

REVIEW ARTICLE

Food allergy and anaphylaxis in pediatrics: update 2010-2012Alexandra F. Santos^{1,2,3} & Gideon Lack¹

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Abstract

This review highlights the progress made in food allergy (FA) and anaphylaxis research in pediatrics published in the journal *Pediatric Allergy and Immunology* since 2010. Putative risk factors for FA are as follows: a family history of allergic disease, particularly in the mother, low birth order, season of birth, and severe atopic eczema. Obstetric practices, antibiotic use, and home environment are factors deserving further research. Diagnostic decision levels and component-specific IgE are useful in the diagnosis of FA; however, oral food challenges remain the gold standard and may also be a means to reduce parental anxiety and to improve education. Oral immunotherapy studies show promise in increasing the threshold of reactivity of allergic patients and therefore improving their quality of life. In single-nut-allergic patients, introduction of other nuts allows broadening the diet and thus reducing the psychological impact of allergen avoidance. Nutritional deficiencies are not uncommon in food-allergic children and should be specifically assessed. The prescription of injectable adrenaline is still insufficient and not consistent among practitioners, requiring improved training and implementation of guidelines. Current research into the epidemiology and immunological mechanisms of FA and tolerance will enable us to devise strategies to both prevent and treat food allergies.

Food allergy (FA) in children has become a significant public health concern, manifesting through both an increasing prevalence and a changing pattern in the disease expression. In recent generations, FA starts earlier in life, with greater severity and persistence into later ages (1). The increased prevalence in FA has resulted in an increased incidence in anaphylaxis. FA can be viewed as a dysregulation of oral tolerance, and an increased understanding of the factors and immune mechanisms responsible for this dysregulation will further the objectives of acquiring definitive treatment and prevention strategies.

Since 2010, about 120 articles in FA and anaphylaxis were published in *Pediatric Allergy and Immunology*. This review summarizes the key findings (Tables 1 and 2).

Food allergy**Epidemiology**

In parallel with the rise in FA in the Western world, an increasing prevalence of FA in developing countries is anticipated. In a recent study of 477 infants consecutively attending

a primary care clinic in Chongqing, China, the prevalence of food sensitization by skin-prick test (SPT) was 11.3% and of challenge-proven FA was 3.8% (2), with egg and cow's milk (CM) allergies being the most common, as in other geographical locations. General population studies at a global level, including both developed and developing countries, are needed.

Different factors have been hypothesized as risk factors or protective factors for FA, namely hereditary factors (e.g., family history of allergy, filaggrin loss-of-function mutations), microbial factors (e.g., gut flora, parasites and infectious agents), dietary factors (e.g., vitamin D, fat, antioxidants), and allergen exposure (e.g., exposure to food allergens in the maternal and in the infant's diet and in the environment). Various research papers published in *Pediatric Allergy and Immunology* address the role of some of these factors.

A family history of allergy is a well-known risk factor for the development of FA. In a Finnish population-based study (3), parental allergic diseases were associated with an increased risk of food sensitization and allergy in the offspring up to the age of 4 yr, greater with additional allergic manifestations in the parents and if both parents were affected. Maternal allergy

Table 1 Progress in food allergy (FA) in pediatrics since 2010

Key messages	
Epidemiology	EuroPrevall birth cohort data show baseline differences in the prevalence of family allergies, obstetric practices, antibiotic use, and home environment factors between the nine participating countries Prevalence of FA decreases with birth order The composition of gut microbiota may influence the development of FA Birth during autumn and winter is associated with a higher prevalence of FA, which negatively correlates with ultraviolet radiation intensity Maternal consumption of vitamin D during pregnancy may have a beneficial effect in reducing allergic sensitization to food and inhalant allergens Maternal supplementation with ω-3 long-chain polyunsaturated fatty acids in pregnancy and lactation may be protective Promoting effect of prolonged breastfeeding on FA disappears when confounding factors are excluded Early introduction of solids reduced the risk of eczema in children with a family history of allergy Severe atopic eczema is associated with earlier and persistent allergic sensitization to foods
Mechanisms	Higher intestinal IgA at 6 months is associated with a reduced risk of IgE-mediated FA In food-sensitized children, Th2-polarized immune responses lead to increased levels of allergen-specific IgE, IgG1, and IgG4
Diagnosis	Children with sensitization or allergy to peanuts and tree nuts are more likely to be sensitized or allergic to sesame but not to coconut The 95% positive predictive value diagnostic decision levels of skin-prick test (SPT) for egg allergy are usually ≥ 6–9 mm (and ≥ 3–5 mm for <2 yr) and for peanut allergy are usually ≥ 7–8 mm (and ≥ 4 mm for <2 yr) Useful components to identify patients at risk of systemic reactions are as follows: Ara h 1, Ara h 2, and Ara h 3 for peanut; Cor a 9 for hazelnut; and Gly m 5 and Gly m 6 for soy, while Ara h 8, Cor a 1, and Gly m 4 are suggestive of peanut, hazelnut, and soy allergies secondary to pollen allergy Parental anxiety is reduced after a positive food challenge A clinical score based on the culprit food, the time between allergen ingestion and symptoms, and specific IgE levels predicts the outcome of oral food challenge (OFC) In children with a positive peanut challenge that continued beyond the threshold of reactivity, a larger weal diameter on SPT and a higher specific IgE level to peanut were associated with more severe allergic exposure
Management	Allergen-specific oral immunotherapy protocols show promise in the treatment of FA and induce an increase in the threshold of reactivity, reducing the risk in case of accidental exposure In single-nut-allergic children, the introduction of other nuts can be performed safely, reducing risk-taking behavior and the psychosocial impact of allergen avoidance and improving patients' quality of life Larger SPT and higher levels of specific IgE to cow's milk (CM), immediate reactions and co-existent asthma, and food allergies were associated with persistent CM allergy SPT to gliadin greater or equal to 5 mm suggests persistent wheat allergy. Positive SPT to gliadin was also associated with asthma and later development of allergic rhinitis and sensitization to birch pollen Food-allergic children have lower weight-for-age and height-for-age than their peers and are at risk of protein energy malnutrition, requiring specialized dietetic assessment
Education	Teenagers constitute an age group that deserves special attention and approach with respect to food allergies Index food-allergic reactions are poorly recognized and treated, justifying improved education of not only patients and the community but also of healthcare professionals and appropriate implementation of existing guidelines

seems to be a stronger determinant of allergic risk, namely maternal atopic dermatitis (4).

