



Review

The optimal diagnostic workup for children with suspected food allergy

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ABSTRACT

Food allergy is defined as an abnormal immunologic reaction to food proteins that causes an adverse clinical reaction. In addition to well-known acute allergic reactions and anaphylaxis triggered by immunoglobulin E antibody-mediated immune responses to food proteins, there is an increasing recognition of cell-mediated disorders such as eosinophilic esophagitis and food protein-induced enterocolitis syndrome. More than 90% of food allergies in childhood are caused by eight foods: cow's milk, hen's egg, soy, peanuts, tree nuts, wheat, fish, and shellfish. The diagnostic workup for a child with suspected food allergy includes a detailed medical history, physical examination, food allergy screening tests, and responses to an elimination diet and an oral food challenge. None of the screening tests, alone or in combination, can definitely diagnose or exclude a food allergy. Novel diagnostic methods including those that focus on immune responses to specific food proteins or epitopes of specific proteins are under active study. Unconventional diagnostic methods are increasingly used, but they lack scientific rationale, standardization, and reproducibility. In selected cases, such as eosinophilic esophageal gastroenteropathies or food protein-induced gastroesophageal reflux disease, invasive procedures are mandatory for an accurate diagnosis. Properly done, an oral food challenge is still the gold standard in the diagnostic workup. An incorrect diagnosis is likely to result in unnecessary dietary restrictions, which, if prolonged, may adversely affect the child's nutritional status and growth.

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Introduction

Food allergy (FA) is a major health issue in Western societies, where some evidence has suggested that the prevalence of the disorder in childhood has increased in recent years [1]. It has been recently reported that, during the past decade in the United States, pediatric FA rates have increased by 18%, but the investigators underlined that they could not determine if these findings were related to increased awareness, reporting, and use of specific medical diagnostic codes for FA or represented a real increase of the disease [2]. A correct diagnosis of FA is important to accurately establish the prevalence and incidence of this condition and to ensure appropriate patient care. In fact, FA may have deleterious effects on family economics, social interactions, school and work attendance, and health-related quality of life. The diagnostic workup in a child with FA includes many steps, but the essential criteria are a thorough medical history and physical examination with a clear response to an oral food challenge (OFC) [3]. Although any food can provoke a reaction,

relatively few foods are responsible for the vast majority of significant food-induced allergic reactions in children: cow's milk, hen's egg, soy, wheat, fish, peanuts, and shellfish [4,5]. There is an increase in the prevalence of new food allergens such as sesame and kiwi [6]. Features common to major food allergens are that they are water-soluble glycoproteins ranging from 10 to 70 kDa in size and are relatively stable to heat, acid, and proteases [7].

Clinical characteristics useful in the diagnostic workup

The FA symptoms are induced through an immunologic mechanism after the ingestion of a particular food. Although FA may be associated with other forms of allergic diseases, not all patients with eczema or respiratory allergies require an evaluation for FA as a trigger of their allergic disease. In fact, only a very small proportion of patients with allergic respiratory problems, such as rhinitis and asthma, and fewer than 40% of young children with severe atopic eczema have associated FA [8]. In addressing possible food-induced allergic disease, the clinician must consider a variety of conditions that are not FA. The differential diagnosis can be particularly difficult in a child with

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Table 1

Main conditions to be considered in the differential diagnosis in the diagnostic approach to a child with suspected food allergy-related gastrointestinal symptoms

Infections
Gastrointestinal functional disorders
Celiac disease
Brush border enzyme deficiencies
Cystic fibrosis and other primitive forms of pancreatic insufficiency
Inflammatory bowel diseases
Anatomic defects (e.g., pyloric stenosis, malrotation)
Metabolic disorders (e.g., galactosemia)
Adverse reaction to drugs
Munchausen's syndrome/Munchausen's syndrome by proxy

