Prevalence, Natural History, Diagnosis, and Treatment of Food Allergy

A Systematic Review of the Evidence

JENNIFER J. SCHNEIDER CHAFEN, SYDNE NEWBERRY, MARC RIEDL, DENA M. BRAVATA, MARGARET MAGLIONE, MARIKA SUTTORP, VANDANA SUNDARAM, NEIL M. PAIGE, ALI TOWFIGH, BENJAMIN J. HULLEY, PAUL G. SHEKELLE

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Executive Summary

Introduction

The US federal government is interested in coordinating the development of guidelines for diagnosing and managing food allergy. A meeting was held on July 19, 2007, entitled “Guidelines for the Diagnosis and Management of Food Allergy.” It was jointly organized by a Coordinating Committee comprising The National Institutes of Allergy and Infectious Diseases (NIAID), American Academy of Allergy Asthma and Immunology (AAAAI), and the Food Allergy and Anaphylaxis Network (FAAN). The attendees included representatives of over twenty professional societies, patient advocacy groups, and several NIH Institutes. They concurred that evidence-based clinical guidelines were needed and outlined steps for their development.

The first step in developing the guidelines is a systematic review of the scientific and clinical literature. To carry out this step, the NIAID contracted with the Southern California Evidence-based Practice Center (EPC) based at RAND.

Methods

Under the auspices of the Coordinating Committee, the NIAID and the food allergy Expert Panel developed an extensive set of key questions, which were further refined in discussions with the EPC. These questions and the corresponding answers are detailed in the Results section of this executive summary. The EPC was provided with a list of specific medical conditions that were either comorbid with food allergy or qualified as food-allergy conditions. Literature searches were performed on PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (Central), and the World Allergy Organization Journal. The principle search topics were diagnosis and testing techniques for food allergies in general, and in the case of the PubMed searches, the specific IgE and non-IgE-related reactions mentioned in the list provided. In most cases, searches were limited to the years 1988 to the present, with no language restrictions. We also sought supplemental publications from experts on our team and others involved in the review process.

Researchers screened all titles found through our searches or that were submitted by experts. We established screening criteria to facilitate the identification of articles concerning definitions, diagnoses, prevention, treatment, management, and other topics as per the NIAID’s and Expert Panel’s questions. Articles were included/excluded based on article type (included: original research or systematic reviews; excluded: background/contextual reviews, non-systematic reviews, commentary, or other types of articles) and study purpose (included: studies that looked at incidence/prevalence/natural history; diagnosis; treatment/management/prevention; excluded: studies that either were not about food allergy or were about some aspect not listed in the “included” category).
Included studies were categorized in two ways. First they were categorized by the food(s) of concern: multiple foods, milk, egg, peanut/tree nut, fish/shellfish, soy, wheat, and/or other foods, as specified. Studies were then categorized by medical condition, e.g., anaphylaxis, eczema, if specified.

Accepted articles were reviewed by topic teams and data were abstracted. The teams reached consensus on inclusion of final article sets for each topic area as well as consensus on data items abstracted from these articles.

The evidence is reported in several forms. Evidence tables offer a detailed description of the studies that we identified, addressing each of the topic areas. They provide information consistent with established criteria about the study design, patient characteristics, inclusion and exclusion criteria, interventions evaluated, and the outcomes. The study sample size offers a measure of the weight of the evidence. (In general, larger studies provide a more precise estimate of the effect in question, although the specific patient population has greater influence on the applicability of any given study.) Narrative text summarizes the findings and provides qualitative analysis of the key questions as they relate to the topic area.

Results

Key Question A. What is the definition of food allergy?

i. What definitions of food allergy are currently being used?
ii. Describe conditions that are described as non-immunologic adverse reactions to food.
iii. Describe conditions that are described as immunologic, but not IgE-mediated, adverse reactions to food.
iv. Describe conditions that are described as immunologic and IgE-mediated adverse reactions to food (and which are considered by some authorities to be equivalent to food allergy).
v. Compare adverse reactions to food that are non-immunologic, immunologic and not IgE-mediated, and immunologic and IgE-mediated.

In the NIAID and Expert Panel’s original definition, for a condition to be considered a food allergy, it must be:

a) an adverse immune response that occurs reproducibly on exposure to a given food and
b) distinct from other adverse responses to food, such as food intolerance, pharmacologic reactions, and toxin-mediated reactions. The NIAID also specified that while food allergy is frequently defined as a disorder caused by IgE-mediated reactions to food, we should review literature on non–IgE-mediated immunologic mechanisms as well.

Non-immunologic adverse reactions to food are also discussed, only as they compare with similar immune mechanism caused symptoms.

In order to provide definitions of food allergy currently being used, we assessed whether or not the characteristics outlined above were included in published reviews of food
allergy. We abstracted such information from several dozen existing review articles, along with what medical conditions they considered as “food allergy.” We also abstracted information from the web sites of 57 professional societies and other related organizations on a list provided by the technical Expert Panel (TEP). Only 19 of the 57 web sites provided a definition of food allergy.

Only 31.0 percent of definitions included in review articles mentioned reproducibility, and 45.1 percent mentioned a particular given food. 78.9 percent mentioned IgE – mediated reactions and 66.2 percent mentioned non-IgE medicated immunologic mechanisms. The web site definitions were less clear. Only 42.1 percent mentioned IgE-mediated reactions and 15.8 percent mentioned non-IgE-mediated immunologic mechanisms.

The NIAID and the Expert Panel developed the explicit list of conditions (below) that are either comorbid with food allergy or qualify as allergic reactions to food. These medical conditions are described in detail in the body of our report.

- Classic food-related anaphylaxis
- Laryngeal edema
- Heiner’s Syndrome (pulmonary hemosiderosis)
- Asthma
- Food-associated, exercise-induced syndromes
- Colitis
- Eosinophilic Esophagitis/Gastroenteritis
- Cow’s milk allergy syndrome:
  - Induced colitis (and blood in the stools)
  - Food-induced enterocolitis syndrome
  - Food-induced proctocolitis syndrome
  - Milk protein allergy of infancy
- Gastrointestinal hypersensitivity (e.g., vomiting, colic, diarrhea)
- Contact dermatitis
- Eczema, atopic dermatitis
- Generalized flushing
- Oral Allergy Syndrome
- Rhinitis, rhinoconjunctivitis conjunctivitis
- Urticaria
- Angioedema
Key Questions B & C: What are the incidence/prevalence of IgE-mediated food allergy (B) and immunologic but non-IgE-mediated adverse reactions to food (C)?

B & C. i. Incidence and prevalence in the adult and pediatric populations
B & C. ii. Incidence and prevalence for specific foods
B & C. iii. Age- or gender-specific changes in specific foods
Two previously-published, acceptable quality systematic reviews found that the prevalence of food allergy overall and allergy to specific foods varied depending on the definition used, and even within the same definition; estimates of prevalence varied widely. Improving the knowledge base on this topic will require better standardization of the definition of a food allergy. For example, the reviews reported a pooled overall prevalence of 13 percent and 12 percent for adults and for children, respectively, of self-report of food allergy to any food. Pooled results for allergy to any food were far lower when assessed by sensitization or food challenge; being about three percent (data stratified by age were not reported). For specific foods, pooled results showed that prevalence was highest for milk (3 percent by symptoms, 0.6 percent and 0.9 percent for Skin Prick Test (SPT) and food challenge) and lowest for fish (0.6 percent by symptoms, 0.2 percent by SPT and 0.3 percent by food challenge).

B & C. iv. Incidence and prevalence of co-morbid conditions
We did not identify any US or Canada studies that had nationally representative populations that assessed the co-occurrence of other conditions in patients with food allergy in general. We did identify several studies that assessed the co-occurrence of other conditions in samples of patients with specific allergies or conditions. The most common co-occurring conditions included asthma, rhinitis, and eczema. All of these conditions are conditions that can be caused by allergy.

B & C. v. Risk factors for development of food allergy
In general, we did not identify any studies specifically addressing risk factors for the development of food allergy, as do exist for conditions such as heart disease, lung cancer, etc. Experimental studies of early life allergen exposure or avoidance suggest that these are believed to be potential risk factors for food allergy; however, the findings on these factors are mixed. One case-controlled study from England reported that household exposure to peanut-containing skin lotions was a significant risk factor for developing food allergy. In addition, there are studies of prevention where infants or pregnant mothers are classified as “high risk” for atopy. This is usually due to a family history of atopy. One family-based study from Chicago reported a strong familial clustering of food allergy. There are emerging data about genetic associations but results are too preliminary to reach conclusions.
Key Question D & E: What are the symptoms and natural history of IgE-mediated (D) and of immunologic but non-IgE mediated (E) adverse reactions to food?

D & E. i. Symptoms and natural history
We identified no published studies from the US or Canada on the natural history of food allergy conditions that reported data from nationally representative or even community-based populations. The only published studies of natural history came from selected populations, usually from a single clinic or hospital. Such patient populations may not be representative of the general patient population with a specific food allergy. Nonetheless, to assist the Expert Panel, we summarized the published studies we did identify, keeping in mind that their findings may not necessarily be extrapolated to all patients with the condition. Detailed descriptions of these natural history studies are contained in the results section of main report.

D & E. ii. Relationship between IgE-mediated and immunologic but non-IgE-mediated food allergy and comorbid conditions.
No additional studies other than those previously described in section B were found.

D & E. iii. Differences in populations related to socioeconomic status (SES), access to health care, stress.
We did not find any US studies that specifically addressed differences in incidence, prevalence, or natural history related to socioeconomic status, access to health care, or stress. A US National Study did report data stratified by race, and some investigators use race as a proxy for socioeconomic status and access to health care. Those data are presented in the tables reporting the US National data. In addition, two US studies already presented (of infant feeding practices and of the NHIS/NHDS databases) reported that black males were more likely to have parent-reported food allergy and the rates of food allergy in Hispanics was lower than in non-hispanics. One cohort study from Sweden reported that the risk of sensitization to food allergens decreased with increasing socioeconomic status, with an odds ratio of 0.65 (95% confidence interval 0.41, 1.02, p=0.03 for trend) in the highest as compared to the lowest socioeconomic group.

Key Questions F & G. What tools are currently used to diagnose IgE-mediated food allergy (F) and non-IgE-mediated adverse reactions (G)?

We combined questions F and G because it can be difficult to distinguish an IgE-mediated from a non-IgE-mediated allergy prior to diagnostic workup, based on history alone; thus, with the exception of a small number of distinct non-IgE-mediated conditions such as eosinophilic esophagitis and celiac disease, IgE-mediated and non-IgE-mediated allergies are usually not addressed separately in the literature. In responding to these questions, we reviewed articles that attempted to establish the validity of each of the diagnostic methods, i.e., against a gold standard, or attempted to optimize methodology.
We included only articles that reported the sensitivity and specificity of the diagnostic test(s) in question, provided: a description of the generalizability of the population, and had a prospective design. For a small number of questions for which no studies could be identified that met these criteria, studies of lesser quality were included.

**F & G. i. Patient history and physical examination**
It is generally accepted that the diagnosis of food allergy must begin with a careful history and physical exam, the results of which guide the use of any further diagnostic tests. One study that met our screening criteria reported a physical finding (umbilical erythema) in patients with suspected cow’s milk protein intolerance with a low sensitivity but a specificity of 1.

**F & G. ii. Immediate skin testing**
Skin prick testing (SPT) is the preferred method of skin testing for suspected IgE-mediated (immediate) allergies as recommended by the AAAAI and ECAAI (European Academy of Allergy and Clinical Immunology). Both organizations recommend against intracutaneous testing for food allergies, citing increased risk of serious reaction and no increase in sensitivity or specificity. Additionally, both the AAAAI and ECAAI recommend against using skin scratch tests due to their low specificity compared to skin prick tests.

No standard exists for administering or interpreting skin prick tests; the studies that utilized skin prick tests and that met our inclusion criteria used several different methods to define a positive test, from measuring the absolute wheal size to measuring the wheal size relative to the negative control. The type of allergen used for SPTs also varies greatly: Both fresh foods and a variety of commercial preparations are used. Two studies that specifically addressed the comparability of these tests met our inclusion criteria. For cow’s milk allergy testing, a large study reported a high degree of concordance between a commercial cow milk allergen (ALK) and milk powder. Another large study of peanut preparations reported a high false negative rate with a commercial peanut extract (Allerbio) compared to fresh peanut, which was 100 percent sensitive compared to double-blind placebo controlled food challenge (DBPCFC, widely considered the gold standard).

**F & G. iii. In vitro testing**
The sensitivity and specificity of serum antigen-specific IgE (sIgE) assays for food allergies varied by food, assay system, and study. For example, for cow’s milk sIgE, the sensitivity ranged from 0.57 to 0.89 and the specificity ranged from 0.49 to 1 when the performance of the test was compared to the use of a food challenge. For peanut allergy, the five studies that satisfied inclusion criteria reported similar maximum sensitivities (0.44-0.60) with one exception: If the decision point was set at the lower limit of detection of the test, the sensitivity rose to 0.98. Studies that compared the performance of several sIgE assay systems found discrepancies, especially for particular foods (wheat and soy), such that one assay might diagnose a particular patient as being allergic whereas another test might find the same patient not to be allergic to the food.
F & G. iv. Atopy patch testing
The atopy patch test (APT) is generally used to assess delayed, or non-IgE-mediated, reactions to an allergen. Seven studies addressing the specificity and sensitivity of APT met our selection criteria, all using food challenge as a reference test. No studies specifically addressed the methodology of atopy patch tests; however, by convention, the standard test is performed by applying a food for 48 hours and with the final reading of the test performed 72 hours after the food was first applied. Additionally, some studies reported checking for immediate reactions 15-30 minutes after the food was applied. No studies compared the use of different food preparations. The sensitivity and specificity of the APT may vary by the timing of the reaction to oral food challenge, but the variation was not consistent either between foods or between studies of the same food. The sensitivity and specificity of this test may also vary by the presence of atopic dermatitis and the age of the patient.

F & G. v. Elimination diets used for diagnosis
We found no studies that used elimination diets as the primary means of diagnosis.

F & G. vi. Oral food challenges used for diagnosis
Oral food challenge tests under controlled conditions are widely used as the gold standard for food allergy diagnosis (at least when implemented under double blind conditions with placebo controls). However, several issues remain to be clarified about these tests, including the actual need for blinding, the effect of the form of food used (e.g., raw vs. cooked, fresh vs. freeze-dried, whole vs. extracts), the optimal time intervals before assessing reactions, and when the tests are needed (given the expense, time, and potential risks involved). A small number of studies that satisfied our inclusion criteria examined issues related to the use of double-blind placebo-controlled food challenge (DBPCFC). One study found no difference in the prevalence of positive responses between double-blind- and open tests. Other studies report “positive” reaction in as many as 13 percent of patients when given placebo. In an effort to overcome problems in assessing outcomes of food challenges, two studies assessed the performance of alternative outcome measures, facial thermography and gastric juice analysis, with good results. These findings we considered to be preliminary. Another study examined the use of intestinal, rather than oral, challenge for persons with GI complaints. This test had high specificity but low sensitivity; its practicality was not discussed. Finally, a study that assessed the use of symptom diaries found that external evaluation of the entries increased the objectivity of diagnosis.

Although we did not specifically conduct a search for all published studies of food challenge testing that reported adverse events, we did track the reporting of adverse events in the published studies of food challenge testing that satisfied our inclusion criteria. We also identified several studies that explicitly addressed the risk of serious adverse (anaphylactic) reactions to blinded food challenges. These studies concluded that the actual risks are quite small.
We performed a meta-analysis using Receiver Operator Characteristic curve methods to compare the diagnostic accuracy of SPT, sIgE, and APT for those foods where sufficient data existed (milk, eggs, wheat) and across food types. There was no evidence to conclude that any test was more accurate than any other test.