Although genetic predisposing factors have been identified, the fact that FA is associated with a Western lifestyle and has increased more rapidly than changes in the genome could occur suggests that environmental factors may have a more important role. The hygiene hypothesis proposes that a lower microbial exposure in early life modifies the immune response toward a greater predisposition to allergic disease. There is limited evidence to support the hygiene hypothesis in relation to FA; however, the results of a questionnaire-based survey administered to parents of school-age children in Kyoto, Japan (5), suggest that the prevalence of FA decreases with birth order, consistent with the hygiene hypothesis.

Early colonization of the infant's gut is thought to protect against the development of allergic disease. Studies have characterized the commensal flora of infants with and without FA and tested the manipulation of the gut microflora through the administration of pre- and/or probiotics (6–8). Thompson-Chagoyan et al. (6) reported that CM-allergic infants had higher total bacteria and anaerobic counts and lower yeast counts than healthy infants. CM avoidance resulted in an increase in the proportion of lactobacilli and in a decrease in the proportion of enterobacteria and bifidobacteria. In another study (7), infants with CM allergy showed a different urinary metabolic profile compared with infants without FA, which may reflect differences in intestinal microbiota. The concentrations of urinary organic acids did not significantly change after 4 weeks of administration of *Lactobacillus rhamnosus*

Table 2 Progress in anaphylaxis in pediatrics since 2010

	Key messages
Mechanisms and diagnosis	Children with food allergy (FA) and asthma have higher FeNO and percentage of eosinophils in the sputum than asthmatic children without FA Baseline serum total tryptase is higher in infants younger than 3 months
Management and education	Autoinjectable adrenaline is currently used only in a minority of cases of anaphylaxis The decision of prescribing adrenaline autoinjectors is inconsistent, and implementation of existing anaphylaxis guidelines is required Development of a specific protocol about the management of anaphylaxis improved medical performance and patients' care in a pediatric emergency department

compared with placebo. A protective effect of certain probiotics against the development of eczema has been reported (9, 10), but an effect in the prevention of FA remains indeed to be seen.

Another possible explanation for the increase in allergic disease is a low vitamin D status, which may result from low sunlight exposure with more time spent indoors. In a study by Mullins et al. (11), hypoallergenic formula prescription rates were more common in the southern and eastern regions of Australia, where sunlight exposure is lower. Another study from the same group (12) showed an association of birth during the autumn and winter with a higher prevalence of FA, including peanut and egg allergies, and with a higher rate of prescription of adrenaline autoinjector (AAI) and of hypoallergenic formulas. Ultraviolet radiation intensity negatively correlated with the relative rate of FA. Maternal consumption of vitamin D during pregnancy may have a beneficial effect in reducing allergic sensitization to food and inhalant allergens (13).

Changes in diet in the Western lifestyle have accompanied the rise in allergic disease. It has been suggested that an unbalanced diet with reduced consumption of ω -3 polyunsaturated fatty acids, present in oily fish, and increased consumption of ω -6 polyunsaturated fatty acids, present in vegetable oils, may contribute to an increased production of prostaglandin E₂ and lead to a Th2-type immune response and inflammation. Following a meta-analysis which led to the conclusion that supplementation with ω -3 fatty acids is unlikely to play a role in primary prevention of allergic disease, in a Swedish study, maternal supplementation with ω -3 long-chain polyunsaturated fatty acids in pregnancy and lactation was related to a lower frequency of sensitization to foods and of IgE-mediated food-allergic reactions compared with placebo, suggesting a protective effect (14).

Given that FA and tolerance are allergen-specific responses, exposure to food allergens in early life has drawn the attention of many investigators. Food allergen exposure may happen via different routes: prenatally through the placenta, orally through the infant's diet, and epicutaneously or via the respiratory route to allergens in the environment. Breast milk is without doubt the best food for infants in the first few months of life and is

often prolonged in high-risk children. Previous reports associated prolonged breastfeeding with allergic disease, but this was probably due to reverse causality. Kusunoki et al. (15) found that the promoting effect of breastfeeding on FA disappeared when confounding factors were excluded. There is little evidence-based guidance on when to introduce allergenic foods in the infant's diet and on whether early or delayed weaning can prevent FA. Interestingly, in children with a family history of allergy, early introduction of solids reduced the risk of eczema (OR: 0.49; 95% CI: 0.32–0.74) (16), which is a predisposing factor for FA. In the 6-yr review of the DARC birth cohort, allergen sensitization was observed in 43% of children with atopic eczema, mainly to foods in younger children followed by sensitization to air-borne allergens at older ages. Severe atopic eczema was associated with early and persistent allergic sensitization, including to food allergens (17). Also in a Chinese study, a higher SCORAD was associated with serum food-specific IgE (18). These studies highlight the role of early-onset severe eczema as a risk factor for sensitization to foods, consistent with previous findings, and raise the question as to whether environmental exposure to food allergens poses a risk for the development of food sensitization and FA.

Baseline demographic data of the EuroPrevall birth cohort showed considerable differences in the prevalence of family history of allergy, obstetric practices, antibiotic use, and home environment factors (such as cigarette smoking, urban vs. rural housing, pet ownership, type of flooring, and mattress in the infant's room) in the nine European participating countries (19). If these differences are shown to relate to geographical differences in FA during the first 2.5 yr of life, this will help establish important risk factors or protective factors for FA.

Mechanisms

Living in a farm is thought to protect against the development of FA and other atopic diseases. Experimentally, farm-reared piglets showed a significantly higher T-regulatory-to-T-effector cells ratio and lower allergen-specific antibody responses than their isolation-reared littermates (20).

Microbial stimulation of the gut may induce secretion of mucosal IgA, which is able to neutralize antigens before they can reach the gut-associated immune lymphoid tissue and may contribute to oral tolerance. In a nested case-control study of infants participating in a randomized double-blind placebo-controlled allergy-prevention trial where a combination of four probiotic strains was administered pre-natally and during 6 months from birth, Kukkonen et al. (21) found that high intestinal IgA at 6 months was associated with fewer IgE-mediated allergic diseases at age 2 yr and that the levels of IgA in the feces positively correlated with the intestinal inflammation markers. Once food sensitization has developed, Th2 polarization of the immune response influences the production of allergen-specific antibodies. Scott-Taylor et al. (22) showed that in children sensitized to milk, egg, and/or peanut, there was an increased production of IL-4 and a decreased production of IFN- γ by T cells and elevated allergen-specific IgG1 and IgG4 compared with non-sensitized children. The allergen-induced cytokine response correlated with the levels of aller-

gen-specific antibodies. In another study (23), higher peanut specific IgE (sIgE), IgG, and IgG4 levels in peanut-sensitized children compared with non-peanut-sensitized children was seen, especially in children avoiding peanuts, who were likely to be peanut allergic. Tomićić et al. (24) showed that, in children tolerant of CM and/or egg who regularly eat the respective food, there was an abrogation of allergen-induced Th1 and Th2 responses, as evaluated by the production of IFN- γ and IL-5, respectively, by allergen-stimulated peripheral blood mononuclear cells.