gastrointestinal symptoms (Table 1). Adverse reactions that are not classified as FA include host-specific metabolic disorders (e.g., lactose intolerance or galactosemia), a response to a pharmacologically active component (e.g., triggered by tyramine in aged cheeses), or toxins (e.g., food poisoning). In addition, psychologic (food aversion and anorexia nervosa) or neurologic (e.g., gustatory rhinorrhea from hot or spicy foods) responses can mimic FA [9]. The wide variety of “true” clinical manifestations of FA depend on the mechanism involved in the reaction (immediate/immunoglobulin E [IgE]-mediated or delayed/non-IgE-mediated or mixed), target organ responses, and characteristics of triggering proteins [10]. Proteins that are easily degraded by heat and digestion, including many of the proteins in fruits, are unlikely to trigger severe reactions. In contrast, stable proteins, such as seed storage proteins in nuts, are more likely to trigger systemic allergic reactions [11]. Interestingly, FA could be at least in part genetically determined. Although specific genes have not been identified, peanut allergy, for example, is about 10-fold more likely to occur in a child with a sibling who is allergic to peanuts compared with the risk in the general population [12]. Recent evidence has suggested potential environmental influences on immune function favoring allergic responses, including decreased exposures to infections, an increased consumption of ω -6 and a decreased consumption of ω -3 polyunsaturated fatty acids, decreased dietary antioxidants, and an excess or a deficiency of vitamin D [13]. In children, the skin and gastrointestinal tract are the most common target organs followed by the respiratory tract, and multiple systems can be involved with rapid progression to systemic anaphylaxis. Food-induced eosinophilic esophagitis in young children is becoming more recognized by pediatricians. Table 2 presents the more common food-induced allergic disorders.

Multistep diagnostic process

The evaluation of a child with suspected FA includes an in-depth patient history, a physical examination, screening tests,

and responses to an elimination diet and an OFC (Fig. 1). In children with multiple FAs, the response to the elimination of single antigens is incomplete, and a lengthy assessment with a very restricted diet is often required. The physician should obtain a detailed patient history focused on the kind and intake of symptom-inducing foods, the time gap from food ingestion to the onset of symptoms, reproducibility, the presence or absence of any other symptom-inducing conditions, and the time of the last symptom. Timing of the first and last occurrences can reveal whether sensitivity is increasing or waning. Immediate reactions, occurring within minutes to 2 h, typically involve IgE-mediated mechanisms. Conversely, delayed reactions occur within several hours to a few days and are thought to typically involve cellular mechanisms. These considerations and the quantity necessary to trigger a reaction are helpful for planning the best procedures to explore the presence of sensitization to particular foods and to perform an OFC. Occasionally, the history can be complicated by the fact that trace amounts of foods may occur in certain products. In general, the history can be more helpful in IgE-mediated disorders, because these reactions occur so soon after food ingestion and because multiple target organs are affected. A history may be more difficult for some gastrointestinal manifestations of FA such as enterocolitis or eosinophilic esophagitis, where symptoms occur hours later or days later.

Food allergy screening tests

The measurement of food-specific IgE and atopy patch tests, which can explore cell-mediated reactions, are the most used FA screening tests in clinical practice. There is no minimum age for these tests, which can be performed in preterm and full-term infants, with useful results [9,14]. In all cases, it is important to emphasize that none of these tests, alone or in combination, can definitely diagnose or exclude an FA. Immediate hypersensitivity skin prick tests (SPTs) examine for the presence of food protein-specific IgE. In general, SPTs have a sensitivity of approximately 90% but a specificity of approximately only 50% [15]. The larger the wheal from an SPT, the more likely a patient will react to the food (Table 3) [15–17]. The size of the wheal or flare from an SPT does not predict the severity of the reaction. Furthermore, the age of the patient, previous exposure/reactions to the food, and the type of food change the predictive value for a wheal size. In general, the younger the age, the smaller the skin test needs to be to have a positive predictive value; a negative skin test for IgE-mediated problems is very helpful because false-negative reactions are rare. An alternative method to detect food protein-specific IgE is by *in vitro* methods. Physicians may prefer to use *in vitro* testing when there is severe eczema, persistent dermatographism, or when it is difficult to discontinue antihistamine drugs. Similar to an SPT, a “cutoff” value can be developed for predicting 95% or even 50% predictive