F & G. vii. Additional diagnostic tests other than those previously described
Only seven studies that met the inclusion criteria examined a test other than DBPCFC, SPT, APT, or sIgE.

One study found that combining an assessment of beta-lactoglobulin-mediated lymphocyte proliferation with that of cow’s milk sIgE was more sensitive than other tests in detecting cow’s milk allergy diagnosed by food challenge.

One study found that the measurement of IgG4 had a sensitivity and specificity comparable to that of other in vitro tests.

Two studies assessed the use of a basophil histamine release assay for diagnosis of allergy to cow’s milk and hen’s egg. Sensitivities ranged from 0.66 to 0.75. Specificities ranged from 0.66 to 0.80.

The findings of three studies suggest that endomysial antibodies may be a better predictor than anti-gliadin antibodies of celiac disease, a non-IgE-mediated condition (Because guidelines already exist for celiac disease, a review of the diagnosis and treatment of celiac disease was not within the scope of this report. However, the evidence regarding differential diagnosis of celiac disease vs. IgE and non-IgE-mediated allergic conditions with similar manifestations is within the scope of the report).

An active area of investigation is whether the combination of two or more tests improves the sensitivity or specificity of diagnosis. Of eight studies that tried to improve diagnostic specificity or sensitivity by combining two or more tests, five paired the APT with SPT, sIgE, or both, in an attempt to capture both immediate and delayed responses to antigen. Pairing the APT with SPT, sIgE, or both, improved sensitivity and specificity over the use of individual tests in most studies; however, the small number of studies that calculated the proportion of patients for whom two or more tests could obviate the need for DBPCFC found these proportions to be quite small.

The diagnosis of eosinophilic esophagitis is defined as esophageal biopsy with the finding of greater than 20 eosinophils per high power field; the gold standard for establishing food allergy as the causal mechanism is resolution of esophageal eosinophilia and symptoms following elimination of the food from diet followed by recurrent esophageal eosinophilia with food challenge. One study that did not meet all inclusion criteria reported high negative predictive value but variable positive predictive value for a combination of APT and SPT for a wide variety of foods.
F & G. viii. Diagnostic tools used by different groups of clinicians to make the diagnosis of food allergy.
A small number of studies indirectly addressed this question. A 2006 case-based survey of pediatricians found that understanding of allergy diagnosis was generally poor among pediatricians who reported that they do not manage allergy cases but better among those who do. A 2007-8 survey conducted among allergists and primary care physicians, which had poor response rate, found that non-allergists and allergists differed greatly in their use of the various allergy tests. No statistical differences were found between allergists and non-allergists in the use of medical history, food diaries, or elimination diets. However, allergists were significantly more likely than non-allergists to use percutaneous skin testing (SPT and APT), sIgE, and food challenge. Allergists were significantly less likely to report using intradermal tests, sIgG4, and sublingual tests than non-allergists (tests that have shown poor PPV compared with DBPCFC). The two groups also differed in their ranking of the most common food allergens, which would affect the diagnostic tests conducted. Finally, a 2009 study conducted in the allergy department of a large regional tertiary care hospital found that patients referred by primary care physicians for suspected food allergy based on the use of sIgE tests were usually able to tolerate the suspected foods on double-blind-placebo-controlled food challenge.

F & G. ix. What tools are used for longitudinal assessment of patients and what are the criteria for such assessments?
No studies that met the inclusion criteria examined the use of diagnostic tests for longitudinal assessment of patients.

Key Question H. What methods are currently used to manage patients diagnosed with IgE-mediated food allergy?

H. i. Dietary avoidance (including cross-reacting allergens and issues of breast feeding and delay of solids) in the context of preventing food allergy.

H i a. What are the effects of early versus delayed introduction of certain foods into an infant’s diet?
The quality of evidence for this key question is low given only two controlled trials of relatively low quality address this question. While both found some association between delayed solids and decreased incidence of atopic symptoms, their findings should be interpreted with caution given that one study was of poor quality and the other evaluated delayed introduction of solid foods in conjunction with breastfeeding, making it difficult to determine the independent effect of delayed introduction of foods. In summary, we found insufficient evidence to support the association between delayed introduction of solid foods in infants and the incidence of atopic disease.

H i. b. What is the effect of maternal diets during pregnancy and lactation on the development of, and clinical course of, food allergy?
One high quality systematic review and one comparative study evaluated the effect of maternal diet during pregnancy and lactation on the development of food allergy. We
found conflicting evidence on maternal diet during pregnancy and/or lactation and its effect on atopic disease among children at high risk for atopic disease. While the systematic review (which included two trials) reported no evidence to support a protective effect of maternal diet, the comparative study found significantly reduced incidence of atopic dermatitis in children whose mothers had a restricted diet during lactation; however, this study was of poor quality. Given these conflicting findings, we conclude that there is insufficient evidence to determine the effect of restricting maternal diet in reducing the risk of atopic disease in infants.

**H i. c. What is the effect of breastfeeding infants on the development of, and clinical course of, food allergy?**

Four studies evaluated the effects of breastfeeding in combination with other interventions but only one comparative study compared breastfeeding alone with cow’s milk formula. That study found lower risk of atopic dermatitis at one year of age in infants who were exclusively breast fed. The quality of evidence for this key question is low.

**H i. d. What are the effects of special diets in infants and young children (e.g., formula, hydrolyzed formula) on the development of, and clinical course of, food allergy?**

The quality of evidence for the key question on special diets in infants and young children is moderate to high. The quality of evidence on use of soy formulas is moderate given that this was addressed by a high quality review that included only three small RCTs; the evidence suggests that there is little difference between soy formula and cow's milk formula for the prevention of allergies in high risk infants. The quality of evidence on use of hydrolyzed formulas is high given that two systematic reviews and four other RCTs address this question; there is some evidence that hydrolyzed formulas (particularly extensively and partially hydrolyzed formulas) may reduce infant and childhood allergy, asthma, and cow's milk allergy syndrome in high risk infants when compared with cow milk formula.

**H i. e. What are the recommendations by professional organizations regarding the avoidance of food allergens during pregnancy, lactation, and early life in order to prevent food allergy?**

The American Academy of Allergy Asthma and Immunology (AAAAI) developed a brochure for parents, which was updated in 2009. It includes these specific guidelines:

- Try to wait until babies are 6 months old before you give them solid foods.
- Wait until they are 1 year old before giving them milk and other dairy (like cheese and yogurt).
- Toddlers should not eat eggs until they are 2 years old.
- Children should not eat peanuts, nuts or fish until they are 3 years old.
- Talk to your doctor about a plan for introducing these foods.

**Additional Information Relevant to H.i. Systematic review of the association of caesarean delivery and allergic diseases.**
There may be a positive association between caesarian delivery and the development of allergic disease later in life; however, the total body of evidence on this issue has significant methodologic concerns necessitating further investigation.

Additional Information Relevant to H.i. Studies on the use of probiotics for the prevention of food allergies.
The quality of evidence for this key question is moderate given five high quality RCTs that address this question but provide some mixed results. The use of probiotics in the prenatal and early neonatal period may be associated with mild reductions in the cumulative incidence of allergic skin disease in children. However, these results are interpreted with caution since the trials with the most significant results used probiotics in conjunction with breastfeeding and/or hypoallergenic formula and thus the independent effects of probiotics cannot be established in these trials.

H ii. What methods are currently used in the management of existing food allergy?

H ii. a. What are the data on the effects of allergen avoidance based on both the primary literature and the recommendations of key organizations? This question should include the effect on nutritional status.
Allergen avoidance is a common treatment strategy for food allergy and may work. However, this intervention has not been adequately studied, and the quality of evidence for this key question is low, given that only one non-randomized comparative study of poor quality addresses this question. Confounding this key question is that allergen avoidance diets are commonly used as a diagnostic test in addition to a treatment strategy. If a patient is placed on an allergen avoidance diet and continues to have symptoms, it is not clear if the allergen avoidance diet is ineffective or if the patient did not in fact, have an allergy to that particular food. Complete absence of cow milk protein may result in decreased energy, protein, and fat consumption while formula and milk-restricted diets may lead to micronutrient deficiencies. The quality of evidence for this key question is low, given that only one small observational study addressed this topic.

H ii. b. What are the data on the benefits and adverse effects of immunotherapy with foods (e.g., parenteral, oral, sublingual) to treat food allergy?
The quality of evidence for this key question—does immunotherapy improve clinical symptoms—is high given six RCTs of allergen-specific immunotherapy (five with oral exposure and one with sublingual) and four RCTs of specific-immunotherapy with cross-reactive allergens (sublingual and subcutaneous). Allergen-specific immunotherapy and specific-immunotherapy with cross reactive allergens improve clinical symptoms of food allergy. The safety of such treatment was reported in only four of six studies of allergen-specific immunotherapy. While symptoms such as local reactions and gastrointestinal symptoms were common, being reported in 35% and 50% of subjects, no serious safety problems were reported. However, as case reports were not specifically searched for in our Medline search, it is possible that a specific search for case reports of harms of allergen-specific immunotherapy might identify some events.
H ii. c. How effective are current standards for food labeling for prevention of food allergic reactions?
Since the implementation of the Food Allergen Labeling and Consumer Protection Act of 2004, no study has explicitly assessed its effect on the frequency of severe symptoms from accidental exposure (e.g., peanut). The identified studies, all of which predated the legislation, mostly assessed knowledge and preferences for food labeling.

H ii. d. What are the allergenic cross-reactivities (with other foods or non-food allergens) of foods (i.e., other legumes in peanut allergic patients, tree nuts in peanut allergic patients, etc)? What are the clinical consequences?
One small RCT evaluated the incidence of adverse reactions or allergies to soy formulas in infants with cow’s milk allergy syndrome and found low rates of adverse events in both the soy formula and the placebo formula. We conclude that there is insufficient evidence to evaluate the allergenic cross-reactivities of foods.

H ii. e. What are the effects of food allergen avoidance, and other food allergy management strategies, on co-morbid conditions such as, but not limited to, atopic dermatitis, asthma, and eosinophilic gastrointestinal disorders?
The quality of evidence for the effect of food allergen avoidance in treating atopic dermatitis is high given that we found two high quality systematic reviews addressing this topic. Both reported no evidence supporting the use of allergen avoidance in treating atopic dermatitis. We did not find any controlled studies specifically addressing food allergen avoidance in other co-morbid conditions.

Additional Information Relevant to H ii. Pharmacological management of food allergies
We identified four RCTs that evaluate pharmacologic agents (astemizole, cromolyn, and steroids) to treat food allergy and one study that used probiotics to treat rectal bleeding caused by food allergy. Given the heterogeneity of the pharmacologic interventions and allergic conditions evaluated, we conclude that there is insufficient evidence to evaluate the extent to which pharmacologic therapy is useful in treating food allergies.

H ii. f. What are the effects of co-morbid conditions on the clinical course of, and management of, food allergy?
No studies were found on the effects of co-morbid conditions on the clinical course of food allergy.

Key Question I. What methods are currently used to manage patients diagnosed with non-IgE-mediated reactions to food, and how do they differ from methods used to manage patients diagnosed with IgE-mediated food allergy?
The literature does not readily separate on the basis of IgE and non-IgE mediated reactions. To the extent possible, we have described interventions for both in H above.
Key Question J. What are the appropriate methods of diagnosis and treatment of acute and life-threatening, IgE-mediated food allergic reactions?

There were no specific trials evaluating methods for the diagnosis of acute or life-threatening allergic reactions to food. We found no RCTs evaluating the management of these serious reactions to food, but did find three cohort studies on this topic. We conclude that there is very little data on effective strategies for the prevention or management of life-threatening food allergies. Anaphylaxis reaction to food allergy is seen most frequently in patients with a peanut allergy—however the literature is insufficient to conclude regarding methods to prevent or treat this.

Conclusions

A principal conclusion of this review is that the quality of evidence is poor for most aspects of food allergy. After screening more than 11,000 titles from which we identified and read in more detail over 1,200 published papers, we found very few areas where we could draw anything more than tentative conclusions. Central to the problem of synthesizing the literature on food allergy is the lack of an agreed-upon criteria for diagnosis. This lack of standardized, operational criteria means that results of incidence, prevalence, and natural history cannot be compared across studies, that there is no single “gold standard” to use for assessing the sensitivity, specificity, and other properties of diagnostic tests, and that studies of treatments may not be comparable due to differing methods used to identify patients with food allergy for inclusion in the study. The lack of standardized criteria for what constitutes a diagnosis of food allergy is a major limitation to further understanding of this.

With that limitation in mind, there are a few consistent findings that we can point to. First, while the prevalence of food allergies varies from study to study and depends greatly on the criteria used for diagnosis, in general it is not much more than 10%, and may be much lower. For specific foods, allergy to cow’s milk is generally greater than allergies to other foods, at least in children, but the prevalence of cow’s milk allergy declines in adults, while the prevalence of allergies to other foods generally remains more constant. Allergies to other foods are common in patients with one identified food allergy, and other conditions such as asthma and atopic dermatitis are extremely common in individuals identified as food-allergic. Cow’s milk allergy clearly lessens in prevalence over time, as does egg allergy. While there are documented cases of some patients “outgrowing” their allergy, in general this does not happen for nuts, peanuts, and shellfish; although reactions to any particular exposure can be variable. In fact, shellfish allergy often appears in adulthood. The natural history of other food allergies – soy, egg, etc., has not been well studied in US populations.

Second, with regard to diagnosis, the double-blind placebo-controlled food challenge remains the gold standard, although concerns exist regarding its practicality, validity, and
safety. As a result, simpler, less intensive tests are often used. The skin prick test is one such method. Studies assessing its utility are plagued by lack of standardization of how to administer the test and what constitutes a positive test. Compared to a food challenge, sensitivities of 60%-95% and specificities of 40%-95% are commonly reported, and depend on food type and wheal size, among other things. Blood tests for antigen-specific IgE are also commonly used, and also suffer from differing thresholds being used to classify a test as “positive”, along with differences in the type of test and type of food. Compared to a food challenge, sensitivities of 44%-57% are reported, with specificities of 95% to 100%. Atopy patch testing is commonly used to assess delayed immunologic response, but also suffers from lack of standardization. A number of other tests have been proposed as useful for diagnosing food allergies, but few have been subjected to rigorous assessment. Combinations of tests offer some benefits, but the incremental value, and optimal sequencing, of series of tests remains uncertain.

Third, with regard to treatment, special diets in infancy seem to help reduce the occurrence of childhood atopic diseases in high-risk babies, some forms of immunotherapy with or without desensitization improve some symptoms of food allergy. While no studies have explicitly assessed the effect of changes in the legislation governing food labeling (requiring description of potential allergenic ingredients) on reducing symptomatic episodes of food allergy, studies conducted prior to implementation of this legislation consistently found that parents could not understand the existing food labels; these findings support the need for the new labeling; studies will be needed to assess its effect.

Fourth, the most common treatment for food allergies—allergen avoidance—was evaluated in only one small non-randomized comparative study, which suggested that it may be an effective means of reducing allergy symptoms. A key gap in the food allergy literature is a detailed evaluation of how to assess a “failed” trial of allergen avoidance. Some forms of allergen specific immunotherapy improve some symptoms of food allergy. Given the potential for anaphylaxis and other significant side effects, coupled with the fact that only four of the six studies of this treatment strategy specifically reported side effects, future studies of immunotherapy should systematically assess and report on common and serious side effects.

