

FOOD ALLERGY IN ATOPIC DERMATITIS: HOW, WHEN AND WHY DO WE TEST?

Claudia L Gray, MBChB, FRCPCH, MSc, DipAllergy, DipPaedNutrition, **Michael E Levin**, MBChB, FCPaed, PhD, DipAllergy

Correspondence:

Division of Allergology and Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital and University of Cape Town

Email: Claudiagray.paediatrics@gmail.com

ABSTRACT

The hallmark of atopic dermatitis is a defective skin barrier. Atopic dermatitis and food allergies are frequently associated, yet food allergies are rarely the direct cause of the eczema. Patients with atopic dermatitis need to be selected prudently for food allergy testing, as many eczema patients show sensitisation to multiple foods, without necessarily being allergic. Failure to interpret food allergy test results correctly in eczema patients, may lead to overuse of nutritionally and socially compromising elimination diets. Oral food challenges form an integral part of food allergy diagnosis in eczema patients. Early onset eczema, eczema that is refractory to treatment and young age are more commonly associated with food allergy.

INTRODUCTION AND BACKGROUND

The relationship between atopic dermatitis (AD) and food allergy is complex and multidirectional.¹ Whilst many patients and medical practitioners believe that AD is caused by diet, the majority of AD is not triggered by foods. Strong evidence is now emerging to show that the defective barrier in eczematous skin acts as a potential portal for food and aeroallergen particles to permeate the skin and initiate the sensitisation process.^{2,3} In such cases, rather than the food allergy causing the eczema, the eczema has, in fact, led to the start of the food allergy cascade.

In some patients with food allergy and AD, dietary modification may help, but they will still need to use a good skin care routine and pharmacological measures to maintain skin integrity, in addition to dietary intervention.^{4,5} Such patients need to be identified and given specific, targeted dietary advice. There is no place for blanket elimination diets in AD.

Patients with AD need to be carefully selected for food allergy testing. Interpretation of allergy test results often requires specialist input or provocation ("challenge") testing, as AD patients tend to have a high rate of false positive blood and skin tests.

EPIDEMIOLOGY OF FOOD ALLERGY IN PATIENTS WITH AD

The strong interaction between AD and food allergies is borne out by studies, mostly in westernised countries, that show a high prevalence of sensitisation (around 60%), as well as proven allergies (around 30-40%), to common foods in children with moderate to severe AD in specialist allergy or dermatology clinics.⁶⁻¹² These figures are far greater than the overall prevalence of food sensitisation and food allergy in the general population of around 5-15% and 2-10% respectively.¹³⁻¹⁷ In less selected populations, the prevalence is much lower. In 50% of patients with a food allergy, the reaction is an immediate hypersensitivity reaction, with (non-eczematous) cutaneous features such as urticarial or morbilliform rashes,¹⁸ with or without gastrointestinal reactions, respiratory symptoms or anaphylaxis. Such reactions occur within two hours of food ingestion. Isolated eczematous reactions occur in 10% of reactions (i.e. 3-4% of all children with moderate to severe AD) and are usually delayed by more than 6 hours after food ingestion.¹⁹⁻²⁰ A combination of non-eczematous and eczematous reactions occurs in 40% of cases (12-16% of AD children).^{21,22} (Figure 1) The vast majority (around 90%) of food reactions in patients with AD are, therefore, at least in part, IgE-mediated, and can be tested for by skin prick test or specific IgE measurement.

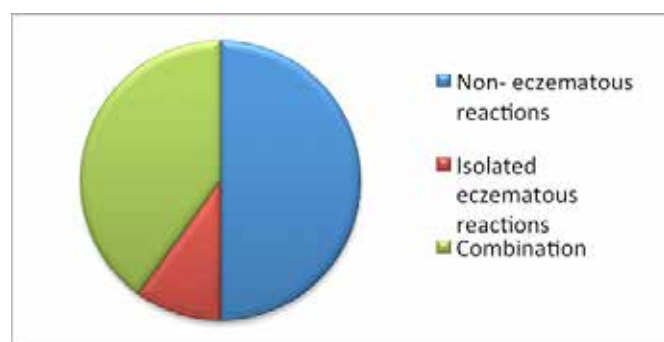


Figure 1: Pattern of cutaneous reactions in patients with food allergy and eczema