Table 2

Food-induced allergic disorders

	IgE-mediated/acute onset	Non-IgE-mediated/delayed onset	IgE- or non-IgE-mediated/delayed onset
Gastrointestinal tract	Oral allergy syndrome; gastrointestinal anaphylaxis	Dietary protein proctitis; colitis; enterocolitis; enteropathy; gastroesophageal reflux disease; food-protein-induced enterocolitis syndrome; chronic constipation; infantile colic	Eosinophilic; esophagitis; gastroenteropathies
Respiratory tract	Rhinitis; conjunctivitis; asthma	Chronic pulmonary disease (Heiner's syndrome)	Asthma
Skin	Urticaria; angioedema	Contact dermatitis	Atopic dermatitis
Systemic	Anaphylaxis; food-associated, exercise-induced anaphylaxis	—	—

IgE, immunoglobulin E

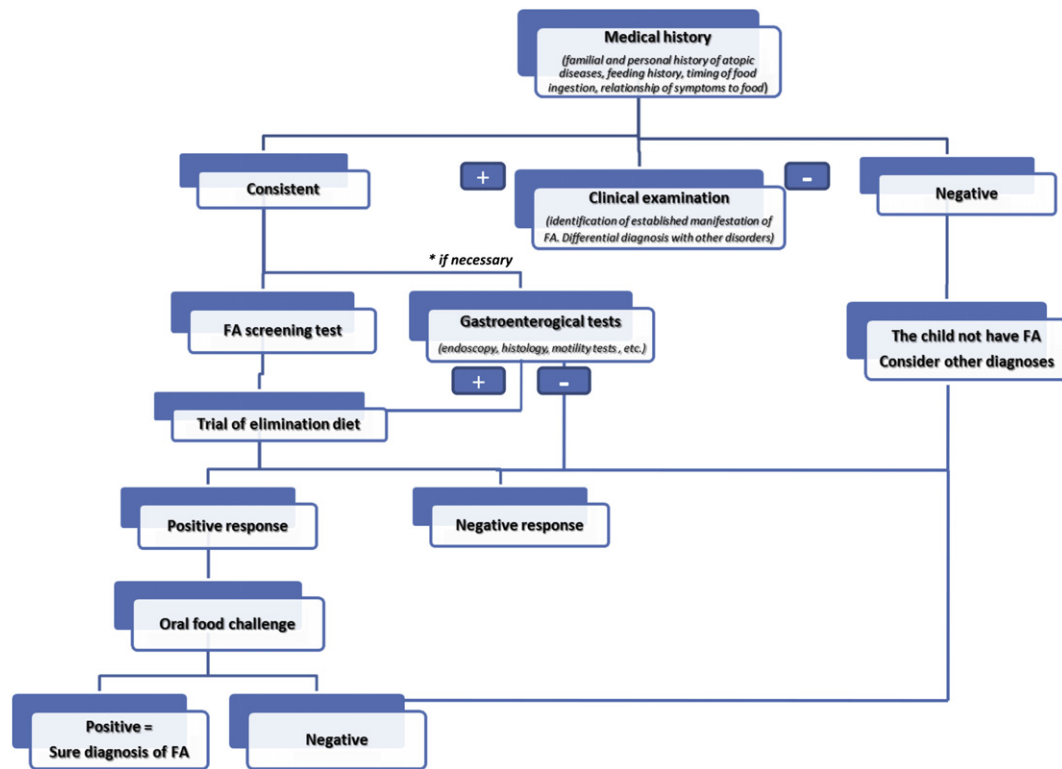


Fig. 1. The diagnostic algorithm for food allergy.

values using OFCs [18]. However, similar to an SPT, the predictive values change for the food, age of the patient, or the history of a previous reaction. Predictive values can be developed only for selected foods (Table 3). The younger patients have a lower cutoff value for a 95% predictive value, whereas no previous exposure to the food or a clear history has a higher predictive value.