The importance of guidelines for the diagnosis and management of food allergy are made clear by two studies we identified as part of this literature review. One demonstrated that having a child with food allergy affected meal preparation and family social activities, while the other study assessed the care for acute food allergy reactions treated in the Emergency Department and found both care that is probably not adequate, and variations in care across sites. Effective practice guidelines will be a first step at improving care for food allergies.
Introduction

Over the past decade, the occurrence of food allergies may have increased, with prevalence estimates as high as 13 percent in US adults. Studies of the severity and prevalence in the scientific literature have been in conflict, and this situation has been further compounded by anecdotal self-reporting. As currently employed, the term “food allergy” can cover a range of reactions that may vary depending on the amount of the triggering food, as well as the developmental stage of the allergic individual. Based on these parameters, suggested treatments and interventions may differ.

While reactions can sometimes be relatively mild, perhaps no more than quickly disappearing hives, more severe reactions can result in anaphylactic shock and death. Such a scale of consequences supports the need for precise, accurate treatment guidelines. The necessity is further heightened by the fact that diagnosis and treatment of true food allergies can be confounded by the occurrence of “food intolerance,” conditions in which symptoms may resemble those of a true allergy but are not actually caused by allergens. One example of such a condition is lactose intolerance, which produces gastrointestinal distress (as do many food allergies), but in which the underlying cause is a mutation that results in the inability to synthesize an enzyme needed to digest lactose, a constituent of dairy products.

Many guidelines for food allergy diagnosis and management are available. For example, professional medical organizations have created clinical guidelines, such as those of the American Gastroenterological Association, published in 2001. However, no comprehensive set of medical guidelines currently exists for all food allergies, coordinated at the federal level. Several states have developed or implemented food allergies guidelines for their public schools; however, these guidelines are more in the nature of risk management policies to contain known allergens, such as peanuts. For example, at the federal level, in 2008, H.R. 2063 The Food Allergy and Anaphylaxis Management Act of 2008 was passed in the House of Representatives. It would have established nation-wide guidelines for schools, but it was not voted on by the Senate and did not become law.

On July 19, 2007, a meeting was held entitled “Guidelines for the Diagnosis and Management of Food Allergy.” It was jointly organized by the NIAID, American Academy of Allergy, Asthma and Immunology (AAAAI), and the Food Allergy and Anaphylaxis Network. The attendees included representatives of over twenty professional societies, patient advocacy groups, and several NIH Institutes. They concurred that evidence-based clinical guidelines were needed and outlined steps for their development.

The first step is a systematic review of the scientific and clinical literature. To carry out this step, the NIAID contracted with the Southern California Evidence-based Practice Center (EPC), based at RAND, for a systematic review of the literature. We now present this draft report as our contribution to the guideline development process. A draft version of this report underwent peer review; this final report incorporates the revisions in response to that review. We now present this final report as our contribution to the
guideline development process. This report will serve as the basis for the further development of guidelines according to the NIAID’s processes.
Methods

Key Questions

This systematic review was conducted at the request of the National Institute of Allergy and Infectious Diseases (NIAID). The following key questions were originally posed in the Request for Task Order (RFTO):

A. Define Food Allergy:
   i. What definitions of food allergy are currently being used?
   ii. Describe conditions that are described as non-immunologic adverse reactions to food.
   iii. Describe conditions that are described as immunologic, but not IgE-mediated, adverse reactions to food.
   iv. Describe conditions that are described as immunologic and IgE-mediated adverse reactions to food (and which are considered by some authorities to be equivalent to food allergy).
   v. Compare adverse reactions to food that are non-immunologic, immunologic and not IgE-mediated, and immunologic and IgE-mediated. Include criteria for differential diagnosis of these conditions.

B. What is the incidence/prevalence of IgE-mediated food allergy? The following should be addressed:
   i. What is the incidence/prevalence of IgE-mediated food allergy in the pediatric and adult populations? Provide a comparison.
   ii. Describe the incidence/prevalence of IgE mediated allergy to specific foods in the pediatric and adult populations.
   iii. Describe age- or gender-specific changes in the specific foods that elicit allergic reactions in children and adults.
   iv. What is the incidence/prevalence of co-morbid conditions among the food allergic population? Co-morbid conditions should include, but are not limited to, atopic dermatitis, asthma and eosinophilic gastrointestinal disorders (eosinophilic esophagitis, eosinophilic colitis, eosinophilic gastroenteritis, etc).

C. What is the incidence/prevalence of immunologic, but non-IgE-mediated adverse reactions to foods? The following should be addressed:
   i. What is the incidence/prevalence of immunologic but non-IgE-mediated adverse reactions to food in the pediatric and adult populations? Provide a comparison.
   ii. Describe the incidence/prevalence of immunologic but non-IgE-mediated adverse reactions to specific foods in the pediatric and adult populations.
   iii. What is the incidence/prevalence of co-morbid conditions among this population?
iv. What is the relationship between the natural history of IgE-mediated food allergy and the natural history of co-morbid conditions such as, but not limited to, atopic dermatitis, asthma, and eosinophilic gastrointestinal disorders?

v. What are the risk factors for the development of non-IgE-mediated food allergy?

D. What are the symptoms and natural history of IgE-mediated food allergy? The following should be addressed:

i. Describe the symptoms and natural history of IgE-mediated food allergy in the pediatric and adult populations (including the incidence/prevalence of unintentional exposure, risk factors for the development of disease, severity of reactions, relationship with environmental factors and exposures). Provide a comparison.

ii. What is the relationship between IgE-mediated food allergy and co-morbid conditions (including atopic dermatitis, other eczematous skin disorders, asthma, and eosinophilic gastrointestinal disorders)?

iii. Where do health disparities in the food allergic population exist?

E. What are the symptoms and natural history of immunologic but non-IgE-mediated adverse reactions to food? The following should be addressed:

i. Describe the symptoms and natural history of immunologic but non-IgE-mediated adverse reactions to food in the pediatric and adult populations (including the incidence/prevalence of unintentional exposure, risk factors for the development of disease, severity of reactions, relationship with environmental factors and exposures). Provide a comparison.

ii. What is the relationship between immunologic but non-IgE-mediated adverse reactions to foods and co-morbid conditions (including atopic dermatitis, other eczematous skin disorders, asthma, and eosinophilic gastrointestinal disorders)?

iii. Describe where health disparities exist in this food allergic population.

F. What tools are currently used to diagnose IgE-mediated food allergy? The following should be addressed:

i. Patient history and physical examination

ii. Immediate skin testing (for IgE antibody)

iii. In vitro testing:
   a. total serum IgE
   b. allergen-specific serum IgE
   c. basophil activation
   d. other tests (e.g. IgG antibody levels in serum)

iv. Atopy patch testing

v. Elimination diets used for diagnosis
vi. Oral food challenges used for diagnosis:
   a. foods used
   b. method of challenge
   c. criteria for positive and negative result

vii. Additional diagnostic tests besides the ones listed above
viii. Diagnostic tools used by different groups of clinicians to make the
diagnosis of food allergy.
ix. What tools are used for longitudinal assessment of patients and what are
the criteria for such assessments?

G. What tools are currently used to diagnose immunologic but non-IgE-
mediated adverse reactions to food, and how is a differential diagnosis made?

i. In vivo and in vitro assays for diagnostic testing.
ii. Oral food challenges used for diagnosis.

H. What methods are currently used to manage patients diagnosed with IgE-
mediated food allergy? The following should be addressed:

i. Dietary avoidance (including cross-reacting allergens and issues of breast
feeding and delay of solids) in the context of preventing food allergy.
   a. What are the effects of early versus delayed introduction of
certain foods, notably allergenic foods, into an infant’s diet?
This question should include the effect on nutritional status.
   b. What is the effect of maternal diets during pregnancy and
lactation on the development of, and clinical course of, food
allergy?
   c. What is the effect of breast feeding infants on the
development of, and clinical course of, food allergy?
   d. What are the effects of special diets in infants and young
children (e.g., formula, hydrolyzed formula) on the
development of, and clinical course of, food allergy?
   e. What are the recommendations by professional organizations
regarding the avoidance of allergens (food and non-food) by
people with food allergy?

ii. Management of existing food allergy.
   a. What are the current recommendations on strictness of
allergen avoidance for established IgE-mediated food
allergy?
   b. What are the data on the benefits and adverse effects of
immunotherapy with foods (e.g., parenteral, oral, sublingual)
to treat food allergy?
c. How effective are current standards for food labeling for prevention of food allergic reactions?

d. What are the allergenic cross-reactivities (with other foods or non-food allergens) of foods (i.e. other legumes in peanut allergic patients, tree nuts in peanut allergic patients, etc)? What are the clinical consequences?

e. What are the effects of food allergen avoidance, and other food allergy management strategies, on co-morbid conditions such as, but not limited to, atopic dermatitis, asthma, and eosinophilic gastrointestinal disorders?

f. What are the effects of these co-morbid conditions on the clinical course of, and management of, food allergy?

I. What methods are currently used to manage patients diagnosed with non-IgE-mediated reactions to food, and how do they differ from methods used to manage patients diagnosed with IgE-mediated food allergy?

These conditions include food protein-induced enteropathy, milk colitis, Heiner’s syndrome, etc. Celiac disease, a special case of immune reaction to food that is not often included in the definition of food allergy is excluded because clinical guidelines for the management of this condition already exist.

J. What are the appropriate methods of diagnosis and treatment of acute and life-threatening, IgE-mediated food allergic reactions?

i. Describe signs, symptoms and diagnostic tests that distinguish food-induced acute allergic reactions and anaphylaxis from asthma or other diseases within the differential diagnosis. This should include acute food allergic reactions that occur only when accompanied by exercise.

ii. What are differences on the severity and ultimate outcome of acute food allergic reactions, of administration of epinephrine auto-injections by self administration versus by a bystander?

iii. What are the effects of medication administration by different patient care personnel (e.g., trained ambulance personnel vs. untrained EMTs vs. personnel in hospital emergency rooms, etc.) on the severity and ultimate outcome of acute food allergic reactions?

iv. What is the time course of acute food allergic reactions, and what are the effects of delays between onset of acute food allergic reaction and seeking medical care on the severity and ultimate outcome of acute food allergic reactions?

v. What medications treat or prevent delayed or biphasic food allergic reactions?

vi. Describe all medications used to treat acute food allergic reactions, including their documented effectiveness in treating specific symptoms. Medications shall include, but are not limited to:
a. epinephrine and route
b. antihistamines and route
c. corticosteroids and route
d. fluids and route

vii. What is the risk of death from acute food allergic reactions?
viii. What populations are at greatest risk of death?

**Refinement of Key Questions**

In consultation with the NIAID and the Expert Panel, we refined the original key questions to allow for greater tractability. The following refinements were made:

**A. Define Food Allergy:**

Regarding sub-question A.i, searching for definitions, *per se*, in Medline would be problematical. The NIAID asked that we search for definitions currently used by major organizations, such as the AAAAI. In addition, we performed Google searches using terms such as “food allergy and definition.” We also looked for definitions in high-impact review articles.

Regarding subquestions ii, iii, and iv, the NIAID agreed that information for descriptions should come from widely-used textbooks.

Sub-question A.v asked us to include “criteria for a differential diagnosis.” This is not an evidence review question, but rather a guideline Expert Panel question. We can search for published studies that test different criteria for distinguishing between various clinical conditions, but interpreting any such results into criteria for a differential diagnosis is a role of the Expert Panel.

**B. What is the incidence/prevalence of IgE-mediated food allergy?**

The NIAID agreed that the scope be confined to the US and Canada. In addition, because there was some suggestion that some of the conditions of interest could be either IgE- or non-IgE-mediated, it was agreed that the conditions would not be so divided. The list of conditions considered in this review appears below.

**C. What is the incidence/prevalence of immunologic, but non-IgE-mediated adverse reactions to foods?**

With input from our researcher reviewers, the NIAID, and their technical Expert Panel (TEP), we developed the explicit list of conditions (below).

After much discussion and preliminary research, the RAND EPC developed a list of food allergy conditions, in collaboration with the NIAID and the Expert Panel. Central to the challenge is that the overarching condition of interest, “food allergies,” is not an index
term in Medline, (for example, the way heart failure or urinary tract infection is). The index term in Medline is “Food Hypersensitivity.” Electronic searches using this index term, “food hypersensitivity,” identified thousands of unrelated articles, while missing many important ones (most on non-IgE-mediated conditions). Therefore, both RAND and the NIAID were convinced that the only feasible way to search was to identify specific conditions as the search subjects. In order to identify which conditions should be considered within the domain of “food allergy” for the search, the NIAID and RAND jointly agreed to the strategy of assessing the frequency with which particular conditions were “included” in or “excluded” from the topic of “food allergy” as reported in a comprehensive set of review articles on this topic. Four RAND researchers collected data on food allergy definitions, and the medical conditions included, from 85 review articles, using a one-page form (see Appendix L). Each review article was independently abstracted by two reviewers, who then came to consensus and submitted one form for each article.

In addition, the NIAID provided RAND with a list of organizations (suggested by the Expert Panel) that might have their own definition of food allergy. RAND abstracted information from the web sites of the 57 professional societies and other related organizations on the Expert Panel’s list. Where available, we abstracted each organization’s definition of food allergy; however, only 19 of the 57 web sites provided a definition. We also abstracted the internet address; whether, how often, and in what context the site mentions food allergy; and a link to guidelines on food allergy if the organization had developed or endorsed them.

The results of the above tasks were presented to the Expert Panel on March 18, 2009. Officials and the Chair of the Expert Panel selected the final list shown here:

- Asthma
- Atopic dermatitis, eczema
- Classic food-related anaphylaxis
- Food-associated, exercise-induced syndromes
- Colitis
- Eosinophilic Esophagitis/Gastroenteritis
- Cow’s milk allergy syndrome:
  - Induced colitis (and blood in the stools)
  - Food-induced enterocolitis syndrome
  - Food-induced proctocolitis syndrome
  - Milk protein allergy of infancy
- Gastrointestinal hypersensitivity (e.g., vomiting, colic, diarrhea)
- Laryngeal edema
- Contact dermatitis
- Generalized flushing
- Oral Allergy Syndrome
- Rhinitis, rhinoconjunctivitis conjunctivitis
- Urticaria
- Angioedema
• Heiner’s Syndrome (pulmonary hemosiderosis)

D. What are the symptoms and natural history of IgE-mediated food allergy?

Per the NIAID’s clarification of sub-question D.iii, regarding “health disparities,” we considered issues such as socio-economic status, access to healthcare, and stress.

E. What are the symptoms and natural history of immunologic but non-IgE mediated adverse reactions to food?

We limited our review for questions D and E to the conditions included in the list above.

F. What tools are currently used to diagnose IgE-mediated food allergy?

The NIAID re-stated this and its sub-questions as a two-part question: first, identify what tools are currently being used, including those of which the NIAID may have initially been unaware; and second, evaluate the utility of the tools. For sub-question F.viii, the objective was to understand if differences existed among physicians of different specialties or in different health care settings in the tools being used; it was agreed that the search should be limited to tools used by physicians.

G. What tools are currently used to diagnose immunologic but non-IgE-mediated adverse reactions to food, and how is a differential diagnosis made?

As with questions B, C, and E above, we limited the review for this question to the predetermined explicit list of conditions and their diagnosis. However, as will be described below, since it would not be apparent whether a patient had an IgE-mediated or non-IgE-mediated condition prior to diagnosis, questions F and G were considered together, with a focus on differential diagnosis.

H. What methods are currently used to manage patients diagnosed with IgE mediated food allergy?

After discussions with the NIAID, this question and its sub-questions were refined to address two concerns: addressing prevention strategies for people at risk for food allergies, and addressing the management of patients with a diagnosis of food allergy. The subsection on pregnant women with a history of food allergy (i.e., prevention strategies) was further refined to make explicit the distinction between management of already allergic pregnant and/or nursing women themselves, and prenatal management directed at trying to prevent allergies developing in offspring.