The prevalence of food allergy in AD depends on the severity of AD, age group tested, clinic-setting, (primary versus referral centre), and geographical location.^{23,24}

The same food allergens that cause reactions in the general population are responsible for the majority of reactions in children with AD. Egg, milk, peanut, wheat and soy cause 90% of food reactions in children with AD.¹⁸

EPIDEMIOLOGY OF FOOD ALLERGY IN SOUTH AFRICAN CHILDREN WITH AD

In 2009, South African infants with AD were shown to have frequent sensitisation to foods, most commonly egg white (47.1%), cow's milk (28.4%) and peanuts (26.8%).²⁵ This study did not, however, explore clinical food allergy. In 2011, South African children attending a tertiary dermatology clinic for AD were shown to have even higher sensitisation rates (66% to at least one food), most commonly to egg (54%), peanuts (44%) and cow's milk (27%).^{1,26,27} (Figure 2) This latter study had stringent criteria for defining food allergy, with incremental oral food challenges where indicated, and found 40% of patients to have an IgE-mediated food allergy, 25% were allergic to egg, 24% to peanut and 2% to cow's milk. (Figure 2)

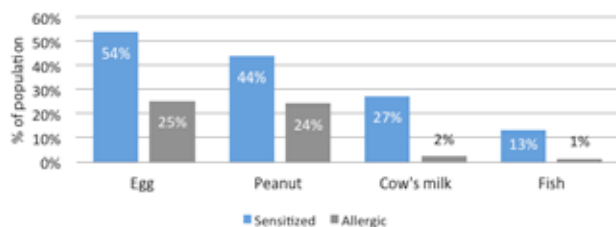


Figure 2 - Overall prevalence of sensitisation and allergy for egg, peanut, cow's milk and fish in South African food allergy-eczema study³²

RISK FACTORS FOR FOOD ALLERGY IN AD

Younger age, more severe eczema and early age of onset of eczema, are major risk factors for food allergy and should be taken into account when selecting patients for food allergy screening.²⁸ The EPAAC study, a large multinational study of allergy prevention in young infants, showed early onset AD to be a risk factor for food sensitisation.^{29,30} Age at the time of assessment also influences food allergy rates, which peak in young children at or below 2 years' age, and fall towards late childhood and adulthood, reflecting natural tolerance acquisition in a proportion of patients.³¹

In the South African food allergy-eczema study, age of onset of AD below 6 months was a significant risk factor for food allergy, with much higher prevalence of food sensitisation (86%) and food allergy (66%) in children with AD onset before 6 months, compared to those with onset between 6-12 months or after 1 year.³² (Figure 3) The study confirmed that in our local population, age of assessment affects allergy prevalence with 50% of patients under the age of 2 years at the time of study having a food allergy, compared with 25% of patients above the age of 4 years. (Figure 4) Greater severity of AD is also associated with higher risk of food allergy.³² (Figure 5)

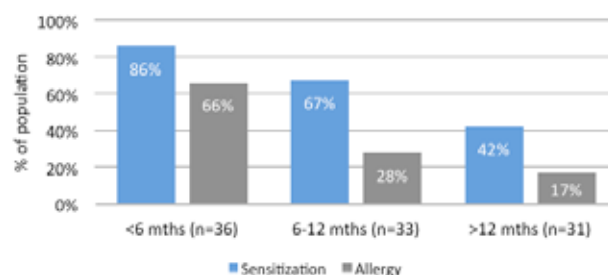


Figure 3 - Influence of Age of Onset of Eczema on Sensitisation and Allergy Rates in South African food allergy-eczema study³²

