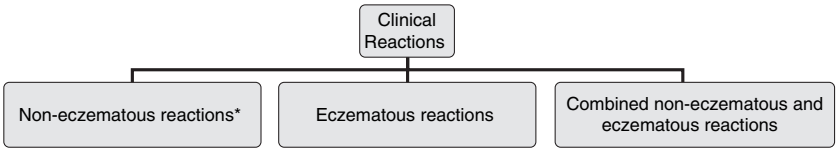

Figure 1. Pattern of clinical reactions to foods. *The clinical symptoms of noneczematous reactions include cutaneous symptoms such as pruritus, urticaria and rashes and/ or noncutaneous gastrointestinal, respiratory or even anaphylaxis.

paper, since it does not differ from the recommended procedure proposed for the diagnosis of food allergy outlined in detail in an EAACI guideline and an EAACI position paper (10, 11).

Identification of eczematous reactions to foods in AE

The diagnostic algorithm is summarized in Fig. 2.

The patient's history can be very helpful to identify a relationship between the clinical symptoms and the ingested food. In particular it gives hints to IgE-mediated reactions. Unfortunately, the patient's history is not reliable in isolated eczematous reactions to food and particularly in case of multiple sensitizations to foods.

This has been shown in many clinical investigations: In a placebo-controlled study on the effects of elimination diets the eczema of children with AE improved in 60% of all patients after removing eggs and milk. However, there was no correlation between the parentś suggestions that milk and/or eggs trigger eczema (21). Furthermore, retrospective analyses by Niggemann (15) and Breuer (16) have shown that the patientś history of food-related eczema does not have a high diagnostic specificity.

If food allergy is expected tests to prove IgE-mediated sensitization (i.e. skin tests and /or *in vitro*-investigations – specific IgE in the serum) should be performed. It was suggested previously that decision points in which the predicted probability of a positive challenge outcome exceed, e.g. 95% may make OFC unnecessary in selected children. At present, such a correlation has only been demonstrated in children and only for few foods (14, 22–24). However, no decision points have been established yet for eczematous reactions to foods.

The APT with foods (cow's milk, hen's egg, cereals and peanut) may increase the identification of food allergy in patients with AE in the following cases (12, 25):

1. Suspicion of food allergy without predictive specific IgE levels or positive SPT
2. Severe and/or persistent AE with unknown trigger factors
3. Multiple IgE sensitizations without proven clinical relevance in patients with AE.

The APT can be considered as an additional diagnostic tool which can be used in specialized institutions. However, APT are still not generally recommended for routine diagnoses of food-induced eczema. Moreover, more series were studied only in patients of lower age groups (infants and young children with AE). Of note, it was concluded from a recent evaluation of a large number of children with AE that the APT does NOT lead to a significant reduction of the need of OFC when food-induced eczema is supposed (33).

In case of suspected food allergy (by history and/or specific sensitization) a diagnostic elimination diet over a period of up to 4 to 6 weeks with the suspected food items is recommended. If the role of food in persistent moderate-to-severe AE is unclear the patients or their parents should write a daily symptom protocol (including the status of AE, intensity of itch and sleep loss) and the individual food intake. These protocols may give an overview of the patientś diet and (rarely) point to a possible relation between the worsening of eczema and