I. What methods are currently used to manage patients diagnosed with non-IgE mediated reactions to food, and how do they differ from methods used to manage patients diagnosed with IgE-mediated food allergy?
Again, in consultation with experts and the NIAID, we agreed to focus on the specific list of conditions above.

**J. What are the appropriate methods of diagnosis and treatment of acute and life threatening, IgE-mediated food allergic reactions?**

The NIAID and their guideline Expert Panel helped us to specify the list of medications in sub-question J.vi, as follows:

- Epinephrine (intramuscular, subcutaneous and intravenous)
- H1 Blockers
- H2 Blockers
- Corticosteroids (intravenous and oral)
- Glucagon
- Alpha adrenergic agonists (intravenous)
- Beta adrenergic agonists (intravenous and inhaled)
- Vasopressors
- Anti-IgE
- Anti-leukotrienes
- Charcoal
- Oxygen
- Intravenous fluids, including normal saline
- Atrovent

**Report Section by Key Question**

Table 1 illustrates the task order questions and how we organized the report to address the NIAID’s priorities. On a conference call with the NIAID in May 2009, RAND reported that most studies found through the literature searches discuss food allergy conditions without regard to whether they are IgE vs. non-IgE mediated. This is especially true for incidence / prevalence studies. RAND requested further guidance regarding where to discuss the findings of such studies. The NIAID advised not to use IgE vs. non-IgE categories for now, but rather to categorize by conditions refined in question C above. The guideline Expert Panel will further classify and categorize during guideline development.
Table 1: Organization of report

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**Evidence Sources and Searches**

**Literature Searches**

Literature searches were performed on PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (Central), and the World Allergy Organization Journal. The principle topics covered were diagnosis and testing techniques for food allergies in general, and in the case of the PubMed searches, specific IgE- and non-IgE-related reactions to food allergies/hypersensitivity, as indicated previously. In most cases searches were limited to the years 1988 to the present (by agreement with the NIAID that the prior 20 years should contain all or nearly all of the data relevant to the current diagnosis and management of food allergy), with no language restrictions. Older studies were included by reference mining or at the suggestion of experts. Complete search strategies are presented in Appendix A.

**Pubmed**

PubMed is a service of the US National Library of Medicine (NLM) that includes over 18 million citations from MEDLINE and other life science journals for biomedical articles back to 1948. PubMed includes links to full text articles and other related resources. MEDLINE is the largest component of PubMed. Approximately 5,200 journals published in the US and more than 80 other countries have been selected and are currently indexed for MEDLINE. A distinctive feature of MEDLINE is that the records are indexed with NLM's controlled vocabulary, the Medical Subject Headings (MeSH). MeSH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts.

**Cochrane Collaboration**

The Cochrane Collaboration is an international, non-profit, independent organization, established to ensure that up-to-date, accurate information about the effects of healthcare interventions is readily available worldwide. It produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of
clinical trials and other studies of the effects of interventions. The Collaboration produces the Cochrane Central Register of Controlled Trials (Central), the Cochrane Database of Systematic Reviews, and the Cochrane Database of Abstracts of Reviews of Effects (DARE).

**DARE**

DARE contains structured abstracts of high-quality systematic reviews published in the scientific literature. DARE also contains references to other reviews that may be useful for background information. The reviews are identified by searching through key medical journals, bibliographic databases, and less widely available “gray literature” which includes non-peer reviewed materials. DARE includes papers that review the effectiveness of healthcare interventions or organization. The quality of the database content relies upon ensuring that all reviewers work to specified guidelines, and that independent checks on the review process are carried out. DARE is produced by contract with the Centre for Reviews and Dissemination (CRD) at the University of York, UK.

**Title & Abstract Screening**

The principal investigator reviewed all titles and abstracts resulting from the literature searches regarding the key questions other than diagnosis; these latter titles were reviewed by two RAND researchers. The principal investigator resolved any questions or needs for clarification that arose throughout the process. Reviewers screened all titles identified through our searches or submitted by content experts for pertinence to the key questions. We established screening criteria to facilitate the identification of articles concerning definitions, diagnoses, and other topics as per the NIAID and Expert Panel’s questions. At the title screening stage, we marked for exclusion citations that were unrelated to any of the medical conditions listed above; we generally retained ambiguous citations.

**Study Screening and Abstraction**

Articles retrieved based on their titles moved on to the screening phase. Articles were dual-reviewed, and we employed the following techniques to improve the reliability and accuracy of our method:

- Reviewers were trained in principles of evidence-based medicine using a “training set” of articles to encourage consistent application of the definitions and criteria of the project.
- The principal investigator served as the “gold standard” reviewer.
- Specific definitions were used for both exclusion criteria and categorization.
- A second review of a random subset of articles from all reviewers was conducted.

Seven researchers, all trained in conducting systematic reviews, participated in the process. These seven reviewers divided into teams of at least two people each to examine which studies merited inclusion in our report, according to the criteria set forth on a Food
Allergies Screener form specifically designed for the review (see Appendix B for copy of form). If the reviewers had questions, they turned to the PI for a final determination. Articles were included/excluded based on the following:

- **Article Type**
  - Included: Original data or systematic reviews.
  - Excluded: Background/contextual reviews; non-systematic reviews, commentary or other types of articles.

- **Study Purpose**
  - Included: Studies that looked at incidence/prevalence/natural history; diagnosis; treatment/management/prevention.
  - Excluded: Studies that either were not about food allergy or had some other purpose than listed above in “included.”

Included studies were then categorized by the food(s) of concern. These categories included multiple foods, milk, egg, peanut/tree nut, fish/shellfish, soy, wheat, and/or other foods, as specified. Studies were then categorized by the medical conditions listed earlier; those that did not pertain to at least one of the explicit conditions were excluded at this point. We then asked a series of questions, keyed to particular types of studies. A number of possible answers were provided with checkboxes, and spaces were included to specify other, unlisted answers. The questions, divided by study types, were as follows:

- **Incidence/prevalence/natural history studies**
  - From where were the patients identified?
  - How were the patients selected?
  - In which country was the study performed/did patients reside?
  - How was food allergy assessed?

- **Diagnosis studies**
  - How were the patients identified?
  - What diagnostic tests were performed?
  - What reference tests were performed?
  - Were data reported on sensitivity or specificity or positive/negative predictive value or false positive/false negative rate?

- **Treatment/management/prevention studies**
  - Who was the target of the intervention?
  - What were the specific interventions?
  - What was the study design?\(^1\)

Accepted articles were reviewed and abstracted by the topic teams. The teams reached consensus on inclusion of final article sets for each topic area as well as consensus on data items abstracted from these articles. Because of the large number of articles and the

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\(^1\) Studies presenting original data were classified as either: controlled trials, cohort studies, case series, case-control studies, decision analyses, or individual case reports. Definitions of these study designs are included in Appendix C.
short time for our review, in practice, not all articles were dual-abstracted even though team members worked together closely.

**Incidence, Prevalence, and Natural History Questions**

For Key Questions B-E, we first searched for high quality systematic reviews or meta-analyses, which we assessed using the AMSTAR criteria:\(^3\)

<table>
<thead>
<tr>
<th>AMSTAR criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>01. Was an a priori study design provided?</td>
</tr>
<tr>
<td>02. Was there duplicate study selection and data extraction?</td>
</tr>
<tr>
<td>03. Was a comprehensive literature search performed?</td>
</tr>
<tr>
<td>04. Was the status of publication (gray literature) used as an inclusion criterion?</td>
</tr>
<tr>
<td>05. Was a listed of studies (included/excluded) provided?</td>
</tr>
<tr>
<td>06. Were the characteristics of the included studies provided?</td>
</tr>
<tr>
<td>07. Was the scientific quality of the included studies assessed and documented?</td>
</tr>
<tr>
<td>08. Was the scientific quality of the included studies used appropriately in formulating conclusions?</td>
</tr>
<tr>
<td>09. Were the methods used to combine the findings of studies appropriate?</td>
</tr>
<tr>
<td>10. Was the likelihood of publication bias assessed?</td>
</tr>
<tr>
<td>11. Was the conflict of interest stated?</td>
</tr>
</tbody>
</table>

Where these were found, in general we did not review the individual studies included in the review or meta-analysis. An exception to this rule was made for some US nationwide studies of prevalence, which were included in a high quality review but which we also reviewed separately as they concerned the population of most interest to the NIAID and Expert Panel.

In addition to applying the AMSTAR criteria, we searched for studies of acceptable design and execution to support generalization to a broad population. As detailed in the results section, this process consisted mainly of identifying studies where the population sampled was national in scope or came from a clearly identified community.

For these studies, we extracted relevant information about the study design, the population, the data sources, how food allergy was defined, and the findings. We created evidence tables for related studies and summarized them narratively.

**Diagnostic Studies**

For Key Questions F & G on tools for diagnosis, our initial screening identified 264 articles (studies) that evaluated diagnostic methods. Of these, three were systematic reviews and 153 appeared on initial screening to evaluate the method(s) by reporting the sensitivity and specificity (or positive and negative predictive value or receiver-operating characteristics) or providing the data to perform this calculation.

These articles underwent additional screening to assess study quality using two of the 8 criteria recommended by Lijmer\(^4\) and later incorporated into the Standards for the Reporting of Diagnostic Accuracy (STARD)\(^5\) criteria: prospective (vs. retrospective) data collection and a modification of generalizability of the population, in that studies that did
not specify how the subjects were assembled were excluded. [The STARD initiative aims to improve the quality of reporting of studies of diagnostic accuracy by applying a checklist of 25 criteria (see Appendix D). STARD is not intended as a tool for assessing the overall quality of a diagnostic study. The 8-item checklist used by Lijmer and colleagues as well as a tool such as the 14-item Quality Assessment of Studies of Diagnostic Accuracy (QUADAS), which relies on similar criteria, can be used for that.] The QUADAS criteria are also shown in Appendix D for this project. Prospective data collection was defined by its distinction from the sole reliance on medical or administrative records for identification of patients and diagnostic test data (however, studies were included if medical record abstraction was used to identify a population of patients seen for a suspected food allergy or other condition of interest and all relevant diagnostic tests were then prospectively performed on that population). Population generalizability was defined very liberally by requiring that there be some statement about how the subjects were assembled. Studies stating “A total of 170 infants who had come to the allergy service for the first time and who were selected consecutively over a 4-year period” were included at this stage, whereas studies were excluded if they used vague statements such as “one thousand patients with a typical history of an acute allergic reaction to nut were included”, “108 individuals with suspected shrimp allergy were included”, and “children younger than 4 years who attended the outpatient pediatric dermatology department because of atopic dermatitis and suspected food allergy were recruited.” Studies that met the criteria of prospective data collection and a defined population were given priority in our synthesis because they are less susceptible to bias. Only in certain cases, such as an explicit key question (or sub-question) for which we found no studies that met these selection criteria, did we include studies of lesser quality. The studies that met the initial inclusion criteria were further evaluated using QUADAS.

Treatment, Management, and Prevention Studies

For Key Questions H-J on topics related to the prevention, treatment, and management of food allergies, we first sought high-quality systematic reviews. From each of the systematic reviews, the following information was abstracted: study question, databases searched, interventions evaluated, inclusion/exclusion criteria, total number of publications included, outcomes reported, and the 11 AMSTAR quality criteria displayed on the previous page. We did not perform additional data abstraction on individual studies that were already included in a systematic review.

For those key questions not addressed in a systematic review, a single investigator abstracted the following information from each controlled trial: study purpose, design, food/condition of interest, population of interest, intervention evaluated, and outcomes evaluated. Although study data were abstracted by a single investigator, they were checked by a second reviewer. If a clear consensus could not be reached as a group, we consulted with the project principal investigator for further input.

From each included controlled trial, we also abstracted study quality information based on the Jadad scale. The Jadad scale measures quality on a scale that ranges from 0 to 5, assigning points for randomization, blinding, and accounting for withdrawals and
dropout. Across a broad array of meta-analyses, an evaluation found that trials scoring 0-2 report exaggerated results compared with trials scoring 3-5. If studies were appropriately randomized, were blinded, performed intention to treat analyses, and had follow up rates in excess of 50 percent, we generally considered them to be of good quality. Studies lacking two or more of these qualities were considered to be of fair quality and studies with fewer than two of these qualities were considered to be of poor quality.

For those key questions not addressed by either a systematic review or high quality controlled trials, we sought information from observational studies. We first sought observational studies with more than 100 patients, since observational studies with small sample sizes have very limited ability to provide information that supplements trials and is also valid. However, if still unable to address a key question, we included observational studies with fewer than 100 patients. Specifically, small observational studies were included for safety of immunotherapy and nutritional status for allergy avoidance. From these observational studies, we abstracted the same study design, population, intervention, and outcome information as for the controlled trials. Because all of the observational studies in this review lack a comparison group, we initially considered them to be of poor quality but then upgraded the quality rating if the study had a high level of follow up (>90 percent), large sample sizes (>500 patients), and made attempts to reduce bias either through study design or statistical analysis.

**Summarizing the Evidence**

In addition to assessing the quality of each of the included studies, for each key question we assessed the quality of the body of evidence based on GRADE. GRADE was developed to help rate the quality of evidence for studies of the treatment of a condition. We assessed the overall quality of evidence for outcomes using a method developed by the Grade Working Group, which classified the grade of evidence across outcomes according to the following criteria:

- **High** = Further research is very unlikely to change our confidence on the estimate of effect.
- **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very Low** = Any estimate of effect is very uncertain.

GRADE also suggests using the following scheme for assigning the “grade” or strength of evidence:
Table 2: Criteria for assigning grade of evidence

<table>
<thead>
<tr>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trial = high</td>
</tr>
<tr>
<td>Observational study = low</td>
</tr>
<tr>
<td>Any other evidence = very low</td>
</tr>
</tbody>
</table>

**Decrease grade if:**
- Serious (-1) or very serious (-2) limitation to study quality
- Important inconsistency (-1)
- Some (-1) or major (-2) uncertainty about directness
- Imprecise or sparse data (-1)
- High probability of reporting bias (-1)

**Increase grade if:**
- Strong evidence of association-significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
- Very strong evidence of association-significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

For example, if a key question was addressed by one or more systematic reviews of high quality and the conclusions of that review are unlikely to be changed by the addition of new RCT data, the quality of the body of evidence was deemed to be high. Similarly, if the key question was addressed by several RCTs, which provide robust, consistent evidence and the conclusions of those RCTs are unlikely to be changed by the addition of new RCT data, the quality of the body of evidence was deemed to be high. If the systematic review or RCT evidence was inconclusive or highly likely to be changed by future studies, the quality of the body of evidence was considered to be moderate. If the RCT evidence was inconclusive, subject to significant methodologic concerns, or not directly applicable to the key question, the quality of the body of evidence was considered to be low.

Recently an adaptation of GRADE has been proposed for use with diagnostic studies.\(^\text{10}\) We used this adaptation to assess the quality of the evidence for diagnosis.

Given the heterogeneity of the included trials, with one exception we were not able to perform quantitative syntheses of the data. Instead we present narrative summaries of the included studies by key question, by common allergenic foods, and by common clinical allergic conditions.
Meta-Analysis of Diagnostic Studies

We examined the distribution of sensitivity and specificity pairs by food allergy, test type, and food allergy by test type. ROC curves were estimated by transforming sensitivity and specificity pairs using logistic transforms and regressing logit sensitivities on logit specificities. Studies were weighted by sample size. ROC curves were calculated by back transforming predicted values from these regression models. We calculated the lower and upper 95% confidence bounds for the ROC curves by re-estimating the curves on bootstrap samples. The bootstrap was also used to test differences in AUC for subsets of the studies. The bootstrap incorporated the clustering of observations within studies by resampling at the study level rather than the sensitivity-specificity pair level.