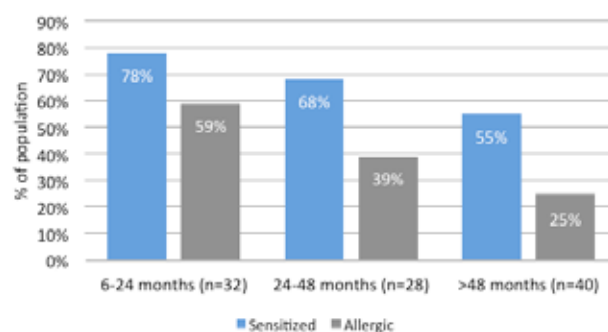


Figure 4 - Influence of Age on Sensitisation and Allergy Rates in South African food allergy-eczema study³²

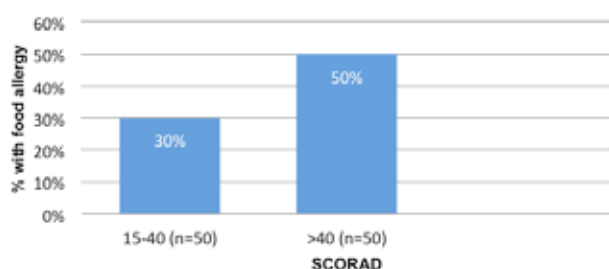


Figure 5 - Influence of eczema severity on food allergy prevalence in South African food allergy-eczema study³²

WHO SHOULD BE TESTED FOR FOOD ALLERGIES?

Investigations for food allergy are not routine in all cases of AD. The following risk factors should prompt testing for concomitant or causative food allergy:

1. Moderate to severe AD that does not respond to appropriate and adequate topical treatment.
2. Early onset AD < 6 months.
3. AD in the infant if accompanied by gut dysmotility.
4. History of immediate-type food reaction.
5. Convincing history of AD exacerbated by foods.

WHAT INVESTIGATIONS SHOULD BE PERFORMED?

The aims of food allergy testing in a patient with AD may be either:¹

- a. To prove that a food allergy results in a non-eczematous immediate (IgE-mediated) hypersensitivity reaction. Such food allergy testing is done in a similar way in patients with or without AD.
- b. To prove that a food allergy results in direct exacerbation of AD. This is much more challenging.

An **accurate history** of what the patient eats, the condition of the skin, possible reactions (both AD and acute reactions) and extra-cutaneous symptoms, can be useful to guide food related investigations.

The vast majority of food reactions in AD are IgE-mediated, hence tests for IgE sensitisation (**SPT and specific IgE ImmunoCAP tests**) are useful in the investigation of food allergy. However, there is no 100% reliable test for identifying which foods trigger AD. Sensitisation rates are far higher than clinically relevant allergy rates, hence frequently food allergy/tolerance needs to be proven by a provocation test (**oral food challenge**).

Tests with no or poor evidence to support their use include IgG testing, ELISA/ACT, applied kinesiology, ALCAT testing,

analysis of hair samples, Vega testing, cytotoxic testing and others.

IMMEDIATE (IgE-MEDIATED) HYPERSENSITIVITY FOOD REACTIONS

The diagnosis of immediate type (IgE-mediated) food allergy is made by taking a thorough history, performing tests, looking for specific IgE sensitisation (SPT and ImmunoCAP), and performing oral food challenges, if indicated.¹ Negative skin and ImmunoCAP tests are good for excluding an immediate type reaction, but cannot exclude a delayed type reaction. The presence of "positive" tests indicating sensitisation is not synonymous with food allergy. The predictive values for a history of a food reaction, positive SPT and positive food specific IgE in isolation are all poor for diagnosing food allergy in AD. The level of sensitisation must be interpreted in conjunction with the history, and in many cases where uncertainty remains, a food challenge test will be the best means to definitively prove food allergy or food tolerance.

Skin-prick tests have high negative predictive values and are a good predictor that subjects will not have an immediate type reaction on exposure, but cannot exclude a delayed type reaction. However, positive predictive values are low,^{33,34} hence a "positive" result does not equal clinical reactivity. Published "cut-off levels" for clinical relevance have been studied for selected allergens (child >2 years: milk ≥ 8 mm, egg ≥ 7 mm, peanuts ≥ 8 mm; child <2 years: milk ≥ 6 mm, egg ≥ 5 mm, peanuts ≥ 4 mm).³⁵ However, these values may not be applicable in South Africa, especially in black African subjects where patients may be clinically tolerant despite high levels of skin prick reactivity.^{15,32} As patients develop tolerance, heightened SPT reactivity may lag behind reductions in specific IgE levels and may remain positive for years after a food has been successfully reintroduced into the diet.