Diagnosis

The diagnosis of FA can be very challenging, especially in the absence of a clear clinical history or when the child has yet to be orally exposed to the food. This is partly because sensitization is more common than clinical FA, that is, the majority of children with a positive skin prick test (SPT) or sIgE to a food are not allergic to that food. The way to clarify this is by doing an oral food challenge (OFC). However, OFCs are time-consuming, require a dedicated team and special resources, and involve the risk of an allergic reaction. OFCs are often not performed leading to overdiagnosis of FA and unnecessary burden of allergen avoidance. A large Canadian study (25), involving 331 children with unclear history of peanut allergy (PA) recruited from a specialized allergy clinic and through allergy advocacy organizations, showed important differences in the methods of diagnosing PA among clinicians and an overall low OFC rate of 5.7%. In a Finnish population-based study of 5920 children, 18% of children had received food-allergy testing by the age of 4 in either hospitals, primary care centers, or private practices (26). Boys, first-borns, and children with a history of parental allergy were more frequently tested. These studies underscore the need to improve current practices of allergy testing and the accuracy of FA diagnosis. Despite the increasing prevalence of FA, when seeing patients outside the specific context of an allergy clinic, one should bear in mind that overall FA is an uncommon cause of acute urticaria in children (27).

Allergy test panels should include suspected foods identified in the clinical history and common food allergens considering patient's age, allergic condition, and geographical location. While theoretically any food can cause allergic reactions, common allergens are limited to a few food families, namely CM, egg, wheat, soya, peanut, sesame, tree nuts, fish, and shellfish. Guidelines concerning CM allergy (28) and a review on fish and shellfish allergies (29) have recently been published in *Pediatric Allergy and Immunology*. Children with certain food allergies (FA) are at risk of developing allergy to other food groups, for example, children with sensitization or allergy to peanuts and tree nuts are more likely to be sensitized or allergic to sesame (OR 10.2, 95% CI 2.7–38.7) but not to coconut (30, 31). SPT is safe, but rarely systemic reactions may occur, highlighting the need for emergency medication and easy access to specialist support (32).

SPT and serum sIgE have high negative predictive value but low positive predictive value (PPV), making them more useful to exclude FA than to confirm the diagnosis. To improve the

utility of SPT and sIgE, various studies have defined diagnostic decision levels (33). The resulting cutoff values are variable depending on the population studied and the methodology adopted, such as the SPT technique, the use of allergen extracts vs. fresh food, selection criteria of patients for challenge, the challenge protocol, the criteria to consider a challenge positive, and the statistical methods used. Peters et al. (33) have systematically reviewed studies where the predictive values of SPT to egg and to peanut were determined. The 95% PPV diagnostic decision levels for egg allergy are usually ≥ 6 –9 mm (and ≥ 3 –5 mm for children under 2 yr of age) and for PA are usually ≥ 7 –8 mm (and ≥ 4 mm for children under 2 yr of age). Although these cutoff values can be useful, given their variability across centers, their application in clinical practice should be done with caution and clinical sense.

Component-resolved diagnosis shows promise in reducing the number of patients referred for OFC (34–38). For instance, in PA, sensitization to the major allergens, Ara h 1, Ara h 2, and Ara h 3, suggests clinical PA with an inherent risk of systemic reactions. This seems to be true not only in Western English-speaking countries but also in Singapore, in Japan, and even in Spain where monosensitization to the lipid transfer protein Ara h 9 has previously shown to be responsible for cases of anaphylaxis (39–41). In hazelnut-sensitized patients in birch pollen-endemic areas, Cor a 9 is useful in identifying patients with systemic reactions, which are more common in infants and children, while Cor a 1 identifies patients with birch pollen allergy and oral allergy syndrome, more common among hazelnut-sensitized adults (34, 35). In birch pollen-allergic children, SPT to soy flour and sIgE to Gly m 4 proved to be more useful in confirming the diagnosis of secondary soy allergy than SPT using the commercial extract, which showed low sensitivity, or sIgE to Gly m 5 and Gly m 6, whose levels were comparable between patients with pollen-related soy allergy and soy-tolerant patients (36).

Oral food challenges (OFCs) are the gold standard for the diagnosis of FA and can contribute to parents' reassurance and education. In a telephone survey about parental satisfaction with peanut challenges, 89% of parents were satisfied with the experience, even when the challenge was positive and anaphylaxis occurred, as it improved their awareness about their child's allergy (42). Another study showed that parental anxiety was reduced after a positive OFC (43). Lower satisfaction levels were observed in the case of inconclusive or equivocal challenges and also when there were difficulties in feeding, distress in seeing their child unwell, and perception of inappropriate follow-up (42).

An OFC is stressful for the patient and family as it involves the risk of developing an allergic reaction that can potentially be severe. It also requires specialized resources and a dedicated experienced team. Furthermore, with increasing frequency and awareness about FA and sensitization, allergy services are overwhelmed with requests for OFC; thus, alternative testing that could confirm the allergic status while reducing the need for OFC would be very useful in clinical practice. Zomer-Kooijker et al. (44) developed a clinical score that accurately predicted the outcome of OFC, based on the culprit food, the

time between allergen ingestion and symptoms, and sIgE levels, and reduced the number of OFC by 24%. However, OFC is still the only reliable diagnostic method in certain circumstances, namely in cases of suspected non-IgE-mediated FA where SPT and sIgE have low sensitivity and PPV (45, 46).

A common concern of parents and healthcare professionals (HCP) dealing with children with FA is the severity of a future accidental reaction. In a study of children with a positive peanut challenge, a larger weal diameter on SPT and a higher sIgE level to peanut were associated with more severe reactions (47). This is in contrast to the findings of previous studies, probably because, in this study, children with large weal on SPT were not excluded based on the SPT result alone and OFC continued beyond the threshold for reactivity, despite the development of mild allergic symptoms.