Narrative Data Synthesis

The remaining data we found would not support statistical pooling of results across studies (meta-analysis) because the studies were judged clinically too heterogeneous to combine; therefore, our synthesis of the data is narrative. (An obvious exception is the situation where an existing meta-analysis has already been performed that pooled those studies on a particular topic judged sufficiently similar to do so.) We report the evidence in several forms. First, the evidence tables offer a detailed description of the studies that we identified, addressing each of the topic areas. The evidence tables provide detailed information consistent with established criteria about the study design, patient characteristics, inclusion and exclusion criteria, interventions evaluated, and the outcomes.

Throughout the report, summary tables report on systematic reviews and original studies in an abbreviated form, using summary measures of the main outcomes. Narrative text summarizes the findings and provides qualitative analysis of the key questions as they relate to the topic area.

Peer Review

A draft version was sent to members of the Expert Panel and to the NIAID staff. After receiving and attending to any comments received, the final report was prepared and submitted.
Results

This section presents the results of the literature synthesis. Figure 1 presents the flow of articles. A conceptual model used to guide the analysis is shown in Figure 2.

Figure 1: Literature Flow

Total titles identified from literature searches: N = 12,378

Total number of titles identified for abstract review: N = 1,820

Total abstracts rejected: N = 544
  - 8 case report
  - 161 Did not have an abstract
  - 18 Not incidence/prevalence/natural history, Treatment/Management/Prevention or Diagnosis
  - 198 Non-systematic review
  - 115 Not food allergy
  - 17 Editorial/Commentary/Guideline
  - 9 Letter
  - 14 Not answering key question
  - 4 Miscellaneous other reasons

Total number of articles ordered: N = 1,276

Never received: N = 25

Total number of articles received: N = 1,251

Not reviewed (Non-English articles): N = 35

Total number of articles reviewed: N = 1,216

Total number of articles that were accepted at screener level: N = 979
  - Background: N=111
  - Incidence/Prevalence/Natural history: N = 415
  - Diagnosis: N = 266
  - Treatment/Management/Prevention: N = 227
  Note: 38 articles had more than one purpose

Total number of articles rejected at screener level: N = 237
  - Rejected, no original data/no systematic review: N = 116
  - Rejected, not food allergy: N = 87
  - Rejected, not incidence/prevalence/natural history, treatment/management/prevention, diagnosis or background: N = 33
  - Rejected, duplicate data: N = 1

Incidence/Prevalence/Natural History
Articles accepted at report level for population based selection or from regional/national sample: N = 48
  - Rejected, non US/Canada: N = 323
  - Rejected, not population based/systematic sample: N = 44

Diagnosis
Articles accepted at report level with sensitivity/specificity info, a well defined population, a gold standard, and prospective data collection: N = 38
  - Rejected, no sensitivity/specificity info: N = 111
  - Rejected, poorly defined population: N = 90
  - Rejected, no gold standard: N = 4
  - Rejected, retrospective data collection: N = 16
  - Rejected, wrong test: N = 1
  - Rejected, Celiac disease: N = 4

Treatment/Management/Prevention
Articles accepted at report level for observational > 180 or RCT; N = 120
  - Rejected, neither RCT nor observational: N = 20
  - Rejected, observational, sample < 100: N = 65
  - Rejected, observational, prevention article: N = 3
  - Rejected, Celiac disease: N = 1
Figure 2: Conceptual model of Key Questions

KQ D/E: Natural History of Food Allergies

Pregnant Women with Fetus at High Risk of Food Allergies

Infants at High Risk of Food Allergies

Children and Adults with Allergic Type Symptoms

Children and Adults with Actual Food Allergies

KQ HI: Prevention Interventions for Pregnant Women (eg, probiotics, special diets)

KQ HI: Prevention Interventions for Nursing Mothers and Infants (eg, breastfeeding, special formulas)

KQ B/C: Incidence and Prevalence of Food Allergies by symptoms (eg, atopy, asthma) and by conditions (eg, eosinophilia, eczema)

KQ F/G: Diagnosis of Food Allergies (eg, skin prick testing, food challenge, IgE)

KQ HI/M/J: Treatment/Manage ment Interventions (eg, elimination diets, allergen-specific immunotherapy, pharmacotherapies)
Section I. What is the definition of food allergy?

Key Question A. Define Food Allergy.

i. What definitions of food allergy are currently being used?

In the NIAID and Expert Panel’s original definition, for a condition to be considered a food allergy, it had to satisfy the following criteria: a) an adverse immune response that occurs reproducibly on exposure to a given food and is b) distinct from other adverse responses to food, such as food intolerance, pharmacologic reactions, and toxin-mediated reactions. In addition, the NIAID initially specified that while food allergy is frequently defined as a disorder caused by IgE-mediated reactions to food, we should review literature relevant to adverse reactions to foods that arise from non-IgE-mediated immunologic mechanisms (but not non-immunologic mechanisms).

In order to assess the definitions of food allergy currently being used, we reviewed all review articles on food allergy published in the past decade (1998-2008). We identified 85 articles, of which 71 (81.7 percent) defined food allergy (see Appendix L). We identified six key characteristics in the draft NIAID definition, and then assessed whether or not each characteristic was included in each review article definition. The specifics included in the definitions are shown in Table 3.

<table>
<thead>
<tr>
<th>Definition – Key Characteristic</th>
<th>Proportion of Reviews including characteristic (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune response</td>
<td>62 (87.3%)</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>22 (31.0%)</td>
</tr>
<tr>
<td>Particular food</td>
<td>32 (45.1%)</td>
</tr>
<tr>
<td>Separate from food intolerance, pharmacologic, or toxin-mediated reactions</td>
<td>35 (49.3%)</td>
</tr>
<tr>
<td>IgE-mediated reactions</td>
<td>56 (78.9%)</td>
</tr>
<tr>
<td>Non-IgE-mediated immunologic mechanisms</td>
<td>47 (66.2%)</td>
</tr>
</tbody>
</table>

Also at the suggestion of the NIAID, we examined the Web sites of 57 organizations concerned with food allergy (suggested by the Expert Panel). These organizations included the American Academy of Allergy, Asthma, and Immunology (AAAAI), American Academy of Pediatrics (AAP), American College of Allergy, Asthma & Immunology (ACAAI), Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA). Nineteen of those sites contained definitions of food allergy, as shown in Table 4.
Table 4: Web sites with food allergy definitions

<table>
<thead>
<tr>
<th>Definition – Key Characteristic</th>
<th>Proportion of sites/definition including characteristic (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune response</td>
<td>18 (94.7%)</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Particular given food</td>
<td>9 (47.4%)</td>
</tr>
<tr>
<td>Separate from food intolerance — pharmacologic or toxin-mediated reactions</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>IgE-mediated reactions</td>
<td>8 (42.1%)</td>
</tr>
<tr>
<td>Non-IgE-mediated immunologic mechanisms</td>
<td>3 (15.8%)</td>
</tr>
</tbody>
</table>

From each article, we also abstracted the medical conditions associated with the definitions of the terms IgE-mediated, Non-IgE mediated, as well as those identified as Mixed IgE- and Non-IgE mediated (as part of the previously described process to identify the conditions that should be included within this review of “food allergy”). The results are shown below in Table 5 through Table 7.

Table 5: Terms associated with IgE-mediated conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Proportion of reviews including this condition as “food allergy” (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioedema</td>
<td>31 (43.7%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>28 (39.4%)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>21 (29.6%)</td>
</tr>
<tr>
<td>Colitis</td>
<td>0</td>
</tr>
<tr>
<td>Food related eosinophilic esophagitis</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Food related exercise induced</td>
<td>15 (21.1%)</td>
</tr>
<tr>
<td>Gastrointestinal hypersensitivity</td>
<td>22 (31.0%)</td>
</tr>
<tr>
<td>Generalized flushing</td>
<td>5 (7.0%)</td>
</tr>
<tr>
<td>Laryngeal edema</td>
<td>3 (4.2%)</td>
</tr>
<tr>
<td>Oral allergy syndrome</td>
<td>35 (49.3%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>20 (28.2%)</td>
</tr>
<tr>
<td>Rhinoconjunctivitis</td>
<td>14 (19.7%)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>38 (53.5%)</td>
</tr>
</tbody>
</table>

* Note: Not all reviews specified a list of conditions
Table 6: Terms associated with Non-IgE-mediated conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Proportion of reviews including this condition as “food allergy” (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>5 (7.0%)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>11 (15.5%)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>19 (26.8%)</td>
</tr>
<tr>
<td>Classic food related anaphylaxis</td>
<td>47 (66.2%)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>9 (12.7%)</td>
</tr>
<tr>
<td>Cow milk induced colitis</td>
<td>6 (8.5%)</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>17 (12.7%)</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>5 (7.0%)</td>
</tr>
<tr>
<td>Eosinophilic gastroenteritis</td>
<td>5 (7.0%)</td>
</tr>
<tr>
<td>Food-induced proctocolitis</td>
<td>24 (33.8%)</td>
</tr>
<tr>
<td>Heiner’s syndrome</td>
<td>15 (21.1%)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Milk protein allergy, infants</td>
<td>7 (9.9%)</td>
</tr>
<tr>
<td>Protein-induced enterocolitis</td>
<td>29 (40.9%)</td>
</tr>
</tbody>
</table>

* Note: Not all reviews specified a list of conditions

Table 7: Terms associated with mixed IgE and non-IgE-mediated conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Proportion of reviews including this condition as “food allergy” (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic eosinophilic esophagitis</td>
<td>20 (28.2%)</td>
</tr>
<tr>
<td>Allergic eosinophilic gastroenteritis</td>
<td>22 (31.0%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>11 (15.5%)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>21 (28.6%)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>2 (2.8%)</td>
</tr>
</tbody>
</table>

* Note: Not all reviews specified a list of conditions

Key Question A (continued)

ii. Describe conditions that are described as non-immunologic adverse reactions to food.

iii. Describe conditions that are described as immunologic, but not IgE-mediated, adverse reactions to food.

iv. Describe conditions that are described as immunologic and IgE-mediated adverse reactions to food (and which are considered by some authorities to be equivalent to food allergy).

v. Compare adverse reactions to food that are non-immunologic, immunologic and not IgE-mediated, and immunologic and IgE-mediated.
In the course of reviewing the literature, we determined that classifying conditions as “IgE-Mediated” and “Non-IgE-Mediated” might engender some controversy; thus, throughout the remainder of this report, with the consent of the NIAID staff who guided us on the review and the preparation of the report, we will not deliberately categorize study findings in this way, but rather will present the results by condition as described in the literature. The following constitutes a brief, basic overview of the medical conditions studied in this report.

**Anaphylactic Conditions**

**Classic food-related anaphylaxis**

Anaphylaxis is a rapid-onset, life-threatening systemic reaction to allergens in which the affected individual may experience cardiovascular shock and/or serious respiratory compromise due to airway obstruction or broncho-constriction. Typically IgE-mediated, food-induced anaphylaxis is believed to involve previously sensitized mast cells and basophils. Mast cells have higher concentrations of tryptase, but samples from victims of food-related anaphylaxis have shown a lack of elevated tryptase (victims of other kinds of anaphylaxis, by contrast, have elevated tryptase). This finding suggests that basophils may play the more predominant role. However, the findings are not definitive enough to support using tryptase as a diagnostic marker.

The most common food triggers of anaphylaxis are peanuts and tree nuts; dairy; eggs; fin fish, and shellfish. Incidence is variable depending on age, regional diets, food preparation, amount of exposure, and timing of first exposure. Most fatalities are associated with a lack of immediate access to epinephrine; oral antihistamines alone can not prevent death. Despite this understanding, physicians often fail to prescribe self-administered epinephrine to individuals with a history of anaphylactic reactions to a food, and emergency responses can vary by region.

Food-induced anaphylaxis is caused by contact with the proteins in allergens, not by inhaling olfactory volatiles (which do not contain proteins). For example, inhaling a sufficient quantity of peanut dust may cause anaphylaxis; however, merely smelling peanuts can not.

The NIH and National Library of Medicine’s Medline Plus lists the following symptoms and signs of anaphylaxis. This list is general and does not distinguish between food-induced anaphylaxis and other causes, such as insect venom- or drug-induced anaphylaxis. The primary cause of death for food-induced anaphylaxis is respiratory collapse.

**Symptoms:**

- Abdominal pain or cramping
- Abnormal (high-pitched) breathing sounds
- Anxiety
- Confusion
Cough  
Diarrhea  
Difficulty breathing  
Fainting, light-headedness, dizziness  
Hives, itchiness  
Nasal congestion  
Nausea, vomiting  
Sensation of feeling the heart beat (palpitations)  
Skin redness  
Slurred speech  
Wheezing  

**Signs:**

- Abnormal heart rhythm (arrhythmia)  
- Fluid in the lungs (pulmonary edema)  
- Hives  
- Low blood pressure  
- Mental confusion  
- Rapid pulse  
- Skin that is blue from lack of oxygen or pale from shock  
- Swelling (angioedema) in the throat that may be severe enough to block the airway  
- Swelling of the eyes or face  
- Weakness  
- Wheezing  

**Food-associated, exercise-induced syndromes**

Food-dependent exercise-induced anaphylaxis (FDEIA) is a relatively rare variant of exercise-induced anaphylaxis.\(^{19}\) FDEIA is an IgE-mediated reaction that requires a sequence of activities to be triggered. First, individuals ingest the food to which they are allergic; then, they exercise within a triggering window, generally two to four hours.\(^ {14}\) The symptoms resemble those of classic food-related anaphylaxis and can be fatal if left untreated. On the AAAAI Web site, Anna Feldweg, M.D. and Al Sheffer, M.D. (authors of a forthcoming chapter on “Exercise Anaphylaxis” for the Joint Council Parameters on Anaphylaxis), warned that FDEIA can be unpredictable—sometimes no reaction is observed with the combination of specific food and exercise; sometimes a severe clinical reaction occurs. They recommend patients who begin to display symptoms be told to stop exercising “immediately, without exception.”

**Generalized flushing**

Generalized Flushing is a sudden and transient reddening of the face, neck, and less frequently, other parts of the upper body and abdomen. While a flushing reaction may
occur when foods that are natural blood vessel dilators (such as hot spices and vinegars) are ingested, flushing is also a common sign of food allergies.\textsuperscript{12, 14, 20, 21}

The following foods may cause generalized flushing as part of allergic reaction:
- Alcohol
- Avocados
- Cantaloupes
- Chocolate
- Dairy Products
- Lima Beans
- Monosodium glutamate
- Soy Sauce
- Spinach
- Tomatoes

Occurrences of food allergy-related generalized flushing are very common in children and often develop simultaneously with gastrointestinal or respiratory symptoms. Flushing is a frequent part of food-induced anaphylaxis, and thus is IgE-mediated.

Occurrences of non-food allergy-related generalized flushing, especially when accompanied by sweating, vomiting, and diarrhea, may suggest scombroid fish poisoning (most often from consuming contaminated tuna and mackerel). Upper body flushing, with watery diarrhea, is also a symptom of carcinoid syndrome.

**Laryngeal edema**

Laryngeal edema is an intense inflammation of the larynx (voice box), and ranges in symptomatology from a moderate swelling of the throat, resulting in a “dry staccato” or croupy cough, to acutely hindered breathing caused by severe obstruction of the upper airway. Recurrence of laryngeal edema is often mistaken for the common cold or laryngitis, but more serious incidents can be life threatening.\textsuperscript{11, 22-25}

The following foods may cause laryngeal edema as part of allergic reaction (not an exhaustive list):
- Celery
- Cheese
- Eggs
- Fish
- Milk
- Peanuts
- Shellfish
- Tree nuts
- Wheat

Occurrences of food allergy-related laryngeal edema come on quite suddenly and most commonly affect children between the ages of 2 and 8, but may also occur in older
children and adults. The first signs are drooling, noisy breathing, high fever, and airway
distress. Laryngeal edema is a frequent part of food-induced anaphylaxis, and thus is IgE-
mediated.