For non-IgE-mediated disorders, fewer diagnostic tools exist. Atopy patch tests have been used for different gastrointestinal conditions related to FA and atopic dermatitis. In particular, the importance of this diagnostic procedure has been underlined in patients with eosinophilic esophagitis [19]. The negative predictive value is close to 90% except for milk, where it is close to 60%. Therefore, an atopy patch test can provide guidance but is not absolute for dietary advice for non-IgE-mediated FA. Some cellular tests, i.e., tests determining the reactivity of blood cells in vitro, have also been available (e.g., determination of histamine release, basophil degranulation, determination of sulfide leukotrienes produced by interleukin-3-primed basophils stimulated by allergens in vitro, and flow cytometric basophil activation test). The low diagnostic accuracy and lack of standardization limit acceptable use in clinical practice [3]. Complementary/alternative tests (e.g., bioresonance, kinesiology, leukocytotoxic test, electrodermal tests, iridology, and hair

analysis) are quite popular in clinical practice, but there is no evidence of their diagnostic value [20]. There are no tests that indicate the severity or which patients are at high risk for severe allergic reaction or anaphylaxis. However, it has been demonstrated that patients with peanut anaphylaxis have increased platelet-activating factor (PAF) and decreased PAF acetylhydrolase (compared with normal controls, patients with FA, and patients with mild peanut reactions), suggesting failure of PAF acetylhydrolase to inactivate PAF contributes to anaphylaxis [21]. Protein microarrays can detect several allergenic proteins simultaneously in children with suspected FA. They also can predict the likelihood of persistence of an allergy to a particular food by identifying the nature of the epitope as IgE against some of these specific epitopes that are more likely to be associated with persistence than others. The advantages include rapidity of the assay and the minute quantities of sera required (50 µL). IgE epitope mapping has the potential to become an additional tool for the diagnosis/prognosis of FA and lead to a better understanding of the pathogenesis and tolerance induction [22].

Diagnostic procedures for gastrointestinal symptoms

Several procedures could be adopted in children with gastrointestinal symptoms possibly related to FA. These include endoscopy with histologic evaluation, esophageal pH monitoring, together with several non-invasive diagnostic tools, such as intestinal permeability, eosinophilic cationic protein, and fecal calprotectin measurement (Table 4) [3,23]. Although these non-invasive markers would be convenient to detect an intestinal mucosal reaction to foods, no conclusive studies are available on the diagnostic accuracy of these tests, alone or in combination, in the approach of a child with suspected FA. Patients with allergic eosinophilic esophagitis or gastroenteritis have peripheral

Table 3

Diagnosis of food allergy with the use of 95% positive predictive value for specific IgE and skin prick tests

	Serum-specific IgE (U/mL)	Skin prick test (wheal diameter, mm)
Cow's milk	15 (5 if child is <2 y old)	8 (6 if child is <2 y old)
Hen's egg	7 (2 if child is <2 y old)	7 (5 if child is <2 y old)
Fish	20	7
Peanuts	15	8 (4 if child is <2 y old)

IgE, immunoglobulin E

Table 4

Possible indications for invasive procedures in the diagnostic workup in a child with suspected food allergy-related gastrointestinal symptoms

Suspected condition	When indicated	Procedures
Eosinophilic esophagitis or gastroenteritis	Always	Upper and/or lower GI endoscopy with multiple biopsies
Dietary protein colitis; enterocolitis; enteropathy	>3–5-y-old patients; severity and persistence of symptoms; lack of unequivocal response to elimination diet	Upper and/or lower GI endoscopy with multiple biopsies
Food allergy-induced gastroesophageal reflux disease	Atypical signs or symptoms of possible gastroesophageal reflux disease	24-h esophageal pH monitoring; combined multiple intraluminal impedance and pH monitoring

GI, gastrointestinal

eosinophilia, and children with severe allergic eosinophilic gastroenteritis may have anemia, blood in the stool, and decreased serum albumin and IgG levels. Endoscopy with biopsies is the most definitive approach and might help the differential diagnoses. A density greater than 15 to 20 eosinophils/high-power field in the esophagus is diagnostic for allergic eosinophilic esophagitis, especially if the esophageal pH monitoring is normal and there is a lack of response to high-dose proton pump inhibitor medication [19]. If gastrointestinal food-induced enteropathies or colitis is suspected, intestinal biopsies disclosing primarily eosinophilic infiltration of the mucosa may be helpful. The mucosal lesions in FA enteropathies are characteristically focal. Thus, sampling error results in negative biopsies in a discrete number of cases. Colonic biopsies often are more helpful in cases with allergic colitis, usually seen in infants with FA-induced hematochezia. In children with FA, electrogastrographic evidence of severe gastric dysrhythmia and delayed gastric emptying during a food challenge has been demonstrated. The assessment of gastrointestinal motility (e.g., multichannel intraluminal electrical impedance testing, micromanometric techniques, gastrointestinal electrophysiologic studies, and measurement of gastric emptying by ^{13}C -octanoic acid breath test) is useful to facilitate investigations of FA-related motility disorders [24].