Management

The mainstay for the treatment of FA is allergen avoidance and emergency medication in case of accidental allergic reactions. Accidental reactions to ubiquitous food allergens, such as egg and milk, are common (48, 49). FA has a significant negative impact in the daily life of allergic children and their families (50–52) due to dietary and social restrictions and to the life-threatening nature of certain allergies. According to a recent study, the worse quality-of-life scores were obtained by older children, girls, children with multiple FA, with a history of severe systemic reactions, or with mothers or siblings also affected by allergies (52).

Trying to find a definitive treatment for FA, protocols for allergen-specific oral tolerance induction (SOTI) to different foods have been developed (53–55). Despite the reported adverse effects and the variability of the threshold for reactivity with non-allergen-specific factors, such as viral infections, menstruation, and exertion, there have been no serious safety concerns or fatal events. Globally, SOTI has been able to increase the threshold of reactivity of allergic children reducing the risks in case of inadvertent exposure to the culprit food and contributing to an improvement in patients' quality of life (56). Whether SOTI induces long-term tolerance or only transient desensitization remains to be seen. Long-term tolerance would be the desirable outcome as it would imply continued effect beyond discontinuation of treatment. After a few months of oral immunotherapy, clinical improvement is accompanied by a decrease in effector T-cell populations and an increase in regulatory T cells and hypoproliferative and non-reactive CD4⁺ T cells (57–59). Understanding the immunological changes that develop with SOIT will help to address that question.

In single-nut-allergic children, the question as to whether avoidance should be generalized to all nuts or limited to the culprit nut is under discussion (60, 61). The general recommendation for peanut or single-tree nut-allergic children used to be to avoid all nuts given the common clinical cross-reactivity between peanut and tree nuts and among tree nuts to reduce the risk of contamination leading to inadvertent exposure. However, current clinical practice tends to change with an increasing number of experienced clinicians supporting

the introduction of selected nuts while still avoiding the culprit nut. Advantages of this new approach are an accurate diagnosis and a reduction in risk-taking behavior and in the psychosocial impact of allergen avoidance. Ball et al. (60) have reviewed the outcome of 145 nut challenges performed in their center over a 5-yr period in children who were either peanut or single-tree nut allergic. Of the 94 peanut-allergic children with negative SPT to tree nuts, all passed the OFC and only 31.2% of the tree-nut-sensitized patients reacted. However, among tree nut allergic, 7.9% of patients with negative SPT and 38% of the sensitized patients had a positive OFC. In a letter to the Editor, Stiefel et al. (61) reported 4.3% of positive OFC to tree nuts in peanut-allergic children with negative SPT to tree nuts, underscoring the risk inherent to home introduction of tree nuts after negative SPT. It remains to be seen whether sIgE to nut extracts and their components could reduce the number of positive OFC and justify home introduction. Other important questions that remain to be answered is whether early introduction of selected nuts in single-nut-allergic patients can prevent the development of further nut allergies and whether it can interfere with the natural history of existing nut allergies.

An important aspect of the management of food-allergic children is the assessment of eventual development of tolerance. For different FA, namely to CM (62), egg (63), and wheat (64), repeated performance of allergen sIgE by SPT or sIgE over time has proved to be useful in deciding when to re-challenge. In CM allergy, large SPT and high levels of sIgE to CM as well as immediate reactions and co-existent asthma and FA were associated with persistent disease (62). In wheat-allergic patients, a SPT to gliadin ≥ 5 mm at the time of diagnosis was associated with persistent wheat allergy. Positive SPT to gliadin was also associated with asthma, and IgE-mediated wheat allergy with later development of allergic rhinitis and sensitization to birch pollen (63). In parallel with the resolution of some FA, new sensitizations may develop to other food and inhalant allergens. Polysensitization is common and may be a marker of a more severe atopic phenotype rather than antibody cross-reactivity between similar allergens (65, 66).

Children with FA are often on elimination diets for long periods of time and therefore at risk of nutritional deficiencies (67–70); thus, nutritional assessment is essential in the follow-up of these children. Flammarion et al. (67) showed in a cross-sectional study that food-allergic children had lower weight-for-age and height-for-age when compared with healthy-matched controls with similar nutrient intake, especially in children with multiple FA. Malnutrition in food-allergic children goes beyond a normal weight gain, which often does not reflect subtle micronutrient or protein deficiencies. Meyer et al. (68) particularly addressed the problem of protein energy malnutrition in CM-allergic children and revised current guidelines and their application in the management of malnourished children with CM allergy. The authors clearly systematize the process in four steps: (i) nutritional evaluation by measuring weight, length/height, and head circumference; (ii) determination of the rate of catch-up growth required based on the weight-for-height or s.d. scores; (iii) considering that 8.9–11.5% of energy should be provided

by protein, establishment of a dietary plan, and selection of the most appropriate hypoallergenic formula, its concentration and vitamin and mineral supplementation, food fortification, and feeding strategies; and (iv) monitoring of the patient and adjustment of the diet.

Choosing the most appropriate CM formula may not always be straightforward and should take into consideration not only clinical indications but also costs (28, 71–73). Additives in the CM formula may modulate the gut immune response. In a study by Francavilla et al. (74), the addition of lactose to an extensively hydrolyzed formula increased the total fecal counts of *Lactobacillus* and *Bifidobacteria* and reduced the populations of *Bacteroides* and *Clostridia*.

The relationship between allergic disease and immunizations is complex. It is not uncommon to find families who have not vaccinated their children for the fear of increasing their risk of developing allergies or the severity of atopic diseases including FA. Studies have shown that childhood immunizations do not confer an increased risk of FA (75, 76), and families should be encouraged to vaccinate their children without delay. An acute and potentially severe allergic reaction to the vaccine preparation is also a common concern in parents of egg-allergic children. While measles–mumps–rubella (MMR) vaccination can be administered to egg-allergic children at the primary care level, anti-influenza and anti-yellow fever vaccines may pose a greater risk due to their egg protein content and justify a two-dose administration in hospital. Recent studies report that anti-influenza vaccines' preparations contain very low quantities of ovalbumin and cause no reaction in the majority of egg-allergic patients following the two-dose protocol and only mild symptoms in those who reacted (77).