Occurrences of non-food allergy-related laryngeal edema, especially when occurring
without additional skin and gastro-intestinal symptoms, may suggest allergic reaction to
external factors such as bee stings and latex.

Gastrointestinal Conditions

Many of the gastrointestinal reactions to food have overlapping symptoms and allergen
triggers; without detailed histories and specialized diagnostic tools, ranging from serum
radioallergosorbent and skin prick tests to histological samples, they can be difficult to
distinguish from each other and from conditions with other causes. They can be IgE- or
non-IgE mediated. IgE-mediated conditions will often occur rapidly as part of
anaphylaxis, while non-IgE mediated symptoms are more often slowly developing and
chronic.26

Sicherer offers this definition: “Gastrointestinal food allergies are a spectrum of disorders
that result from adverse immune responses to dietary antigens. The named disorders
include immediate gastrointestinal hypersensitivity (anaphylaxis), oral allergy syndrome,
allergic eosinophilic esophagitis, gastritis, and gastroenterocolitis; dietary protein
enterocolitis, proctitis, and enteropathy; and celiac disease. Additional disorders
sometimes attributed to food allergy include colic, gastroesophageal reflux, and
constipation”.27

The World Allergy Organization offers a Web page of definitions and a chart of food
triggers linked to age and anaphylaxis:
http://www.worldallergy.org/public/allergic_diseases_center/foodallergy

Colitis

(see also Cow’s milk allergy syndrome)

Two major allergy textbooks with recent copyright dates (2008 and 2009 respectively) do
not list colitis in their indexes.11, 28 Nevertheless, the medical literature linking colitis and
food allergy goes back decades. The introduction to one of the earliest papers covers
much of what is currently known: “Simple colitis associated with varying degrees of
diarrhea, abdominal soreness, cramping, tenesmus and mucus frequently is due to
specific food allergies. Wheat, egg, milk, fish, honey, various vegetables, fruits and other
foods and condiments have been incriminated. Milk allergy, especially, is a common
cause of colitis.”29

Eosinophilic Esophagitis/Gastroenteritis

Eosinophilic esophagitis (EE) involves “a localized eosinophilic inflammation of the
esophagus.”30, 31 It affects both children and adults, although symptoms may vary with
age.30 “In children it is responsible for feeding disorders, vomiting, reflux symptoms and
abdominal pain and in adults it causes dysphagia and esophageal food impactions,”
according to Ferguson and Foxx-Orenstein.32

While food allergens have been implicated in EE, the precise etiology remains unknown. It
appears that both IgE and non-IgE mediated reactions occur, with non-IgE cell-
mediated responses predominating.30, 33 According to DeBrosse and Rothenberg, “Recent
advances have highlighted the role of Th2(T-helper type 2 cell)-driven cytokines in the
development of EGID (eosinophil-associated gastrointestinal disorders), and clinical
studies have verified that children and adults with EGID often have positive skin testing
to food allergens.”34

Eosinophilic gastroenteritis is “a general term that describes a constellation of symptoms
and a pathologic infiltration of the GI tract by eosinophils.”30 It is also both IgE- and non-
IgE mediated and linked to food allergies.35, 36 Together with EE, it is part of the group of
diseases dubbed EGIDs.37 EGIDs often have similar symptoms (vomiting, regurgitation,
nausea, heartburn) to gastroesophageal reflux disease or dysphagia, and it is
recommended clinicians also consider a possible diagnosis of EE when encountering
such symptoms.30 According to an UpToDate report, “It is becoming increasingly
apparent that the esophagus (normally devoid of eosinophils) is an immunologically
active organ which, similar to the colon, is capable of recruiting eosinophils in response
to a variety of stimuli.”31, 38

Regarding EE, the Metcalfe text cautions that many patients continue to have symptoms
after elimination of the suspect foods.11 The chapter on EE recommends a specific amino-
acid based diet, citing studies that showed a 95 percent successful resolution in
children.39, 40 Elemental diet and other treatments are also discussed in Pasha, et. al.41 As
for EG, elemental diets are also recommended, though such diets have not been as
“uniformly successful” as they have been for EE.30

Cow’s Milk Allergy Syndrome
(see also Colitis; Gastrointestinal hypersensitivity)

- Induced colitis (blood in the stools)
- Food-induced enterocolitis (and blood in the stools)
- Food-induced proctocolitis syndrome
- Milk protein allergy in infancy

All of these terms are part of a constellation of symptoms/diagnoses, associated with an
early-life allergy to cow’s milk, which is a major concern in pediatric practice.42 The
current research is summarized in a review abstract by Heine and colleagues, “Cow’s
milk allergy affects approximately two percent of infants under 2 years of age. Apart
from IgE-mediated atopic manifestations, T cell-mediated reactions have been
demonstrated in infants with cow's milk allergy. The clinical spectrum ranges from
immediate-type reactions, presenting with urticaria and angioedema to intermediate and
late-onset reactions, including atopic dermatitis, infantile colic, gastro-oesophageal
reflux, oesophagitis, infantile proctocolitis, food-associated enterocolitis and constipation. The exact mechanisms of these disorders are still poorly understood. Double-blind, placebo controlled food challenge, the definitive diagnostic test for cow's milk allergy, is increasingly being replaced by the measurement of food-specific antibodies, in combination with skin-prick or atopy patch testing. The treatment of cow's milk allergy relies on allergen avoidance and hypoallergenic formulae, or maternal elimination diets in breast-fed infants.43

Sicherer describes a non IgE-mediated condition called Dietary Protein-Induced Proctitis/Proctocolitis in this manner: “Infants with dietary protein-induced proctitis/proctocolitis seem generally healthy but have visible specks or streaks of blood mixed with mucus in the stool… The disorder manifests in the first several months of life, with a mean age at diagnosis of 2 months… The lack of systemic symptoms, vomiting, diarrhea, and growth failure help to differentiate this disorder from other gastrointestinal food allergies that may also include colitis. Cow milk proteins and, less commonly, soy protein are the common triggers. Most infants present while being breastfed and are symptomatic as a result of maternally ingested proteins excreted in breast milk. The disorder has also been noted in infants who take casein hydrolysates.”27

Jones and Burks describe Food protein-induced enterocolitis syndrome as a condition in infancy that manifests with vomiting and diarrhea severe enough to cause dehydration and shock.26 The condition is linked to both cow’s milk and soy protein, although some studies also report reactions to solid food, including rice, oats, other cereal grains and poultry.27 While the disorder is not associated with IgE antibodies, a few patients may eventually establish IgE antibody responses. Due to the severity of the condition, Sicherer warns: “Caution is needed when performing oral food challenges because approximately 20 percent of reactions lead to shock.”27

Regarding milk protein allergy in infancy, Arvola and colleagues concluded, “Cow's milk allergy among (infants with rectal bleeding) is more uncommon than previously believed. Cow's milk challenge is thus essential in infants who become symptom-free during a cow's milk-free diet to reduce the number of false-positive cow's milk-allergy diagnoses”.44

Paajanen and colleagues pursued the idea of cow’s milk allergy in young adults and concluded: “Food-related gastrointestinal symptoms in young adults are caused by unspecific and unknown traits of altered mucosal immune response rather than by cow milk, as is often suspected by the patient.”45

Gastrointestinal hypersensitivity (e.g., vomiting, colic, diarrhea)

Immediate gastrointestinal hypersensitivity is a textbook term that refers specifically to an IgE-mediated food allergy, in which upper GI symptoms may occur within minutes, with lower GI symptoms occurring either immediately or with a delay of up to several hours.26 According to Sicherer, “The usual offenders are milk, egg, peanut, soy, wheat, and seafood. Similar to other IgE-dependent allergic disorders, allergy to milk, egg,
wheat, and soy generally resolves, whereas allergies to peanuts, tree nuts, and seafood are more likely to persist.”

Sicherer offers a cautionary note about food allergy linkage with colic: “There is some evidence that infantile colic is associated with CMA (cow’s milk allergy), but the strength of the relationship is not well-defined. Infants who are experiencing symptoms of CMA have a high rate (44 percent) of colic, and hypoallergenic formulas are more efficacious for colic than antacids or low-lactose formula. However, the role of allergy as opposed to other causes among those with colic and without other symptoms of food allergy remains controversial and in need of additional study.”

**Oral Allergy Syndrome**

According to the World Allergy Organization, oral allergy syndrome (OAS) “is a form of contact urticaria from ingesting a food (usually fresh fruit) confined to the lips, mouth and throat, which most commonly affects patients who are allergic to pollens. Symptoms include itching of the lips, tongue, roof of the mouth and throat, with or without facial swelling, and/or tingling of the lips, tongue, roof of the mouth and throat.”

Sicherer writes, “Individuals with oral allergy syndrome, an IgE antibody-mediated disorder, experience prompt oral pruritus and sometimes angioedema of the lips, tongue, and palate when ingesting certain fresh fruits and vegetables. The expression of this allergic response requires initial sensitization via the respiratory route to pollens that contain proteins that are homologous to those found in particular fruits and vegetables. Individuals with this syndrome, therefore, usually have a history of seasonal allergic rhinitis (hayfever). Examples of the associated pollens and foods include reactions to melons in individuals with ragweed allergy and reactions to apples, peaches, and cherries in those with birch pollen allergy. The proteins are labile, and cooked forms of the fruits and vegetables generally do not induce symptoms. Similarly, it is assumed that systemic reactions are averted because the proteins are easily digested. However, 9 percent of individuals experience symptoms beyond the mouth, and one percent to two percent experience severe reactions. Allergy skin tests using fresh extracts of the implicated food are characteristically positive.”

**Heiner’s Syndrome (pulmonary hemosiderosis)**

Jones and colleagues offer this definition: “a rare syndrome in infants characterized by recurrent pneumonia with pulmonary infiltrates, hemosiderosis, gastrointestinal blood loss, iron-deficiency anemia, and failure to thrive. Symptoms are associated with non-IgE mediated hypersensitivity to cow’s milk with evidence of peripheral eosinophilia and the presence of cow’s milk precipitins on diagnostic testing. Deposits of immunoglobulins and C3 may also be found on lung biopsy. Strict dietary elimination of milk results in reversal of syndromes.” The World Allergy Organization says that egg and pork have also been found to be involved, but does not cite a specific source. In a review of eight cases, Moissidis and colleagues found, “Milk elimination resulted in remarkable improvement in symptoms within days and clearing of the pulmonary infiltrate within weeks.”
Skin Conditions

Fasano offers a good general summary of the inter-relationship of various dermatologic adverse food reactions, and why differential diagnosis can be challenging: “Cutaneous reactions to foods represent one of the most common presentations of food allergy in children. IgE-mediated (urticaria, angioedema, flushing, pruritus), cell-mediated (contact dermatitis, dermatitis herpetiformis), mixed IgE- and cell-mediated (atopic dermatitis), and nonimmune-mediated (irritant contact dermatitis, Frey's syndrome) reactions to foods have all been reported.”

Contact dermatitis

Skypala and Venter give this textbook definition: “an inflammation of the epidermis and dermis that occurs as a result of direct contact between a substance and the surface of the skin. This type of cutaneous reaction is most commonly seen in occupational food handlers, involving the hands, but it can also involve the face, especially around the mouth, in children. This type of skin reaction may be IgE- and/or cell-mediated, and symptoms therefore may be immediate (within 10 minutes to two hours) or delayed (2-48 hours). Research has reported contact dermatitis with a wide variety of foods, including raw and processed foods, spices, food additives, and a variety of nuts.” Several articles also implicate mangos. Amadoa and Jacobs summarize means of direct and indirect exposure, including kissing (5 percent of cases) and contact with particles that become aerosolized during cooking. They include a full list of food triggers involving non-food substances, including metals present in foods (nickel, cobalt, chrome) and fragrances, such as Peru balsam. The North American Contact Dermatitis Group’s analysis of food-associated contact dermatitis concluded, “nickel, Myroxilon pereirae, and propylene glycol were the most common allergens identified with a food source. Of food-related occupational disease, irritation was more common than allergy.”

Eczema, atopic dermatitis

Incorvaia and colleagues state: “the pathogenesis of [atopic dermatitis] is linked to a complex interaction between skin barrier dysfunction and environmental factors such as allergens and microbes. In particular, an important advance was the demonstration that the mutation of the skin barrier protein filaggrin is related strictly to allergen sensitization and to the development of asthma in subjects with AD. The altered skin barrier function, caused by several factors, results in the passage of allergens through the skin and to systemic responses. A pivotal role in such a response is exerted by Langerhans cells which, via their immunoglobulin E (IgE) receptor, capture the allergens and present them to T cells. When T helper type 2 (Th2) cells are activated, the production of a proinflammatory cytokines and chemokines pattern sustains the persistence of inflammation. Known AD-related cytokines are interleukin (IL)-5, IL-13 and tumor necrosis factor (TNF)-alpha, with emerging importance for IL-17, which seems to drive airway inflammation following cutaneous exposure to antigens, and IL-31, which is expressed primarily in skin-homing Th2 cells. Skin-homing is another crucial event in
AD, mediated by the cutaneous lymphocyte-associated antigens (CLA) receptor, which characterizes T cell subpopulations with different roles in AD and asthma.53

According to Waterish, “the role of food allergy in the pathogenesis of atopic dermatitis is still controversial; however, there is no doubt that, particularly in infants and young children, food allergens can induce atopic dermatitis or aggravate skin lesions. In adults, food allergy as a cause or a trigger of atopic dermatitis is very rare. However, in food-allergic patients with atopic dermatitis, the ingestion of the food item can provoke the whole spectrum of IgE-mediated symptoms, from oral allergy syndrome to severe anaphylaxis.”54

While dietary exclusion is frequently recommended for such reactions, which have been attributed to milk and other foods,55 there are some counter-examples in the literature. Bath-Hextall and colleagues performed a systematic review of randomized controlled trials to assess the effects of dietary exclusion for the treatment of established atopic eczema. They concluded, “Despite their frequent use, we find little good quality evidence to support the use of exclusion diets in atopic eczema.”56 Schafer concludes: “Atopic eczema is not necessarily associated with allergic sensitization. Sensitization to house dust mites, however, seems to be clinically relevant. The impact of food allergy on atopic eczema is difficult to assess on the basis of epidemiological studies, and more detailed studies are needed.”57

Urticaria

(see also Angioedema)

According to Bindslev-Jensen and colleagues, “IgE and non-IgE mediated reactions of the skin exclusive of eczema usually present as urticaria and/or angioedema.”11 In contact urticaria, wheals appear only on the skin where direct contact has been made with the trigger; in acute urticaria, wheals can appear anywhere.11 Burks notes, “Acute urticaria is a common manifestation of an allergic skin response to food, but food is rarely a cause of chronic urticaria.”58

Muller gives a precise description: “Urticarial lesions are polymorphic, round or irregularly shaped pruritic wheals that range in size from a few millimeters to several centimeters. Lesions can develop anywhere on the body and are spread by scratching, combining into large, fiery-red patches. Sometimes a vascular wheal phenomenon causes lesions to appear hyperemic in the center with a white halo along the circumference.”59

In their guidelines, the British Association of Dermatologists state, “For clinical purposes it is often more helpful to classify urticaria by presentation than by etiology, which is often difficult to establish. It is usually possible to distinguish clearly recognizable patterns of urticaria on the clinical presentation, supported, where appropriate, by challenge tests and skin biopsy…The presentation of urticaria in childhood is similar to that in adults. Clinical and etiological classifications should be complementary rather than exclusive: for example, chronic ordinary urticaria (COU) is most appropriate when the etiology remains uncertain. Where there is evidence of histamine-releasing autoantibodies the patient has autoimmune COU (synonym, chronic autoimmune
urticaria) but where there is no evidence of functional autoantibodies the patient has idiopathic COU (synonym, chronic idiopathic urticaria)."60

Bindslev-Jensen and Osterballe include a chart with urticaria triggering foods identified through a literature survey.11 In descending order, they are:

- cow’s milk
- egg
- peanut
- additives
- mustard
- cod fish
- wheat
- goat’s milk
- kiwi
- sesame seeds
- soy
- hazelnut
- cashew
- apple
- orange
- celery
- shrimp
- potato
- garlic
- pea
- corn
- walnut
- pineapple

In addition, Raap and colleagues describe one patient who developed urticaria in response to lychee fruit.61

Charlesworth advises: “Urticaria and angioedema are frustrating problems for both physicians and their patients; however, the problem can best be approached by considering urticaria as a symptom that may be part of a larger clinical spectrum. The physical examination and medical history remain the two most important pieces of information. The allergist frequently overlooks the value of a skin biopsy as an aid in sorting out the pathophysiology of urticaria and the biopsy results may help to classify urticaria into subgroups which respond differently to treatment.”62
Angioedema

(See also Urticaria)

Muller and colleagues summarize the distinction between angioedema and urticaria: “Urticaria (i.e., pruritic, raised wheals) and angioedema (i.e., deep mucocutaneous swelling) occur in up to 25 percent of the US population. Vasoactive mediators released from mast cells and basophils produce the classic wheal and flare reaction. Diagnosis can be challenging, especially if symptoms are chronic or minimally responsive to therapy.”