Oral food challenge

The OFC still represents the gold standard for the diagnosis of FA to avoid unjustified diets. In cases in which the challenge food is still part of a patient's diet, a strict elimination diet should be prescribed for at least 2 wk before the OFC. The optimal duration of an elimination diet before an OFC depends mainly on symptom severity and the particular condition related to the FA. If the patient has experienced a severe reaction recently, an OFC

is not indicated before 12 mo. Different FA-related gastrointestinal diseases require different durations of an elimination diet before an OFC (Fig. 2). The OFC is done by gradually feeding increasing amounts of the suspected food under observation by a physician over hours or days. Because the procedure carries a small risk of anaphylaxis, it should be conducted in a supervised medical setting where resuscitation equipment is available. Several studies have been published recently on this topic aiming to standardize the procedure [25–27]. The main problems are related to the wide variety of symptoms possibly related to an FA that lead to difficulties in the interpretation of test results and to the optimal timing and dosage of this procedure. A double-blind, placebo-controlled food challenge, routinely used in research, is recommended in clinical settings in which patients report subjective symptoms, whereas an open OFC without placebo is commonly used in children younger than 3 y and for diagnosing objective symptoms [28–30].

Conclusions

A correct diagnosis of FA is crucial to ensure appropriate patient care. The essential criterion is a clear response to an elimination diet, and other diagnostic tests are secondary to this. The OFC plays a crucial role in the diagnosis of FA, but it is largely underused even by allergy specialists. Potential responsible factors contributing to the lack of a correct diagnostic workup in the vast majority of cases in our study population could be numerous and include a lack of training in the procedure, an increased reliability on screening methods (skin testing, in vitro tests), the extensive time needed, a fear of risk, and suboptimal fee reimbursement. The issue is pressing because a large number of suspected FA diagnoses could be incorrect, leading to unnecessary elimination diets and economic and social costs.

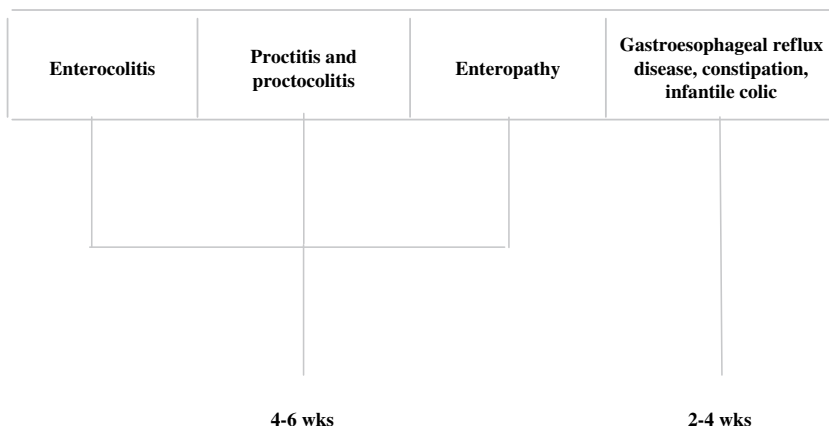


Fig. 2. The optimal timing for an oral food challenge in a child with gastrointestinal conditions possibly related to a food allergy.