Patient education is extremely important in adherence to an elimination diet and in the treatment of an accidental allergic reaction should it occur (78–80). Providing access to clear and concise information, namely through the Internet and support groups, contributes to reducing anxiety and improving the quality of life of allergic children and their parents. Focus groups conducted in two academic centers in the United States helped to identify the most important areas to cover in the education of parents of children recently diagnosed with one or more FA, namely early manifestations, cross-contamination, label reading, AAI, and becoming an advocate (78). A particularly challenging group of patients is teenagers, where the responsibility is progressively transferred from parents to the patient (51, 81). Evaluating teenagers' experiences of living with FA and their strategies to cope with it is important to ensure that patients understand the information they are given as well as to ensure their safety and quality of life (51).

Training of non-allergy-specialized HCP is desirable to ensure the best possible care to food-allergic patients (78, 82). In an online survey, Jacobs et al. (83) reported that initial episodes of allergic reactions are poorly recognized and treated, with a minority of patients who suffer from food-induced anaphylaxis being administered adrenaline, referred to an allergist, given an emergency action plan, or prescribed and trained in how to use an AAI. There is still a lot to be done to increase awareness and to improve education about FA and anaphylaxis.

Anaphylaxis

Food allergy is the main cause of anaphylaxis in children (84–86), particularly allergy to peanut and tree nuts. Co-existent asthma increases the risk of severe reactions in food-allergic children (85), possibly due to underlying eosinophilic airway inflammation. In a retrospective study of 75 children attending a pediatric asthma center, asthmatic children with FA had higher fractional exhaled nitric oxide (median of 22.4 vs. 10.3 p.p.b., $p = 0.01$) and sputum eosinophil percentage (15.5 vs. 2.0, $p < 0.001$) compared with asthmatic children without FA (87). In another study of 94 peanut-allergic children attending a pediatric allergy clinic, children with outgrown asthma or untreated wheeze had higher fractional exhaled nitric oxide levels than children with treated asthma or non-asthmatic children (88). Registries of cases of anaphylaxis can be very useful in identifying causes, aggravating factors, and current management of anaphylaxis (84).

One of the first challenges with respect to anaphylaxis is the accurate recognition of this entity. The definition remains essentially clinical (89), and diagnostic markers are needed. Serum tryptase is a potential biomarker, particularly in cases where clinical diagnosis is more challenging, especially in infancy. However, in this age group, results may be difficult to interpret as there is no established normal range. Belhocine et al. (90) showed that total serum tryptase levels are higher in the first 3 months of life, decreasing progressively over time, and that atopic infants tend to have higher levels of total serum tryptase.

A common finding in the analysis of registries and observational studies is that AAI is used only in a minority of cases of anaphylaxis, implying that not only education of patients and families (91–93) but also of school staff (94) and HCP is highly needed. In a Dutch study (95), only a small proportion of food-allergic teenagers at risk of anaphylaxis were prescribed an AAI. In an online survey about the practices in the prescription of AAI of pediatric allergists and general pediatricians (96), the prescribing decisions were very inconsistent and although the clinicians were familiar with anaphylaxis guidelines, these have not influenced their daily practice. In a recent editorial article, Niggemann and Beyer (97) clearly systematize the main practical issues related to the prescription of adrenaline as part of an emergency treatment plan for FA. The application of a specific protocol about the management of anaphylaxis in a pediatric emergency department significantly improved medical performance and care (98). Overall, the previous studies highlight the importance of developing strategies for implementation of existing anaphylaxis guidelines.

Summary

Research in FA and anaphylaxis in the recent years has allowed us to gain more insight into the epidemiology and mechanisms of these conditions and to improve patients' care. Component testing has improved diagnostic accuracy, but OFCs are still required in a significant proportion of cases and can be a means to reassure patients and improve education. SOTI show promise in the treatment of FA, but the question as to whether it induces

long-term tolerance or only transient desensitization remains to be answered. New approaches to single-nut-allergic patients with introduction of other nuts in the diet can be performed safely and improve their quality of life. Continued patients' education and training of HCP is essential in the care for children and teenagers with FA and anaphylaxis.