The same authors also give a more precise description: “Angioedema, which can occur alone or with urticaria, is characterized by nonpitting, nonpruritic, well-defined, edematous swelling that involves subcutaneous tissues (e.g., face, hands, buttocks, and genitals), abdominal organs, or the upper airway (i.e., larynx). Angioedema tends to occur on the face and may cause significant disfigurement. Laryngeal angioedema is a medical emergency requiring prompt assessment. Acute intestinal and stomach swelling may mimic symptoms of an abdominal surgical emergency.”

Respiratory and Related Conditions

Rhinitis, rhinoconjunctivitis, conjunctivitis

The “Guideline on the Clinical Development of Medicinal Products for the Treatment of Allergic Rhino-Conjunctivitis” produced by the European Medicines Agency summarizes these conditions in its introduction: “Allergic rhinoconjunctivitis is an allergen-induced inflammatory response. The non-infective, seasonal (SAR) and perennial allergic rhinoconjunctivitis (PAR) are the most common types and result from an immunological response mediated by IgE. There is also a Th2 cell component accounting for chronic symptoms. Histamine is a well-known mediator responsible for the signs and symptoms of SAR but many other mediators including leukotrienes and prostaglandin D2 are involved. SAR is caused by allergens released by tree, grass or weed pollination (and spores and moulds), whereas PAR results from allergens such as animal dander, dust mites and less frequently from allergens such as cockroaches or mould spores. Asthma and allergic rhinoconjunctivitis are common co-morbidities. Symptoms are both nasal and non-nasal. The most prominent nasal symptoms are itching, sneezing, rhinorrhea and congestion. Non-nasal symptoms commonly associated with allergic rhinitis include tearing, eye itching and redness. Allergic rhinoconjunctivitis is most prevalent during school age years. Allergic rhinoconjunctivitis is rare before 5 years of age.”

Malik and colleagues write that patients, influenced by the Internet, have come to believe in a frequent association between rhinitis and food. Instead, their review states, it is a relatively rare reaction: “Food allergy usually presents with multi-system involvement, most commonly cutaneous and gastrointestinal symptoms. Food allergy induced rhinitis is less common, and isolated rhinitis due to food allergy is extremely rare. Treatment for rhinitis due to food allergy is therefore rarely indicated.”

Eigenmann and James concur, “Chronic or recurrent rhinitis, mostly in pre-school children, is sometimes associated to allergic reactions mostly to milk. While some
patients claim of a significant decrease of the symptoms on an avoidance diet, a clear relation has not been reproduced by validated studies. Some patients also link consumption of milk-protein-containing products to increased amounts of secretion of the nose and the upper respiratory tract. Again there is no evidence of an allergy-related mechanism.”65
Section II. Incidence and Prevalence of different types of food allergies; including the symptoms and natural history of different types

Introduction to Key Questions B, C, D, and E

The Key Questions B-E are thematically related in that they concern issues about estimation of incidence, prevalence, symptoms, natural history, and co-morbid conditions in the general population. For this reason, the selection of articles for review is critically dependent on the sample of patients contributing data to the article and the degree to which conclusions about the general population may be inferred. In this case, as described in the section entitled “Refinement of Key Questions,” the general population of interest for this report is the US and Canada. Because genetic or environmental factors are likely important in determining factors such as incidence, prevalence, and natural history, and these factors certainly vary from country to country, the EPC was directed to restrict the articles to those from the US or Canada. A list of non-US/Canada articles identified but not included in this synthesis, their titles, and the countries of origin, is included in Appendix E.

In addition to restriction based on country of origin, how a sample of patients is selected is vitally important in being able to draw conclusions about the general population. From what population the subjects were sampled, and the degree to which people sampled actually participated in the study (the dropout rate), are the two most important factors in determining the validity of applying the results from a study to the population as a whole. Ideally, a random sample of US and/or Canadian residents would be selected for study and all or nearly all would agree to participate. As the population from which the sample is drawn is more restricted, and as the dropout rate rises, inference to the general population becomes more problematic. No universally agreed upon threshold defines how big the dropout rate or how narrow the sample population can be; however, in general, dropout rates above 30 percent (i.e., retention rates below 70 percent) are a cause for concern, and most authorities would require at a minimum that the sampled population represent a community. Thus, studies that assess factors such as incidence, prevalence, and natural history within a defined geographic region – such as a state or a city or a metropolitan statistical area, in general, have greater validity as estimates of the population parameters than studies that assess samples of patients derived from a particular clinic or hospital. For this synthesis, we aimed to include studies with samples drawn from a recognizable community-based population, and did not include studies of patients from single clinics or hospitals. When no community-based studies were available for certain key questions, we relaxed this requirement and summarized the available data from hospital/clinic studies, and supplied the appropriate caveat that inference to the general population is problematic.
A third critical factor when considering studies of incidence, prevalence, natural history, and risk factors is the criteria used to make the diagnosis. In the case of food allergies, the diagnostic criteria varied in the identified articles from symptoms (assessed by direct questioning, survey, or by proxy) to skin prick tests or serum IgE or IgG levels (the latter with thresholds that varied from article to article in terms of making the diagnosis), to food challenges, to medical record review, to ICD codes in administrative databases. Each of these methods has certain advantages and limitations. Patient and parent report of symptoms with ingestion of various foods does not correlate well with other tests for food allergies. Wood and colleagues used dietary questionnaires to assess symptoms of possible food allergy in 457 young adults who were part of a population-based epidemiologic cohort, and then also assessed these same young adults with skin prick testing (SPT). Twenty-two percent of subjects reported an illness to food nearly every time they ate it, with dairy products, fruits, and seafood topping the list. Thirteen percent of subjects were sensitized to at least one food allergen extract, with peanut, shrimp, and whole grain topping the list. Only seven subjects who reported illness in response to a food had a positive SPT to the same food. In a study of cow’s milk allergy, Eggesbo and colleagues compared children with a parentally perceived reaction to milk to children with a parentally perceived reaction to egg and to children with no perceived reaction to food. All children were then subjected to a diagnostic test protocol, which included SPT, egg- and milk-specific Serum IgE, and food challenges. Among 54 children with parentally perceived reactions to milk, 33 percent had cow’s milk allergy confirmed or deemed “possible.” Among 32 children with parentally perceived reactions to egg (but not milk), one had cow’s milk allergy identified on double blind placebo-controlled food challenge (DBPCFC) and two other children had “possible” cow’s milk allergy. Among 17 children with no parentally perceived reaction to food, one had a positive DBPCFC reaction to cow milk. In a study of 15 patients with DBPCFC sensitivities to cow’s milk, egg, wheat and rye flour, none had a positive skin prick test or specific IgE to food. Consequently, different criteria for the diagnosis of food allergy will identify different proportions of subjects as allergic. We did not exclude articles based on their method of making the diagnosis. However, the results of studies vary by the diagnostic criteria used, which then limits the conclusions that can be drawn.

**Description of the Evidence**

For these key questions, we identified 415 articles from our overall literature search, which was unrestricted to country of origin. Of these, 92 were from the US or Canada, 58 were the United Kingdom, Australia, or New Zealand, 185 were from Scandinavia or Europe, 31 were from the Mediterranean countries, 20 were from Japan, Korea, or China, and 34 were from other countries. Among the 92 from the US or Canada, 48 contained data from community-based populations. Two recent studies were available only as abstracts and were therefore excluded. Across all studies, the largest proportion concerned multiple food allergies, followed by roughly equal proportions of studies solely about cow’s milk allergy syndrome, asthma and eczema, and then only a small number of studies about any other condition.
Key Question B/C: What are the incidence/prevalence of IgE-mediated food allergy and immunologic but non-IgE-mediated adverse reactions to food?

i. Incidence and prevalence in the adult and pediatric populations
ii. Incidence and prevalence for specific foods
iii. Age- or gender-specific changes in specific foods

Prior Systematic Reviews and Meta-Analyses

We identified two prior systematic reviews/meta-analyses relevant to these key questions, using the criteria proposed by Whitlock and colleagues. Both publications resulted from the same literature search and screening process, which was comprehensive and in general followed the methods used by the Cochrane Collaboration. MEDLINE, EMBASE, and the Cochrane Database were searched using multiple key words from 1990-2005. Articles were selected if they included data about the prevalence of food allergies from community-based populations; articles from clinic-based populations and articles that estimated the proportion of patients with asthma, eczema, or allergic rhinitis due to food allergy were excluded. Both publications scored acceptably on the AMSTAR criteria for evaluating systematic reviews. Details of each publication are presented in Table 8. Although studies from numerous countries were included, and data from the US and Canada were not reported separately, we nevertheless discuss the results of these systematic reviews/meta-analyses here, and then compare and contrast their findings with the more limited data from original research studies based in the US.

The first publication from this effort was a meta-analysis of the prevalence of food allergy overall, stratified by adults and by children, and separate analyses of the prevalence for each of the five main foods: cows’ milk, hen’s egg, peanut, fish, and shellfish. Data were further stratified by the method used to establish the diagnosis of food allergy: self-report, sensitization (either skin prick test or serum IgE levels), or DBPCFC. Data were pooled across studies, although the authors acknowledge that for most pooled analyses, there was substantial heterogeneity in the results. Given that caveat, the authors report a pooled overall prevalence of 13 percent and 12 percent for adults and for children, respectively, of self-report of food allergy to any food. Note that these numbers plus all others reported here were taken from the authors’ graphs, in that the numerical pooled result was not actually presented in the publication. Pooled results for allergy to any food were far lower when assessed by sensitization or food challenge, being about three percent (data stratified by age were not reported). For specific foods, pooled results showed that prevalence was highest for milk (3.5 percent by symptoms, 0.6 percent by SPT, and 0.9 percent for food challenge) and lowest for fish (0.6 percent by symptoms, 0.2 percent by SPT, and 0.3 percent by food challenge) (Table 8). Again, it is worth noting that for most pooled analyses, there was statistically significant heterogeneity in the results, indicating unexplained differences between studies, and
additionally, the 95% confidence intervals for many pooled results were quite wide, indicating a lack of precision in the estimate. The authors note the need for better data and suggest that future studies should use similar methods to minimize the influence of different methods on the results seen across studies.

The second publication presented this group’s findings for other foods of interest: fruits, vegetables/legumes, tree nuts, wheat, and soy. Additional data on cereals and seeds were presented in an online supplement. Data in most cases were summarized narratively, presenting ranges of prevalence reported in different studies. Results are summarized in Table 8. In general, as with the previous analysis, the prevalence of food allergy was much higher when assessed using self-report than when using sensitization or food challenge. Reported prevalence for these foods was much lower than for the five foods in their prior assessment.

In sum, prior acceptable quality systematic reviews (from the same literature search) found that the prevalence of food allergy overall and allergy to specific foods varied depending on the definition used, and even within the same definition, estimates of prevalence varied widely. Improving the knowledge base on this topic will require better agreement on an acceptable definition of food allergy for use in studies of prevalence.
### Table 8: Systematic Reviews and Meta-Analyses of the Prevalence of Food Allergies

<table>
<thead>
<tr>
<th>Author/ Year</th>
<th>Study Question</th>
<th>Food Allergies Included</th>
<th>Databases Searched/ Years</th>
<th>Excludes</th>
<th>Total Publications Included</th>
<th>AMSTAR Criteria</th>
<th>Prevalence of food allergy</th>
<th>Findings</th>
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<td>Rona, 2007 †</td>
<td>To assess the prevalence of food allergy</td>
<td>Cow’s Milk Hen’s Egg Peanut Fish Shellfish</td>
<td>Medline, EMBASE Cochrane 1990-2005</td>
<td>Prevalence of food allergy in asthma, eczema, or allergic rhinitis; estimates from selected populations not representative of a community</td>
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<td>Overall</td>
<td>Peanut</td>
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**Self Report of Symptoms**

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<th>Adults</th>
<th>All Ages</th>
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<td>Overall</td>
<td>12%</td>
<td>13%</td>
<td>0.75% 3.5%* 1% 0.6% 1.1%</td>
</tr>
</tbody>
</table>

**Symptoms and Skin Prick Test or Serum IgE**

<table>
<thead>
<tr>
<th></th>
<th>All Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3% 0.75% 0.6% 0.9% 0.2% 0.6%</td>
</tr>
</tbody>
</table>

**Meta-Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.22% (Symptoms) 0.1% (Symptoms) N.E.</td>
<td>0.4% (symptoms) 2% (sensitization) N.E.</td>
</tr>
</tbody>
</table>

Note: Almost all analyses had marked heterogeneity and wide 95% confidence intervals, indicating unexplained differences between studies.

* Greater prevalence in children than adults, not specifically estimated but it appears to be about 6-7 percent in children and 1-2 percent in adults.

N.E. Not estimated
Data from US National Studies

We next describe the prevalence data from US studies that included representative samples of the entire population. (We did not identify any national Canadian studies). No studies were identified that assessed the prevalence of cow’s milk or egg allergy.