ImmunoCAP testing for food specific IgE has high negative predictive values, but positive predictive values are low.^{33,35} Published "cut-off levels" for clinical relevance have been studied for selected allergens. The values that achieved a 95% PPV are known for milk (≥ 15 kU/L; ≥ 5 kU/L if age <2), egg (≥ 7 kU/L; ≥ 2 kU/L if age <2), peanuts (≥ 14 kU/L) and fish (≥ 20 kU/L).^{35,36} It is not currently known whether these results are applicable in South Africa.

Atopy Patch Testing has not been shown to add significant information to a skin test, as a diagnostic test for food triggers of acute or delayed reactions to foods.^{37,38}

If the diagnosis of food allergy or tolerance is not absolutely clear or the clinical relevance of a positive food allergy test is not certain, a food challenge should be performed. The gold standard is the double-blind, placebo-controlled food challenge.^{39,40} This requires two separate challenges with a suitable vehicle, one with and one without the food under consideration, to avoid the patient and the operator from knowing which of the challenges contains the active food. For an open challenge, the food is given in its usual form and therefore both the observer and the patient know the food is being ingested. Although this may be associated with false positive reactions, it is acceptable in infants and young children with objective symptoms and as a preliminary screening of foods that are at a low level of suspicion as a negative challenge is definitive.

DELAYED ECZEMATOUS FOOD ALLERGY REACTIONS

The diagnosis of delayed eczematous reactions is more difficult than the diagnosis of immediate reactions¹. In such cases specific IgE and skin prick tests may not correlate with the presence or absence of a delayed food reaction. In these cases, an elimination-reintroduction diet is the only reliable way of determining whether or not a food is a trigger. Such diets must be done under supervision of a dietician. If patients respond to any dietary intervention, it is highly recommended that the food should be reintroduced to confirm the diagnosis. This may be a formal food challenge in hospital in the presence of any sensitisation or history of immediate reactions to the food(s), or a home challenge/reintroduction in the absence of sensitisation or a history of only delayed symptoms. If a formal food challenge is performed for AD, the schedule may need to be prolonged to observe the patient for up to six hours after the maximum dose, for immediate and intermediate reactions. It is important to review the patient at 24 hours for scoring to formally document delayed-type worsening of AD. In cases of prolonged avoidance of a food, it is recommended to perform SPT or ImmunoCAP tests in patients prior to reintroduction of the food, even in cases where there has not been a history of any immediate reactions, as immediate reactivity may have developed over time.⁴¹ After prolonged avoidance of a food, or if there is any evidence of IgE-mediated sensitisation having occurred, food challenge should be performed under controlled circumstances.

The process of elimination-rechallenge testing for diagnosis of food allergy involves:^{1,42}

- Removing all sources of the suspected food or foods for four to six weeks to bring about an improvement in the

AD. If the AD does not improve within four weeks, it is unlikely that food allergy is a relevant trigger and oral food challenges are not necessary. In this case, a normal diet should resume immediately.

- Even if the AD has resolved, foods should be reintroduced sequentially, to assess for a return (or worsening) of the dermatitis, prior to ascribing the improvement to the exclusion diet. This is because the improvement may be coincidental or reflect a placebo effect. Concomitant therapies and other environmental factors should not be changed during the period of assessment for food allergies. In addition, if multiple foods have been excluded, it is imperative to see which of these foods is truly responsible and exclude only those foods, while allowing the return of non-contributory foods into the diet.
- Food reintroduction may be performed as a standard food challenge with a single food in incremental doses. If there is no immediate reaction, then give the food for three to four days successively and monitor AD scores daily. In selected cases where there has not been prolonged exclusion of the food, and there was no immediate type reaction, a home challenge may be performed.
- Should the skin not react to the introduction of this food, challenge with a new food every three to four days.
- However, should the food exacerbate the AD, it may be considered a causal food allergen and be removed from the diet to bring about the improvement in the symptoms for the second time. Where doubt still exists, a second re-challenge may be necessary.

