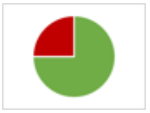
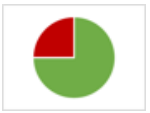
Dietary interventions in atopic eczema

We **recommend** to identify individual dietary trigger factors in patients with AE, to avoid these in the future, with the aim of prolonging remission or clearance.	↑↑	>75%  (16/17) Expert Consensus

<u>IgE-mediated food allergy (immediate reactions):</u> We **recommend** diagnostic procedures for the elucidation of IgE-mediated food allergy (food specific IgE and/or SPT, diagnostic elimination diets and challenge tests) in AE patients with a history of *food-induced immediate symptoms*.	↑↑	>75%  (16/18)[1] Expert Consensus
<u>IgE-mediated food allergy (immediate reactions) plus food-induced AE "delayed hypersensitivity":</u> We **recommend** diagnostic procedures for the elucidation of combined reactions to foods (immediate reactions plus food-induced eczema (food specific IgE and/or SPT, diagnostic elimination diets and challenge tests)) in AE patients with a history of *food-induced symptoms, including worsening of AE*.	↑↑	
<u>History or suspicion of food-triggered AE "delayed hypersensitivity":</u> We **suggest** diagnostic procedures for the elucidation of food as a trigger factor of AE (food specific IgE and/or SPT, diagnostic elimination diets and challenge tests) in patients with moderate-to-severe AE and with a *history or suspicion of food-triggered AE*.	↑	

[1]1 Abstention

A therapeutic elimination diet is **recommended** after the individual diagnosis of food allergy or food–induced eczema in AE.	↑↑	100%  (17/17) Expert Consensus
We **recommend** re-evaluation of a child's IgE mediated food allergy after one to two years after strict elimination diet.	↑↑	100%  (17/17) Expert Consensus
We **recommend against** general dietary interventions (e.g. other supplements, general avoidance of certain foods e.g. cow´s milk, gluten) for the management of AE.	↓↓	100%  (19/19) Expert Consensus
We **cannot make a recommendation** on probiotics for the management of AE.	0	100%  (19/19) Expert Consensus
We **recommend against** vitamins as a treatment for AE.	↓↓	100%  (17/17) Expert Consensus

Food allergens, pre- and probiotics

Food allergy has been documented in approximately one-third of children with moderate-to-severe AE.[1, 2] Among food allergens, cow's milk, hen's egg, peanut, soya, nuts and fish are most frequently responsible for immediate-type food allergy and AE exacerbation in young children, with age-dependent variations in causally incriminated food.[3] In older children, adolescents and adults pollen-associated food allergy should also be taken into account.[4-6]

Response patterns to food allergens

Three different clinical reaction patterns in patients with AE have been described, depending on the type of symptoms and their time of onset.[3, 7]

Immediate-type, non-eczematous reactions are usually IgE-mediated, occur within a maximum of 2 hours after the administration of the allergen, with skin manifestations such as urticaria, angioedema, flushing and pruritus or other immediate-type reactions of the gastrointestinal tract, the respiratory tract or the cardiovascular system in the case of anaphylaxis. Cutaneous manifestations occur in 74% of patients. In addition, children might develop a transient morbilliform rash 6–10 h after the initial immediate reaction, disappearing within a few hours and considered as 'late-phase' IgE-mediated response.[7, 8]

Isolated eczematous delayed-type reactions typically occur 6–48 h after the ingestion of the allergen, including flares of eczema in predilection sites of AE. However, such isolated eczematous reactions are rare.[4]

A combination of the two above-mentioned patterns with an immediate-type reaction followed by an eczematous delayed-type reaction has been described in approximately 40% of children with food and adolescents /adults with birch pollen associated reactions.[6, 9]

Sensitization to food should be identified by means of a detailed clinical history in combination with *in vivo* tests (skin prick tests - SPT) and *in vitro* tests (serum-specific IgE), as described in detail in food allergy guidelines.[10] *In vitro* tests are particularly valuable when SPT material for certain food is not available for routine diagnostics or when SPT cannot be applied (e.g. dermographism or UV- and drug-induced skin hyporeactivity, widespread eczema, or the inability to stop antihistamines). Moreover, *in vitro* specific IgE to food allergens may give better quantitative data for the grade of sensitization, which helps to estimate the probability of the risk of a clinical reaction. However, precise decision points are not available, but it offers the opportunity to test single recombinant allergens, which may have a better diagnostic specificity than testing with food extracts for some foods (e.g., Gly m 4 in pollen-related soya allergy, Ara h2 in peanut allergy).