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References

- Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol* 2011; **22**: 155–60.
- Chen J, Hu Y, Allen KJ, Ho MH, Li H. The prevalence of food allergy in infants in Chongqing, China. *Pediatr Allergy Immunol* 2011; **22**: 356–60.
- Pyrhonen K, Hiltunen L, Kaila M, Nayha S, Laara E. Heredity of food allergies in an unselected child population: an epidemiological survey from Finland. *Pediatr Allergy Immunol* 2011; **22**: e124–32.
- Kim J, Chang E, Han Y, Ahn K, Lee SI. The incidence and risk factors of immediate type food allergy during the first year of life in Korean infants: a birth cohort study. *Pediatr Allergy Immunol* 2011; **22**: 715–9.
- Kusunoki T, Mukaida K, Morimoto T, et al. Birth order effect on childhood food allergy. *Pediatr Allergy Immunol* 2012; **23**: 250–4.
- Thompson-Chagoyan OC, Vieites JM, Maldonado J, Edwards C, Gil A. Changes in faecal microbiota of infants with CM protein allergy—a Spanish prospective case-control 6-month follow-up study. *Pediatr Allergy Immunol* 2010; **21**: e394–400.
- Salmi H, Kuitunen M, Viljanen M, Lapatto R. CM allergy is associated with changes in urinary organic acid concentrations. *Pediatr Allergy Immunol* 2010; **21**: e401–6.
- Eiwegger T, Stahl B, Haidl P, et al. Prebiotic oligosaccharides: in vitro evidence for gastrointestinal epithelial transfer and immunomodulatory properties. *Pediatr Allergy Immunol* 2010; **21**: 1179–88.
- Kim JY, Kwon JH, Ahn SH, et al. Effect of probiotic mix (*Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial. *Pediatr Allergy Immunol* 2010; **21**: e386–93.
- van der Aa LB, Heymans HS, van Aalderen WM, Sprinkelman AB. Probiotics and prebiotics in atopic dermatitis: review of the theoretical background and clinical evidence. *Pediatr Allergy Immunol* 2010; **21**: e355–67.
- Mullins RJ, Clark S, Camargo CA Jr. Regional variation in infant hypoallergenic formula prescriptions in Australia. *Pediatr Allergy Immunol* 2010; **21**: e413–20.
- Mullins RJ, Clark S, Katelaris C, Smith V, Solley G, Camargo CA Jr. Season of birth and childhood food allergy in Australia. *Pediatr Allergy Immunol* 2011; **22**: 583–9.
- Nwaru BI, Ahonen S, Kaila M, et al. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. *Pediatr Allergy Immunol* 2010; **21**: 29–37.
- Furuhjelm C, Warstedt K, Fageras M, et al. Allergic disease in infants up to 2 years of age in relation to plasma omega-3 fatty acids and maternal fish oil supplementation in pregnancy and lactation. *Pediatr Allergy Immunol* 2011; **22**: 505–14.
- Kusunoki T, Morimoto T, Nishikomori R, et al. Breastfeeding and the prevalence of allergic diseases in schoolchildren: does reverse causation matter? *Pediatr Allergy Immunol* 2010; **21**: 60–6.
- Sariachvili M, Droste J, Dom S, et al. Early exposure to solid foods and the development of eczema in children up to 4 years of age. *Pediatr Allergy Immunol* 2010; **21**: 74–81.
- Eller E, Kjaer HF, Host A, Andersen KE, Bindslev-Jensen C. Development of atopic dermatitis in the DARC birth cohort. *Pediatr Allergy Immunol* 2010; **21**: 307–14.
- Hon KL, Chan IH, Chow CM, et al. Specific IgE of common foods in Chinese children with eczema. *Pediatr Allergy Immunol* 2011; **22**: 50–3.
- McBride D, Keil T, Grabenhenrich L, et al. The EuroPrevall birth cohort study on food allergy: baseline characteristics of 12,000 newborns and their families from nine European countries. *Pediatr Allergy Immunol* 2012; **23**: 230–9.
- Lewis MC, Inman CF, Patel D, et al. Direct experimental evidence that early-life farm environment influences regulation of immune responses. *Pediatr Allergy Immunol* 2012; **23**: 265–9.
- Kukkonen K, Kuitunen M, Haataela T, Korpela R, Poussa T, Savilahti E. High intestinal IgA associates with reduced risk of IgE-associated allergic diseases. *Pediatr Allergy Immunol* 2010; **21**: 67–73.
- Scott-Taylor TH, Hourihane JOB, Strobel S. Correlation of allergen-specific IgG subclass antibodies and T lymphocyte cytokine responses in children with multiple food allergies. *Pediatr Allergy Immunol* 2010; **21**: 935–44.
- Sverremark-Ekstrom E, Hultgren EH, Borres MP, Nilsson C. Peanut sensitization during the first 5 yr of life is associated with elevated levels of peanut-specific IgG. *Pediatr Allergy Immunol* 2012; **23**: 224–9.
- Tomicic S, Falth-Magnusson K, Bottcher MF. Dysregulated Th1 and Th2 responses in food-allergic children—does elimination diet contribute to the dysregulation? *Pediatr Allergy Immunol* 2010; **21**: 649–55.
- Ben-Shoshan M, Kagan R, Primeau MN, et al. Establishing the diagnosis of peanut allergy in children never exposed to peanut or with an uncertain history: a cross-Canada study. *Pediatr Allergy Immunol* 2010; **21**: 920–6.
- Pyrhonen K, Hiltunen L, Nayha S, Laara E, Kaila M. Real-life epidemiology of food allergy testing in Finnish children. *Pediatr Allergy Immunol* 2011; **22**: 361–8.
- Konstantinou GN, Papadopoulos NG, Tavladaki T, Tsekoura T, Tsimiligiaki A, Grattan CE. Childhood acute urticaria in northern and southern Europe shows a similar epidemiological pattern and significant meteorological influences. *Pediatr Allergy Immunol* 2011; **22**: 36–42.
- Fiocchi A, Brozek J, Schunemann H, et al. World Allergy Organization (WAO) diagnosis and rationale for action against CM allergy (DRACMA) guidelines. *Pediatr Allergy Immunol* 2010; **21**(Suppl. 21): 1–125.
- Tsabori S, Triga M, Makris M, Kalogeromitros D, Church MK, Priftis KN. Fish and shellfish allergy in children: review of a persistent food allergy. *Pediatr Allergy Immunol* 2012; **23**: 608–15.
- Stutius LM, Sheehan WJ, Rangsihienchai P, et al. Characterizing the relationship between sesame, coconut, and nut allergy in children. *Pediatr Allergy Immunol* 2010; **21**: 1114–8.
- Dalal I. Allergy to seeds. *Pediatr Allergy Immunol* 2011; **22**: e150–4.
- Pitsios C. Generalized allergic reactions during skin testing. *Pediatr Allergy Immunol* 2010; **21**: 557.
- Peters RL, Gurrin LC, Allen KJ. The predictive value of skin prick testing for challenge-proven food allergy: a systematic review. *Pediatr Allergy Immunol* 2012; **23**: 347–52.