References

- [1] Kuehn BM. Food allergies becoming more common. *JAMA* 2008;300:2358.
- [2] Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009;124:1–7.
- [3] Berni Canani R, Ruotolo S, Discepolo V, Troncone R. The diagnosis of food allergy in children. *Curr Opin Pediatr* 2008;20:584–9.
- [4] Ramesh S. Food allergy. Overview in children. *Clin Rev Allerg Immunol* 2008;34:217–30.
- [5] Bush RK. Approach to patients with symptoms of food allergy. *Am J Med* 2008;121:376–8.
- [6] Dias RP, Summerfield A, Khakoo GA. Food hypersensitivity among Caucasian and non-Caucasian children. *Pediatr Allergy Immunol* 2008;19:86–9.
- [7] Ferreira CT, Seidman E. Food allergy: a practical update from the gastroenterological viewpoint. *J Pediatr* 2007;83:7–20.
- [8] Gerez IFA, Shek LPC, Chng HH, Lee BW. Diagnostic tests for food allergy. *Singapore Med J* 2010;51:4–9.
- [9] Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2010;125(2 suppl. 2):S116–25.
- [10] Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2006;117: S470–5.
- [11] Steckelbroeck S, Ballmer-Weber BK, Vieths S. Potential, pitfalls, and prospects of food allergy diagnostics using recombinant allergens or synthetic sequential epitopes. *J Allergy Clin Immunol* 2008;121:1323–30.
- [12] Sicherer SH, Furlong TJ, Maes HH, Desnick RJ, Sampson HA, Gelb BD. Genetics of peanut allergy: a twin study. *J Allergy Clin Immunol* 2000;106: 53–6.
- [13] Lack G. Epidemiological risk factors for food allergy. *J Allergy Clin Immunol* 2008;121:1331–3.
- [14] Dupont C, Soulaïnes P, Lapillonne A, Donne N, Kalach N, Benhamou PH. Atopy patch test for early diagnosis of cow's milk allergy in preterm infants. *J Pediatr Gastroenterol Nutr* 2010;50:463–4.
- [15] Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1998;9:186–91.
- [16] Eigenmann PA, Calza AM. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. *Pediatr Allergy Immunol* 2000;11: 95–100.
- [17] Spergel JM, Beausoleil JL, Fiedler JM, Ginsberg J, Wagner K, Pawlowski NA. Correlation of initial food reactions to observed reactions on challenges. *Ann Allergy Asthma Immunol* 2004;92:217–24.
- [18] Cianferoni A, Spergel JM. Food allergy: review, classification and diagnosis. *Allergol Int* 2009;58:457–66.
- [19] Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, et al. FINGERS Subcommittees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133:1342–63.
- [20] Robinson M, Smart J. Allergy testing and referral in children. *Aust Fam Phys* 2008;37:210–3.
- [21] Vadas P, Gold M, Perelman B, Liss GM, Lack G, Blyth T, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med* 2008;358: 28–35.
- [22] Jing Lin J, Sampson HA. The role of immunoglobulin E-binding epitopes in the characterization of food allergy. *Curr Opin Allergy Clin Immunol* 2009;9:357–63.
- [23] Mansueto P, Montalto G, Pacor ML, Esposito-Pellitteri M, Ditta V, Lo Bianco C, et al. Food allergy in gastroenterologic diseases: review of literature. *World J Gastroenterol* 2006;12:7744–52.
- [24] Heine RG. Gastroesophageal reflux disease, colic and constipation in infants with food allergy. *Curr Opin Allergy Clin Immunol* 2006;6: 220–5.
- [25] Ito K, Urisu A. Diagnosis of food allergy based on oral food challenge test. *Allergol Int* 2009;58:467–74.
- [26] Nowak-Węgrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work group report: oral food challenge testing. *J Allergy Clin Immunol* 2009;123:S365–83.
- [27] Niggemann B. When is an oral food challenge positive? *Allergy* 2010;65:2–6.
- [28] Niggemann B, Beyer K. Pitfalls in double-blind, placebo-controlled oral food challenges. *Allergy* 2007;62:729–32.
- [29] Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Gant C, et al. Comparison of open and double-blind placebo controlled food challenges in diagnosis of food hypersensitivity amongst children. *J Hum Nutr Diet* 2007;20:565–79.
- [30] Bahana SL. Food challenge procedure: optimal choices for clinical practice. *Allergy Asthma Proc* 2007;28:640–6.