Atopy patch tests (APT) are not considered a routine instrument since standardised test materials are still not available. APT are performed with self-made food material using a 1/10 dilution in saline of the fresh food applied for 24–48 h on non-lesional skin.[11] So far, APTs have demonstrated to improve the accuracy of skin testing in the diagnosis of allergy to cow's milk, hen's eggs, cereals and peanuts in patients with AE.[12-15] Whereas immediate-type reactions are associated with SPT positivity, delayed reactions are related to positive responses to APTs. However, double-blind placebo-controlled food challenge (DBPCFC) remains the 'gold standard' for the diagnosis of food allergy.[10]

Oral food challenge should be performed under medical supervision with emergency equipment available, particularly after long-term removal of the culprit food from the diet. Home introduction for cow's milk may be considered in the absence of evidence of sensitisation and without active eczema. In practice, oral food challenge should be performed according to standardized protocols.[16] In AE, the

major flaw is that it might not offer the opportunity to exclude placebo reactions or coincidental influences of other trigger factors of AE during the challenge period. Therefore, the evaluation of delayed reactions after 24 h or 48 h by trained personell is mandatory.[9, 10] Challenge tests based on repeated exposure to food enable the assessment of delayed adverse responses.[9]

All foods that are associated with immediate reactions should be avoided. It is suggested, however, to re-evaluate cow's milk and hen's egg allergy in infants and young children with AE after one to two years, as these might have been outgrown. According to the the Milk Allergy in Primary (iMAP) Care guideline reintroduction of cow's milk should be between 9-12 months of age or at least 6 months after diagnosis is made: https://gpifn.files.wordpress.com/2019/10/imap-treatment-algorithm.pdf.

In a systematic review[17], eight randomized controlled studies examined the effect of an elimination diet on existing AE. Based on this, there is no convincing evidence that a cow's milk- or hen's egg-free diet is beneficial in general, when unselected groups of patients with AE were studied. There is also no evidence for a benefit in the use of elementary or few food-restricted diets in unselected patients with AE. This comes with the caveat that elimination diets are difficult to carry out even in a motivating atmosphere during a clinical study and the dropout rate in AE studies is particularly high in studies on diets.

A Cochrane systematic review based on nine randomized controlled trials concluded that eliminating hen's egg from the diet in those who had evidence of significant sensitisation to hen's egg proved beneficial to AE control.[18] Accordingly, the American Academy of Dermatology recommends hen's egg restriction in the subset of patients with AE, who were found to be clinically allergic to hen's egg.[19] This approach should also be followed for other food allergens proven relevant in individual patients.

Pre- and probiotics and dietary supplements

Probiotics such as lactobacillus mixtures have been studied in AE and have been shown to induce improvement in some settings.[20] Other studies failed to show significant effects.[21, 22] In a study with 800 infants, the effect of a prebiotic mixture was investigated and found to have beneficial effects in preventing the development of AE.[23] A recent Cochrane review identified 39 randomised controlled trials involving 2599 randomised participants.[24] The authors concluded that compared with no probiotic, currently available probiotic strains probably make little or no difference in improving patient-rated eczema symptoms. However, in 2020, the systematic review by Tan-Lim et al found that certain probiotic preparations (Bifidobacterium animalis subsp lactis CECT 8145, Bifidobacterium longum CECT 7347, and Lactobacillus casei CECT 9104); Lactobacillus casei DN-114001) show benefit in reducing allergic symptoms in paediatric AE.[25]

A systemic review on dietary supplements including fish oil, vitamin D or vitamin E came to the conclusion that there is no convincing evidence of the benefit of dietary supplements in AE.[26]

Vitamins

A double blind, randomized clinical trial evaluated the effects of multistrain synbiotic (prebiotic+probiotic) versus vitamin D3 supplements or conventional therapy (topical steroid, emollients, antihistamine) on the severity of atopic eczema among 81 infants under 1 year of age for a period of two months; results showed a significant difference in SCORAD reduction between synbiotic ($p<0.001$) and vit D3 ($p=0.001$) groups compared to control group and no significant difference between vit D3 and synbiotic groups ($p=0.661$).[27]

In another randomized, controlled, investigator -blinded study on 26 young patients a product containing Licochalcone A lotion (LA+omega6+ceramide3+glycerin) was compared with an hydrocortisone lotion twice daily for 4 weeks in an intrapatient comparison. A significant reduction of SCORAD was observed in the LA side ($p<0.001$), but no statistical significant difference between the two sides ($p=0.199$) were found. Relapses were lower in the LA side; patients satisfaction was high with both therapies but HC lotion induced a faster resolution of oedema, erythema, excoriation and pruritus (no statistical difference between two sides).[28]

The effects of pre-natal folic acid and iron supplementation was studied by administering standardized questionnaire to 344 women who delivered babies in an Italian hospital. Women were supplemented before childbirth with iron only, folic acid only, iron+folic acid or no supplements. Results of this study showed that iron+folic acid supplementation during pregnancy had protective effect for AE in the offspring while smoking during pregnancy and family history of AE increased risk of AE in the offspring. No association between AE and body mass index, psychological distress condition, maternal food antigen avoidance during pregnancy, vegetables and fruit as antioxidants intake was found.[29]

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