34. De Knop KJ, Verweij MM, Grimmelikhuijsen M, et al. Age-related sensitization profiles for hazelnut (*Corylus avellana*) in a birch-endemic region. *Pediatr Allergy Immunol* 2011; **22**: e139–49.
35. Verweij MM, Hagendorens MM, De Knop KJ, et al. Young infants with atopic dermatitis can display sensitization to Cor a 9, an 11S legumin-like seed-storage protein from hazelnut (*Corylus avellana*). *Pediatr Allergy Immunol* 2011; **22**: 196–201.
36. De Swert LF, Gadisseur R, Sjolander S, Raes M, Leus J, Van Hoesveld E. Secondary soy allergy in children with birch pollen allergy may cause both chronic and acute symptoms. *Pediatr Allergy Immunol* 2012; **23**: 117–23.
37. Palacin A, Quirce S, Sanchez-Monge R, et al. Sensitization profiles to purified plant food allergens among pediatric patients with allergy to banana. *Pediatr Allergy Immunol* 2011; **22**: 186–95.
38. Borres MP, Ebisawa M, Eigenmann PA. Use of allergen components begins a new era in pediatric allergology. *Pediatr Allergy Immunol* 2011; **22**: 454–61.
39. Chiang WC, Pons L, Kidon MI, Liew WK, Goh A, Wesley Burks A. Serological and clinical characteristics of children with peanut sensitization in an Asian community. *Pediatr Allergy Immunol* 2010; **21**: e429–38.
40. Ebisawa M, Moverare R, Sato S, Maruyama N, Borres MP, Komata T. Measurement of Ara h 1-, 2-, and 3-specific IgE antibodies is useful in diagnosis of peanut allergy in Japanese children. *Pediatr Allergy Immunol* 2012; **23**: 573–81.
41. Pedrosa M, Boyano-Martinez T, Garcia-Ara MC, Caballero T, Quirce S. Peanut seed storage proteins are responsible for clinical reactivity in Spanish peanut-allergic children. *Pediatr Allergy Immunol* 2012; **23**: 654–9.
42. Nguyen M, Wainstein BK, Hu W, Ziegler JB. Parental satisfaction with oral peanut food challenges; perception of outcomes and impact on management of peanut allergy. *Pediatr Allergy Immunol* 2010; **21**: 1119–26.
43. Zijlstra WT, Flinterman AE, Soeters L, et al. Parental anxiety before and after food challenges in children with suspected peanut and hazelnut allergy. *Pediatr Allergy Immunol* 2010; **21**: e439–45.
44. Zomer-Kooijker K, Sliker MG, Kentie PA, van der Ent CK, Meijer Y. A prediction rule for food challenge outcome in children. *Pediatr Allergy Immunol* 2012; **23**: 353–9.
45. Costa AJ, Sarinho ES, Motta ME, Gomes PN, de Oliveira de Melo SM, da Silva GA. Allergy to CM proteins: what contribution does hypersensitivity in skin tests have to this diagnosis? *Pediatr Allergy Immunol* 2011; **22**: e133–8.
46. El-Hodhod MA, Younis NT, Zaitoun YA, Daoud SD. CM allergy related pediatric constipation: appropriate time of milk tolerance. *Pediatr Allergy Immunol* 2010; **21**: e407–12.
47. Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. *Pediatr Allergy Immunol* 2010; **21**: 603–11.
48. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, et al. Inadvertent exposures in children with peanut allergy. *Pediatr Allergy Immunol* 2012; **23**: 133–9.
49. Martin-Munoz MF, Fortuni M, Caminoa M, Belver T, Quirce S, Caballero T. Anaphylactic reaction to probiotics. CM and hen's egg allergens in probiotic compounds. *Pediatr Allergy Immunol* 2012 (Epub ahead of print).
50. Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. *Pediatr Allergy Immunol* 2010; **21**: 586–94.
51. MacKenzie H, Roberts G, van Laar D, Dean T. Teenagers' experiences of living with food hypersensitivity: a qualitative study. *Pediatr Allergy Immunol* 2010; **21**: 595–602.
52. Wassenberg J, Cochard MM, Dunngalvin A, et al. Parent perceived quality of life is age-dependent in children with food allergy. *Pediatr Allergy Immunol* 2012; **23**: 412–9.
53. Sopo SM, Onesimo R, Giorgio V, Fundaro C. Specific oral tolerance induction (SOTI) in pediatric age: clinical research or just routine practice? *Pediatr Allergy Immunol* 2010; **21**: e446–9.
54. Mori F, Pucci N, Rossi ME, de Martino M, Azzari C, Novembre E. Oral desensitization to milk: how to choose the starting dose!. *Pediatr Allergy Immunol* 2010; **21**: e450–3.
55. Rodriguez del Rio P, Sanchez-Garcia S, Escudero C, et al. Allergy to goat's and sheep's milk in a population of CM-allergic children treated with oral immunotherapy. *Pediatr Allergy Immunol* 2012; **23**: 128–32.
56. Meglio P, Giampietro PG, Carello R, Gabriele I, Avitabile S, Galli E. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. *Pediatr Allergy Immunol* 2012 (Epub ahead of print).
57. Fuentes-Aparicio V, Alonso-Lebrero E, Zapatero L, et al. Oral immunotherapy in hen's egg-allergic children increases a hypo-proliferative subset of CD4⁺ T cells that could constitute a marker of tolerance achievement. *Pediatr Allergy Immunol* 2012 (Epub ahead of print).
58. van Esch BC, Schouten B, de Kivit S, et al. Oral tolerance induction by partially hydrolyzed whey protein in mice is associated with enhanced numbers of Foxp3⁺ regulatory T-cells in the mesenteric lymph nodes. *Pediatr Allergy Immunol* 2011; **22**: 820–6.
59. van Esch BC, Schouten B, Hofman GA, et al. Acute allergic skin response as a new tool to evaluate the allergenicity of whey hydrolysates in a mouse model of orally induced CM allergy. *Pediatr Allergy Immunol* 2010; **21**: e780–6.
60. Ball H, Luyt D, Bravin K, Kirk K. Single nut or total nut avoidance in nut allergic children: outcome of nut challenges to guide exclusion diets. *Pediatr Allergy Immunol* 2011; **22**: 808–12.
61. Stiefel G, Keeton D, Morenas R, Roberts G, Lucas JS, Erlewyn-Lajeunesse M. Tree nut introduction in peanut allergic children is not without risk. *Pediatr Allergy Immunol* 2012; **23**: 205–6.
62. Santos A, Dias A, Pinheiro JA. Predictive factors for the persistence of CM allergy. *Pediatr Allergy Immunol* 2010; **21**: 1127–34.
63. Montesinos E, Martorell A, Felix R, Cerdá JC. Egg white specific IgE levels in serum as clinical reactivity predictors in the course of egg allergy follow-up. *Pediatr Allergy Immunol* 2010; **21**: 634–9.
64. Kotaniemi-Syrjänen A, Palosuo K, Jartti T, Kuitunen M, Pelkonen AS, Makela MJ. The prognosis of wheat hypersensitivity in children. *Pediatr Allergy Immunol* 2010; **21**: e421–8.
65. de Jong AB, Dikkeschei LD, Brand PL. Sensitization patterns to food and inhalant allergens in childhood: a comparison of non-sensitized, monosensitized, and polysensitized children. *Pediatr Allergy Immunol* 2011; **22**: 166–71.
66. Melioli G, Marcomini L, Agazzi A, et al. The IgE repertoire in children and adolescents resolved at component level: a cross-sectional study. *Pediatr Allergy Immunol* 2012; **23**: 433–40.
67. Flammarion S, Santos C, Guimber D, et al. Diet and nutritional status of children with food allergies. *Pediatr Allergy Immunol* 2011; **22**: 161–5.
68. Meyer R, Venter C, Fox AT, Shah N. Practical dietary management of protein energy malnutrition in young children with CM protein allergy. *Pediatr Allergy Immunol* 2012; **23**: 307–14.
69. Reche M, Pascual C, Fiandor A, et al. The effect of a partially hydrolysed formula based on rice protein in the treatment of infants with CM protein allergy. *Pediatr Allergy Immunol* 2010; **21**: 577–85.