THERAPEUTIC ELIMINATION DIETS

There is no specific diet for the treatment of unselected patients with AD, so patients should not routinely be placed on exclusion diets.⁴² Elimination diets are potentially harmful. Food allergy should only be considered in specific cases, and elimination diets reserved for those children who have been proven to be allergic and tailored to the individual after appropriate investigations, including challenge tests where necessary, have been performed to assess possible food triggers. They must be done under the supervision of a dietician and should always be combined with atopic skincare.

Removing foods from one's diet requires support and education, especially in cases where the food is common and present in many hidden sources. A dietician must be consulted to ensure the allergen is completely eliminated from the diet, as well as to provide alternatives to ensure nutritional adequacy of the residual diet.

NATURAL HISTORY OF FOOD ALLERGY IN AD

The natural history of food allergy resolution is variable and may differ in those with and without AD. It varies between allergens, with milk, egg, soy and wheat resolving earlier, and more commonly than allergies to peanuts or tree nuts.⁴³ Allergy to fish and shellfish, which more commonly develops later, may be life-long. In AD, approximately 25% of patients will outgrow their food allergy after one year.^{44,45} Patients with severe concomitant IgE-mediated food allergy/anaphylaxis should be followed up very frequently, but all patients should be reassessed after 12 months. Repeat testing should be followed by food reintroduction in the form of a formal food challenge to reduce the risk of immediate reactions that may be present or may have developed, in order to restore a normal diet wherever possible.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Gray C. Allergies in eczema. *Current Allergy & Clinical Immunology* 2011;24:185-91.
- Mattila P, Joenvaara S, Renkenen J et al. Allergy as an epithelial barrier disease. *Clinical and Translational Allergy* 2011;1:5.
- Van den Oord RAHM, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitization and allergic disorders: systemic review and meta-analysis. *Br Med J* 2009;339:b2433.
- Suh K-Y. Food allergy and atopic dermatitis: separating fact from fiction. *Semin Cutan Med Surg* 2010;29:72-8.
- Guillet G, Guillet MH: Natural history of sensitizations atopic dermatitis. A 3-year follow-up in 250 children: Food allergy and high risk of respiratory symptoms. *Arch Dermatol* 1992;128:187-92.
- Sampson H, McCaskill C. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatrics* 1985;107(5):669-75.
- Ellmann LK, Chatchatee P, Sicherer SH, Sampson HA. Food hypersensitivity in two groups of children and young adults with atopic dermatitis evaluated a decade apart. *Pediatr Allergy Immunol* 2002;13:295-8.
- Burks AW, James JM, Hiegal A et al. Atopic dermatitis and food hypersensitivity reactions. *J Pediatrics* 1998;132(1):132-6.
- Eigenmann PA, Sicherer SH, Borkowski TA et al. Prevalence of IgE-Mediated Food Allergy Among Children with Atopic Dermatitis. *Pediatrics* 1998;101(3):e8.
- Eigenmann PA, Calza A-M. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. *Pediatr Allergy Immunol* 2000;11:95-100.
- Garcia C, El-Qutob D, Martorell A et al. Sensitisation in early age to food allergens in children with atopic dermatitis. *Allergol Immunopath (Madr)* 2007;35(1):15-20.
- Kim HO, Cho SI, Kim JH, et al. Food hypersensitivity in patients with childhood atopic dermatitis in Korea. *Ann Dermatol* 2013;25(2):196-202.
- Venter C, Arshad SH. Epidemiology of Food Allergy. *Pediatr Clin N Am* 2011;58:327-49.
- Burney P, Summers C, Chinn S et al. Prevalence and distribution of sensitization to foods in the European Community Respiratory Health Survey: a EuroPrevall analysis. *Allergy* 2010;65:1182-1188.
- Levin ME, Muloia R, Motala C. Associations between asthma and bronchial hyper-responsiveness with allergy and atopy phenotypes in urban black South African teenagers. *S Afr Med J* 2011;101(7):472-6.
- Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Thiele L, Tang ML, Ponsonby AL, Dharmage SC, Allen KJ; HealthNuts Study Investigators. The HealthNuts population-based study of paediatric food allergy: validity, safety and acceptability. *Clin Exp Allergy* 2010;40(10):1516-22.
- Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlstrom J, McBride D, Madsen C. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120(3):638-46.
- Sicherer S, Sampson H. Food Hypersensitivity and Atopic Dermatitis: Pathophysiology, Epidemiology, Diagnosis and Management. *J Allergy Clin Immunol* 1999;104:S114-S122.
- Werfel T, Ballmer-Weber B, Eigenmann P et al. Eczematous reactions to food in atopic dermatitis: position paper of the EAACI and GA2LEN. *Allergy* 2007;62:723-728.
- Werfel T, Breuer K. Role of food allergy in atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2004;4(5):379-385.
- 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.
- Breuer K, Heratizadeh A, Wulf A et al. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 2004;34:817-824.
- Koplin JJ, Dharmage SC, Ponsonby A-L, Tang MLK, Lowe AJ, Gurrin LC et al. Environmental and demographic risk factors for egg allergy in a population-based study of infants. *Allergy* 2012;67:1415-22.
- De Benedictis FM, Franceschini F, Hill D, Naspietz C et al. The allergic sensitization in infants with atopic eczema from different countries. *Allergy* 2009;64:295-303.
- Potter PC, Longueville M. Sensitisation to aero-allergens and food allergens in infants with atopic dermatitis in South Africa. *Curr Allergy Clin Immunol* 2005;18:131-2.
- Gray C. A prospective descriptive study to determine the prevalence of IgE-mediated food allergy in South African children with atopic dermatitis attending a tertiary medical centre: Review of the first 80 patients. Abstract. *S Afr J Child Health* 2011;5(3):99.
- Gray C, Kung SJ. Food allergy in South Africa: Joining the food allergy epidemic? *Curr Allergy Clin Immunol* 25(1):24-9.
- Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: an epidemiologic study. *Pediatr Allergy Immunol* 2004;15:421-7.
- Hill DJ, Hosking CS, De Benedictis FM et al. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: An international study. *Clin Exp Allergy* 2008;38:161-8.
- Niggemann B, Reibel S, Roehr C et al. Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;108(6):1053-8.
- Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989;115:23-7.
- Gray CL, Levin ME, Zar H, Potter PC et al. Food allergy in South African children with atopic dermatitis. *Pediatr Allergy Immunol* 2014, in print.
- Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984;74:26-33.
- Atopic Eczema in Children. Management of Atopic Eczema in Children from Birth up to the Age 12 Years. NICE Clinical Guidelines, No. 57. National Collaborating Centre for Women's and Health (UK). London: RCOG Press; 2007.
- Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;30:1540-6.
- Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *Allergy Clin Immunol*. 2001;107(5):891-6.
- Lipozencic J, Wolf R. The diagnostic value of atopy patch testing and prick testing in atopic dermatitis: facts and controversies. *Clin Dermatol* 2010;28(1):38-44.
- Turjanmaa K. The role of atopy patch tests in the diagnosis of allergy in atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2005;5:425-8.
- NIAID-sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126:S1-S8.
- Nowak-Węgrzyn A, Assa'ad AH, Bahna SL et al, on behalf of the adverse reactions to food committee of the American Academy of Allergy, Asthma and Immunology. Work Group Report: Oral food challenge testing. *J Allergy Clin Immunol* 2009;123(6):S365-383.
- Flinterman AE, Knulst AC, Meijer Y, et al. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. *Allergy* 2006;61:370.
- Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for improving established atopic eczema in adults and children: systemic review. *Allergy* 2009;64:258-64.
- Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlstrom J, McBride D, Madsen C. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120(3):638-46.
- Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989;115:23-7.
- Bock SA. The natural history of food sensitivity. *J Allergy Clin Immunol* 1982;69:173-177.