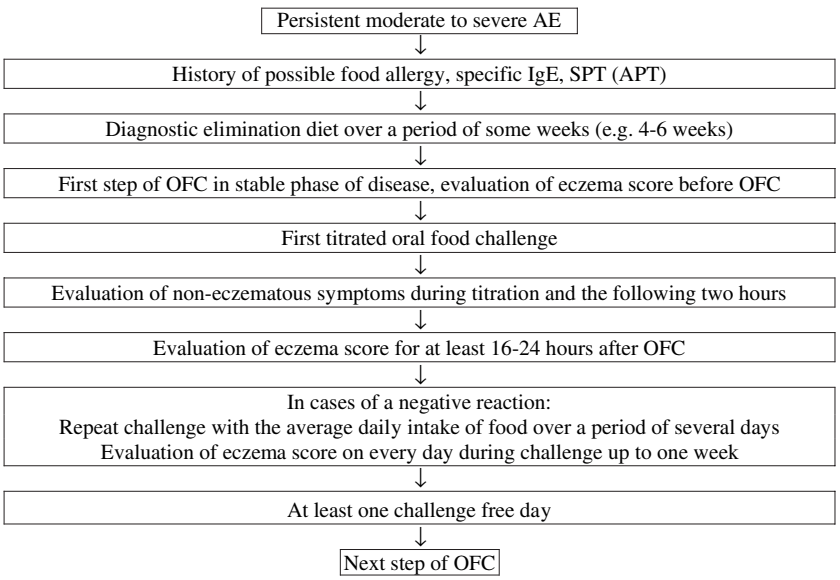

Figure 2. Diagnostic algorithm for the identification of food allergy in atopic eczema. Ideally DBPCFC should be performed. In this case 'first food' resp. 'second food' can be a suspected food OR placebo. OFC: oral food challenge, APT: Atopy Patch Test, SPT: Skin prick test, AE: atopic eczema.

specific food intake. If there is no such association and the diagnostic procedures outlined above do not provide helpful information, the introduction of a diagnostic oligoallergenic diet over a period of at least 3 weeks can be helpful in severe AE. Infants can be exclusively fed with an extensive hydrolysed or an amino acid formula. Older patients should perform an individually tailored diet with a few foods which only rarely induce allergy to food (26).

If the condition of eczema remains stable or decreases during diagnostic elimination diet within 4 weeks, it is unlikely that food allergy is a relevant trigger factor of AE and OFC are not necessary. It has to be taken into account that in rare cases, a food which was 'allowed' during the elimination diet may be responsible for persistent symptoms.

The indications for OFC were already outlined in the position paper of the EAACI 2004 (11). With regard to the recommended procedure in AE the following aspects have to be stressed:

1. If there is an improvement of the symptoms during a diagnostic elimination diet OFC should usually be performed. It is not sufficient to 'trust' the outcome of diagnostic elimination diets in AE which may be coincidental or reflect a 'placebo' effect particularly among adults.
2. Patients with AE and proven noneczematous reactions to foods will not have to undergo food challenges for the detection of eczematous reactions to the same foods.

Due to practical reasons OFC can be performed after a diagnostic diet with a few foods by introducing single foods stepwise in those patients who improved after 4–6 weeks. New foods can be introduced after a minimal interval of 4 to 7 days.

The limits of open OFC are over-interpretation (27) and expected difficulties to diagnose eczematous reactions in patients with AE. If eczema worsens upon open OFC a repetition of the challenge with the same food in a double-blinded and placebo-controlled manner is, therefore, highly recommended.

Recommended challenge protocol for the detection of eczematous reactions in AE

Oral food challenges should be performed in intervals without symptoms or during a consistent period with regard to AE. If no consistent situation of the skin condition is achieved by an elimination diet alone, the topical therapy has to be intensified before starting OFC. The concomitant therapy and individual 'environmental factors' should neither be changed during the diagnostic elimination diet nor during the days of the oral food challenge. If it is not possible to avoid steroids, it is recommended to treat the patient daily with a low potency topical corticosteroid. In this case treatment with corticosteroids should be continued through the entire phase of the oral food challenge procedure. No other anti-inflammatory substances, anti-histamines nor UV-therapy should be applied in parallel.

Provocation tests should always be performed by persons with experience in OFC and emergency equipment must be available at all times. Even if immediate reactions are not expected the food must be administered in a titrated manner since it can cause severe symptoms up to fatal reactions particularly in patients with AE after a long elimination of the corresponding food (27). Patients who had performed a long elimination need special attention. More information about the titrated food challenge procedure is given in detail in the EAACI position paper (11).