70. Diamanti A, Pedicelli S, D'Argenio P, Panetta F, Alterio A, Torre G. Iatrogenic Kwashiorkor in three infants on a diet of rice beverages. *Pediatr Allergy Immunol* 2011; **22**: 878–9.
71. Petrus NC, Hulshof L, Rutjes NW, de Vreede I, van Aalderen WM, Sprickelman AB. Response to: cost-effectiveness of using an extensively hydrolysed formula compared to an amino acid formula as first-line treatment for cow milk allergy in the UK. *Pediatr Allergy Immunol* 2012; **23**: 686.
72. Taylor RR, Sladkevicius E, Panca M, Lack G, Guest JF. Cost-effectiveness of using an extensively hydrolysed formula compared to an amino acid formula as first-line treatment for cow milk allergy in the UK. *Pediatr Allergy Immunol* 2012 (Epub ahead of print).
73. Taylor RR, Sladkevicius E, Panca M, Lack G, Guest JF. Cost-effectiveness of using an extensively hydrolysed formula compared to an amino acid formula as first-line treatment for cow milk allergy in the UK. *Pediatr Allergy Immunol* 2012; **23**: 240–9.
74. Francavilla R, Calasso M, Calace L, et al. Effect of lactose on gut microbiota and metabolome of infants with CM allergy. *Pediatr Allergy Immunol* 2012; **23**: 420–7.
75. Matheson MC, Haydn Walters E, Burgess JA, et al. Childhood immunization and atopic disease into middle-age—a prospective cohort study. *Pediatr Allergy Immunol* 2010; **21**: 301–6.
76. Silverberg JI, Kleiman E, Silverberg NB, Durkin HG, Joks R, Smith-Norowitz TA. Chickenpox in childhood is associated with decreased atopic disorders, IgE, allergic sensitization, and leukocyte subsets. *Pediatr Allergy Immunol* 2012; **23**: 50–8.
77. Goldis ME, Bardina L, Gimenez G, Lin J, Sampson HA. Evaluation of flu vaccines with regard to their egg protein content. *Pediatr Allergy Immunol* 2011; **22**: 642–3.
78. Vargas PA, Sicherer SH, Christie L, et al. Developing a food allergy curriculum for parents. *Pediatr Allergy Immunol* 2011; **22**: 575–82.
79. Gupta RS, Springston EE, Smith B, et al. Food allergy knowledge, attitudes, and beliefs of parents with food-allergic children in the United States. *Pediatr Allergy Immunol* 2010; **21**: 927–34.
80. Ng IE, Turner PJ, Kemp AS, Campbell DE. Parental perceptions and dietary adherence in children with seafood allergy. *Pediatr Allergy Immunol* 2011; **22**: 720–8.
81. Mackenzie H, Roberts G, Van Laar D, Dean T. A new quality of life scale for teenagers with food hypersensitivity. *Pediatr Allergy Immunol* 2012; **23**: 404–11.
82. Springston EE, Lau CH, Patel P, et al. A brief intervention to improve food allergy knowledge among US pediatricians: lessons learned. *Pediatr Allergy Immunol* 2012; **23**: 642–7.
83. Jacobs TS, Greenhawt MJ, Hauswirth D, Mitchell L, Green TD. A survey study of index food-related allergic reactions and anaphylaxis management. *Pediatr Allergy Immunol* 2012; **23**: 582–9.
84. Hompes S, Kohli A, Nemat K, et al. Provoking allergens and treatment of anaphylaxis in children and adolescents—data from the anaphylaxis registry of German-speaking countries. *Pediatr Allergy Immunol* 2011; **22**: 568–74.
85. Calvani M, Cardinale F, Martelli A, et al. Risk factors for severe pediatric food anaphylaxis in Italy. *Pediatr Allergy Immunol* 2011; **22**: 813–9.
86. Hoffer V, Scheuerman O, Marcus N, et al. Anaphylaxis in Israel: experience with 92 hospitalized children. *Pediatr Allergy Immunol* 2011; **22**: 172–7.
87. Kulkarni N, Ragazzo V, Costella S, et al. Eosinophilic airway inflammation is increased in children with asthma and food allergies. *Pediatr Allergy Immunol* 2012; **23**: 28–33.
88. Hughes JL, Brown T, Edgar JD, Shields MD. Peanut allergy and allergic airways inflammation. *Pediatr Allergy Immunol* 2010; **21**: 1107–13.
89. Vetander M, Helander D, Lindquist C, et al. Classification of anaphylaxis and utility of the EAACI Taskforce position paper on anaphylaxis in children. *Pediatr Allergy Immunol* 2011; **22**: 369–73.
90. Belhocine W, Ibrahim Z, Grandne V, et al. Total serum tryptase levels are higher in young infants. *Pediatr Allergy Immunol* 2011; **22**: 600–7.
91. Bakirtas A, Arga M, Catal F, Derinoz O, Demirsoy MS, Turkas I. Make-up of the epinephrine autoinjector: the effect on its use by untrained users. *Pediatr Allergy Immunol* 2011; **22**: 729–33.
92. Arga M, Bakirtas A, Catal F, et al. Training of trainers on epinephrine autoinjector use. *Pediatr Allergy Immunol* 2011; **22**: 590–3.
93. Kranke B, Schuster C, Wiednig M, Reiter H. A simple method to improve safety of epinephrine auto-injectors. *Pediatr Allergy Immunol* 2012; **23**: 399–400.
94. Ercan H, Ozen A, Karatepe H, Berber M, Cengizler R. Primary school teachers' knowledge about and attitudes toward anaphylaxis. *Pediatr Allergy Immunol* 2012; **23**: 428–32.
95. Flokstra-de Blok BM, Dorien van Ginkel C, Roerdink EM, et al. Extremely low prevalence of epinephrine autoinjectors in high-risk food-allergic adolescents in Dutch high schools. *Pediatr Allergy Immunol* 2011; **22**: 374–7.
96. Johnson MJ, Foote KD, Moyses HE, Roberts G. Practices in the prescription of adrenaline autoinjectors. *Pediatr Allergy Immunol* 2012; **23**: 124–7.
97. Niggemann B, Beyer K. Adrenaline autoinjectors in food allergy: in for a cent, in for a Euro? *Pediatr Allergy Immunol* 2012; **23**: 506–8.
98. Arroabarren E, Lasa EM, Olaciregui I, Sarasqueta C, Munoz JA, Perez-Yarza EG. Improving anaphylaxis management in a pediatric emergency department. *Pediatr Allergy Immunol* 2011; **22**: 708–14.