The skin must be scored by an established eczema score (e.g. SCORAD) before OFC and at least after 24 h. It is not sufficient to 'score' eczema just before and immediately after OFC, since eczematous reactions will otherwise be missed in many cases. A difference of at least 10 SCORAD points is usually considered as a positive reaction.

In case of a negative outcome after 24 h, the suspected food should ideally administered over a period of several days in an outpatient setting. It is mandatory to assess the skin condition by a trained physician during this period by the same observer.

The next challenge step (new food and placebo, respectively) should not be started before the skin has recovered from the previous challenge.

Which procedure is recommended in suspected food allergy in AE?

Due to the patient's history and clinical findings three constellations affecting the question of possible food allergy in AE often occur in clinical practice:

I. AE and a history of an immediate reaction against one or more foods:

IgE-mediated sensitization should be tested and OFC should be performed. The skin should be scored at least on the next morning or later after OFC. If possible, repeated challenges with the same food should be performed afterwards.

II. Persistent, moderate-to-severe AE, no history of immediate-reactions to food, no suspected eczematous reactions to food:

Screening tests (*in vitro* or SPT) to detect specific sensitizations against common food allergens are recommended. Pollen associated foods should not be forgotten in older children, adolescents and adults. In case of a 'mono-sensitization' or very strong sensitization to one

food a specific diagnostic elimination diet and subsequent OFC should be performed. If multiple sensitizations are known or suspected a diagnostic diet is recommended followed by a stepwise reintroduction of single foods every 4–7 days. In case of worsening of eczema during the reintroduction phase DBPCFC should be performed. The skin should at least be scored on the next morning after OFC. If possible repeated challenges with the same food should be performed up to 1 week afterwards.

III. Food is suspected by patients or parents as trigger factor of persistent AE (although no immediate reactions are known).

Particularly in the case of infants or young children it is strongly recommended to test the relevance of suspected food allergy to important foods (e.g. milk, eggs and wheat). IgE-mediated-sensitization should first be checked Followed by OFC. Again, the skin should at least be scored on the next morning after OFC. If possible repeated challenges with the same food should be performed afterwards.

Decision points for specific IgE levels as proposed by several groups have not been integrated into this diagnostic work-up since they were only established for few foods and not for isolated eczematous reactions yet.

Therapeutic diets are recommended for a period of 12–24 months in early childhood. After this period the clinical relevance of food allergy should be re-evaluated in order to avoid long-term, unnecessary or even harmful diets.

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References

1. Johnston GA, Bilbao RM, Graham-Brown RA. The use of dietary manipulation by parents of children with atopic dermatitis. Br J Dermatol. 2004;**150**: 1186–1189.
2. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. Pediatrics 1998;**101**:E8.
3. Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. Pediatr Allergy Immunol 1998;**9**:13–19.
4. Rancé F. What is the value of allergologic tests for the diagnosis and management of atopic dermatitis? Ann Dermatol Venereol. 2005;**132**:S53–S63.
5. Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. J Allergy Clin Immunol. 1999;**104**:S114–S122.
6. Ottens S, Breuer K, Alter M, Kapp A, Werfel T. More than 50% of positive challenges with foods are associated with late eczematous reactions in atopic dermatitis. Allergy Clin Immunol Int 2006 (in press)
7. Reekers R, Busche M, Wittmann M, Kapp A, Werfel T. Birch pollen related food trigger atopic dermatitis with specific cutaneous T-cell responses to birch pollen antigens. J Allergy Clin Immunol 1999;**104**:466–472.
8. Werfel T, Ahlers G, Schmidt P, Boeker M, Kapp A, Neumann C. Milk-responsive atopic dermatitis is associated with a casein-specific lymphocyte response in adolescent and adult patients. J Allergy Clin Immunol 1997;**99**:124–133.
9. Worm M, Forschner K, Lee H, Roehr C, Edenharter G, Niggemann B et al. Frequency of Atopic Dermatitis and Relevance of Food Allergy in Adults in Germany. Acta Derm Venereol 2006;**86**:119–122.
10. Bruijnzeel-Koomen C, Ortolani C, Aas K, Bindslev-Jensen C, Bjorksten B, Moneret-Vautrin D et al. Adverse reactions to food. European Academy of Allergology and Clinical Immunology Subcommittee. Allergy 1995;**50**:623–635.
11. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J et al. Standardization of food challenges in patients with immediate reactions to foods – position paper from the European Academy of Allergology and Clinical Immunology. Allergy 2004;**59**:690–697.
12. Turjanmaa K, Darsow U, Niggemann B, Rancé F, Vanto T, Werfel T. Position Paper of the Section on Dermatology and the Section on Pediatrics of the European Academy of Allergy and Clinical Immunology (EAACI). Allergy 2006; **61**:1377–1384.
13. Werfel T, Breuer K. Role of food allergy in atopic dermatitis. Curr Opin Allergy Clin Immunol 2004;**4**:379–385.
14. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. Clin Exp Allergy 2005;**35**:268–273.
15. Niggemann B, Sielaff B, Beyer K, Binder C, Wahn U. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. Clin Exp Allergy 1999;**29**:91–96.
16. Breuer K, Hetatizadeh A, Wulf A, Baumann U, Constien A, Tetau D et al. Late eczematous reactions to food in children with atopic dermatitis. Clin Exp Allergy 2004a;**34**:817–824.
17. Breuer K, Wulf A, Constien A, Tetau D, Kapp A, Werfel T. Birch pollen related food as provocation factor of allergic symptoms in children with atopic eczema/dermatitis syndrome. Allergy 2004b;**59**:988–994.
18. Worm M, Ehlers I, Sterry W, Zuberbier T. Clinical relevance of food additives in adult patients with atopic dermatitis. Clin Exp Allergy 2000;**30**:407–414.
19. Ehlers I, Worm M, Sterry W, Zuberbier T. Sugar is not an aggravating factor in atopic dermatitis. Acta Dermatol Venereol 2001;**81**:282–284.
20. Eigenmann PA. Do we have suitable in vitro diagnostic tests for the diagnosis of food allergy? Curr Opin Allergy Clin Immunol. 2004;**4**:211–213.

21. Atherton DJ, Sewell M, Soothhill JF, Wells RS, Chilvers C. A double-blind controlled crossover trial of an antigen avoidance diet in atopic eczema. Lancet 1978;**1**:401–403.
22. Boyano MT, Garcia-Ara C, Diaz-Pena JM, Munoz FM, Garcia SG, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. Clin Exp Allergy 2001;**31**:1464–1469.
23. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001;**107**:891–896.
24. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol. 1997;**100**:444–451.
25. Turjanmaa K. The role of atopy patch tests in the diagnosis of food allergy in atopic dermatitis. Curr Opin Allergy Clin Immunol 2005;**5**:425–428.
26. Mabin DC, Sykes AE, David TJ. Nutritional content of few foods diet in atopic dermatitis. Arch Dis Child 1995;**73**:208–210.
27. Flinterman AE, Knulst AC, Meijer Y, Bruijnzeel-Koomen CA, Pasmans SG. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. Allergy 2006;**61**:370–374.
28. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. J Pediat 1985;**107**:669–675.
29. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. J Pediatr 1988;**113**:447–451.
30. Sampson HA. The immunopathogenic role of food hypersensitivity in atopic dermatitis. Acta Derm Venereol 1992;**176**:34–37.
31. Burks AW, James JM, Hiegel A, Wilson G, Wheeler JG, Jones SM et al. Atopic dermatitis and food hypersensitivity reactions. J Pediatr 1998;**132**:132–136.
32. Eigenmann PA, Calza AM. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. Pediatr Allergy Immunol 2000;**11**:95–100.
33. Mehl A, Rolinck-Werninghaus C, Staden U, Verstege A, Wahn U, Beyer K et al. The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. J Allergy Clin Immunol 2006;**118**:923–929.