Peanut or tree nut allergy

We identified two US studies of prevalence of peanut or tree nut allergy.71, 72 The two studies were from a nationwide, cross-sectional telephone interview of households. A random sampling of telephone numbers was generated by computer. A preliminary study71 was conducted between April and June 1997 and a subsequent larger study72 was conducted from June to August 2002. The results from the 2002 study were similar to those of the 1997 study. In the 2002 study, a total of 9,252 households were contacted; 4,397 refused to participate or were ineligible for the study (language barrier or confusion about the study). A total of 4,855 households representing 13,493 individuals participated in the study. The participation of barely over half the families contacted is a limitation of this study. A total of 155 (3.2 percent of households) reported one or more individual with peanut allergy, tree nut allergy or both. The authors reported the prevalence of peanut and tree nut allergy by age, race, and, gender:
## Table 9: Prevalence of peanut and tree nut allergy in 2002 by age

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Sample Population, n = 13,493</th>
<th>Any nut*</th>
<th>Both peanut and TN</th>
<th>Isolated peanut</th>
<th>Isolated TN</th>
<th>Unspecified nut</th>
<th>% (95% CI)</th>
<th>% (95% CI)</th>
<th>% (95% CI)</th>
<th>% (95% CI)</th>
<th>% (95% CI)</th>
<th>% (95% CI)</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 y</td>
<td>869</td>
<td>9</td>
<td>1.0 (0.4-1.7)</td>
<td>1</td>
<td>0.1 (0.0-0.3)</td>
<td>7</td>
<td>0.8 (0.2-1.4)</td>
<td>1</td>
<td>0.1 (0.0-0.3)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-10 y</td>
<td>851</td>
<td>9</td>
<td>1.1 (0.4-1.8)</td>
<td>2</td>
<td>0.2 (0.0-0.6)</td>
<td>5</td>
<td>0.6 (0.1-1.1)</td>
<td>2</td>
<td>0.2 (0.0-0.6)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-17 y</td>
<td>1228</td>
<td>10</td>
<td>0.8 (0.3-1.3)</td>
<td>4</td>
<td>0.3 (0.0-0.6)</td>
<td>2</td>
<td>0.2 (0.0-0.4)</td>
<td>3</td>
<td>0.2 (0.0-0.5)</td>
<td>1</td>
<td>0.1 (0.0-0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-20 y</td>
<td>579</td>
<td>5</td>
<td>0.9 (0.1-1.6)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0.5 (0.0-1.1)</td>
<td>2</td>
<td>0.4 (0.0-0.8)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-30 y</td>
<td>1491</td>
<td>19</td>
<td>1.3 (0.7-1.8)</td>
<td>3</td>
<td>0.2 (0.0-0.4)</td>
<td>6</td>
<td>0.4 (0.1-0.7)</td>
<td>10</td>
<td>0.7 (0.3-1.1)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-40 y</td>
<td>1556</td>
<td>18</td>
<td>1.2 (0.6-1.7)</td>
<td>3</td>
<td>0.2 (0.0-0.4)</td>
<td>7</td>
<td>0.5 (0.1-0.8)</td>
<td>7</td>
<td>0.5 (0.1-0.8)</td>
<td>1</td>
<td>0.1 (0.0-0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-50 y</td>
<td>1809</td>
<td>19</td>
<td>1.1 (0.6-1.5)</td>
<td>4</td>
<td>0.2 (0.0-0.4)</td>
<td>4</td>
<td>0.2 (0.0-0.4)</td>
<td>10</td>
<td>0.6 (0.2-0.9)</td>
<td>1</td>
<td>0.1 (0.0-0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-60 y</td>
<td>1352</td>
<td>24</td>
<td>1.8 (1.1-2.5)</td>
<td>8</td>
<td>0.6 (0.2-1.0)</td>
<td>6</td>
<td>0.4 (0.1-0.8)</td>
<td>6</td>
<td>0.4 (0.1-0.8)</td>
<td>4</td>
<td>0.3 (0.0-0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61-64 y</td>
<td>355</td>
<td>7</td>
<td>2.0 (0.5-3.4)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.3 (0.0-0.8)</td>
<td>5</td>
<td>1.4 (0.2-2.6)</td>
<td>1</td>
<td>0.3 (0.0-0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 y</td>
<td>1345</td>
<td>22</td>
<td>1.6 (1.0-2.3)</td>
<td>2</td>
<td>0.2 (0.0-0.4)</td>
<td>6</td>
<td>0.5 (0.1-0.8)</td>
<td>9</td>
<td>0.7 (0.2-1.1)</td>
<td>5</td>
<td>0.4 (0.1-0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child (&lt;18 y), age not specified</td>
<td>179</td>
<td>9</td>
<td>5.0 (1.8-8.3)</td>
<td>2</td>
<td>1.2 (0.0-2.7)</td>
<td>3</td>
<td>1.7 (0.0-3.6)</td>
<td>1</td>
<td>0.6 (0.0-1.7)</td>
<td>3</td>
<td>1.7 (0.0-3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult (&gt;18 y), age not specified</td>
<td>1394</td>
<td>12</td>
<td>0.9 (0.4-1.4)</td>
<td>3</td>
<td>0.2 (0.0-0.5)</td>
<td>2</td>
<td>0.1 (0.0-0.3)</td>
<td>1</td>
<td>0.1 (0.0-0.2)</td>
<td>6</td>
<td>0.4 (0.1-0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age not known</td>
<td>485</td>
<td>3</td>
<td>0.6 (0.1-1.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>13493</td>
<td>166</td>
<td>1.2 (1.0-1.4)</td>
<td>32</td>
<td>0.2 (0.0-0.3)</td>
<td>52</td>
<td>0.4 (0.3-0.5)</td>
<td>57</td>
<td>0.4 (0.3-0.5)</td>
<td>25</td>
<td>0.2 (0.1-0.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table adapted from Sicherer, 2003\(^2\)
Peanut allergy was noted in 0.4 percent of the population, while allergy to any nut was reported as 1.2 percent. Although the rate of allergy was reported lowest among black subjects, it was not significantly lower than that among white subjects (p=0.25). There is an overall predominance of peanut/tree nut allergy reported in children compared with adults (p=0.02) and, among adults, predominance among females (p=0.0008). In contrast, in children, allergy to any nut was higher among males.
Table 10: Prevalence of peanut and tree nut allergy by race, ethnicity, and sex by age

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Population</th>
<th>Any nut*</th>
<th>Both peanut and TN</th>
<th>Isolated peanut</th>
<th>Isolated TN</th>
<th>Unspecified nut</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>White</td>
<td>9867</td>
<td>113</td>
<td>0.3 (0.2-0.4)</td>
<td>37</td>
<td>0.4 (0.3-0.5)</td>
<td>42</td>
</tr>
<tr>
<td>Black</td>
<td>1222</td>
<td>9</td>
<td>0.3 (0.0-0.5)</td>
<td>2</td>
<td>0.2 (0.0-0.4)</td>
<td>1</td>
</tr>
<tr>
<td>Hispanic</td>
<td>765</td>
<td>10</td>
<td>0.3 (0.0-0.6)</td>
<td>3</td>
<td>0.4 (0.0-0.8)</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>825</td>
<td>12</td>
<td>0.6 (0.1-1.1)</td>
<td>5</td>
<td>0.7 (0.2-1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Not Reported</td>
<td>814</td>
<td>22</td>
<td>0.5 (0.0-1.0)</td>
<td>4</td>
<td>0.3 (0.0-0.6)</td>
<td>15</td>
</tr>
<tr>
<td>Sex/age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (&lt;18 y)</td>
<td>1526</td>
<td>26</td>
<td>0.26 (0.01-0.52)</td>
<td>15</td>
<td>0.98 (0.49-1.48)</td>
<td>5</td>
</tr>
<tr>
<td>Female (&lt;18 y)</td>
<td>1473</td>
<td>10</td>
<td>0.27 (0.01-0.54)</td>
<td>3</td>
<td>0.20 (0.00-0.43)</td>
<td>2</td>
</tr>
<tr>
<td>Male (&gt;18 y)</td>
<td>4338</td>
<td>37</td>
<td>0.16 (0.04-0.28)</td>
<td>12</td>
<td>0.28 (0.12-0.43)</td>
<td>15</td>
</tr>
<tr>
<td>Female (&gt;18 y)</td>
<td>4962</td>
<td>82</td>
<td>0.32 (0.16-0.48)</td>
<td>22</td>
<td>0.44 (0.26-0.63)</td>
<td>35</td>
</tr>
</tbody>
</table>

Table adapted from Sicherer, 2003

58
The authors reported the symptoms of peanut or tree allergy as follows: throat tightness, 53 percent; dyspnea, 41 percent; wheezing, 29 percent; angioedema, 51 percent; urticaria, 47 percent; vomiting, 17 percent; diarrhea, 6 percent; and loss of consciousness, 6 percent.

**Seafood allergy**

We identified one US study of the prevalence of seafood allergy. The study was a nationwide, cross-sectional telephone interview of households. A random sampling of telephone numbers was generated by computer. The study was conducted between October and December, 2002. A total of 10,966 households were contacted; 3,585 refused to participate, and an additional 1,592 were ineligible (language barrier, confusion, and hearing problems). A total of 5,789 households (67.3 percent participation rate) representing 14,948 individuals participated in the study. A total of 327 households (5.9 percent) reported one or more individual with allergy to seafood. The authors reported the prevalence of fish, shellfish, and seafood allergy by age, race, and, gender (Table 11).

Table 11: Prevalence of seafood allergy by race/ethnicity and sex/age

<table>
<thead>
<tr>
<th>Age</th>
<th>Type of allergy</th>
<th>Fish</th>
<th>% (95% CI)</th>
<th>Shellfish</th>
<th>% (95% CI)</th>
<th>Both fish and shellfish</th>
<th>% (95% CI)</th>
<th>Any seafood</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sample Population, n = 14,498</td>
<td>Fish</td>
<td>11176</td>
<td>28</td>
<td>0.3 (0.2-0.4)</td>
<td>197</td>
<td>1.8 (1.5-2.0)</td>
<td>12</td>
<td>0.1 (0.0-0.2)</td>
<td>213</td>
</tr>
<tr>
<td>White</td>
<td>Shellfish</td>
<td>1508</td>
<td>16</td>
<td>1.1 (0.6-1.7)</td>
<td>47</td>
<td>3.1 (2.3-4.1)</td>
<td>7</td>
<td>0.5 (0.2-1.2)</td>
<td>56</td>
</tr>
<tr>
<td>Other</td>
<td>Both fish and shellfish</td>
<td>1909</td>
<td>11</td>
<td>0.6 (0.3-1.0)</td>
<td>41</td>
<td>2.2 (1.6-2.9)</td>
<td>4</td>
<td>0.2 (0.0-0.5)</td>
<td>48</td>
</tr>
<tr>
<td>Refused/Not Reported</td>
<td>Any seafood</td>
<td>355</td>
<td>3</td>
<td>0.9 (0.2-2.5)</td>
<td>18</td>
<td>5.0 (3.0-7.8)</td>
<td>2</td>
<td>0.6 (0.0-2.0)</td>
<td>19</td>
</tr>
<tr>
<td>Male (&lt;18 y)</td>
<td>Fish</td>
<td>1936</td>
<td>4</td>
<td>0.2 (0.0-0.4)</td>
<td>13</td>
<td>0.7 (0.3-1.0)</td>
<td>2</td>
<td>0.1 (0.0-0.3)</td>
<td>15</td>
</tr>
<tr>
<td>Female (&lt;18 y)</td>
<td>Shellfish</td>
<td>1726</td>
<td>3</td>
<td>0.2 (0.0-0.4)</td>
<td>7</td>
<td>0.4 (0.1-0.7)</td>
<td>2</td>
<td>0.1 (0.0-0.3)</td>
<td>8</td>
</tr>
<tr>
<td>Male (&gt;18 y)</td>
<td>Both fish and shellfish</td>
<td>5018</td>
<td>11</td>
<td>0.2 (0.1-0.4)</td>
<td>93</td>
<td>1.9 (1.5-2.2)</td>
<td>5</td>
<td>0.1 (0.0-0.2)</td>
<td>99</td>
</tr>
<tr>
<td>Female (&gt;18 y)</td>
<td>Any seafood</td>
<td>5726</td>
<td>39</td>
<td>0.7 (0.5-0.9)</td>
<td>183</td>
<td>3.2 (2.7-3.7)</td>
<td>15</td>
<td>0.3 (0.1-0.4)</td>
<td>207</td>
</tr>
</tbody>
</table>

The total lifetime prevalence rate for reported seafood allergy in the total populations was 2.3 percent, and it was 0.4 percent, 2.0 percent, and 0.2 percent for fish allergy, shellfish allergy, and both, respectively. The rates for children were significantly lower than for adults, as follows: fish allergy, 0.2 percent versus 0.5 percent (p=0.02); shellfish allergy, 0.5 percent versus 2.5 percent (p<0.001); and any seafood allergy, 0.6 percent versus 2.8 percent (p=0.001). Female subjects reported a higher rate of shellfish (2.6 percent vs. 1.5 percent, P<0.001) and fish allergy (0.6 percent vs. 0.2 percent, p<0.001) than male subjects. However, the differences in prevalence rate by age and sex indicate a tendency toward a higher rate of seafood allergy in boys compared with girls (0.8 percent vs. 0.5 percent, P=NS) and women compared with men (3.6 percent vs.
2.0 percent, p<0.001). Regarding race or ethnicity, the highest rates of seafood allergy were reported in black subjects.

The authors reported the symptoms of shellfish allergy as follows: urticaria, 60 percent; edema, 70 percent; vomiting, 20 percent; diarrhea, 21 percent; cough, 19 percent; dyspnea, 54 percent; wheezing, 32 percent; oral pruritis, 39 percent; throat tightness, 51 percent; and lightheadedness, 34 percent. Multiple reactions commonly occurred in each subject.

The authors reported the symptoms of finfish allergy as follows: urticaria, 69 percent; edema, 71 percent; vomiting, 27 percent; diarrhea, 23 percent; cough, 23 percent; dyspnea, 48 percent; wheezing, 47 percent; oral pruritis, 52 percent; throat tightness, 62 percent; and lightheadedness, 45 percent. Multiple reactions commonly occurred in each subject.

Two additional studies deserve mention here because they analyze national US databases for issues related to food allergy. In the first, investigators at the Center for Food Safety and Applied Nutrition analyzed data from the Infant Feeding Practices Study II, a longitudinal national mail survey of pregnant women who gave birth to a healthy single child of at least 35 weeks duration, beginning in the third trimester of pregnancy and periodically thereafter up to age 1 of the infant. In this analysis, probable food allergy was defined as a doctor-diagnosed food allergy or food-related symptoms of swollen eyes or lips or hives. In this study of 2441 mothers, 60 percent completed all serial questionnaires with detailed questions about problems with food. About 500 infants were characterized as having a food-related problem, and 143 were classified as probable food allergy. Infants were statistically significantly more likely to be classified as “probable food allergy” if they had a family history of food allergy, were male, black, or live in a rural or urban (as opposed to suburban) area on univariate analysis. Multivariate analyses were not reported.

The second study was a National Center for Health Statistics data brief that used data from both the 2007 National Health Intervention Survey (NHIS) and the 1998-2006 National Hospital Discharge Survey (NHDS) to estimate the prevalence of food allergy in children and number of hospital discharges for children. Both national databases are probability samples which when weighted can produce national estimates. ICD codes for allergic rhinitis due to food, allergic gastroenteritis and colitis, contact dermatitis due to skin contact, dermatitis due to foods taken internally, and anaphylaxis shock with specific codes for peanuts, fish etc, and food additives were included. While contact dermatitis and reactions due to food additives are outside the scope for this report, because this study reports national data and because the cases are likely to represent a minority of the sample, we include it here, but note the inclusion of these other conditions as a potential limitation.

The national estimate for the prevalence of food allergy in children was 3.9 percent, with higher prevalence in children less than 5 (4.7 percent) than others aged 5-17 years (3.7 percent). Prevalence in girls and boys was similar (4.1 percent vs. 3.8 percent, respectively). Rates in Hispanics were lower than in non-Hispanic whites or blacks (3.1 percent vs. 4.1 percent and 4.0 percent, respectively). Comparing these data to those collected back to 1997 showed a

2 “Food Allergy was assessed by an affirmative answer to the signle question “During the past 12 months, has (child) had any kind of food or digestive allergy?”
A statistically significant upward trend, from about 3.5 percent to 3.9 percent. Children classified as having food allergy also reported having asthma (29 percent), eczema or skin allergy (27 percent), or respiratory allergy (32 percent). The national estimate of hospital discharges was 9,537 per year, and this represented a more than 3-fold increase since 1998-2000. However, as the authors note, increases could be due to increased awareness or reporting, or a real increase in children experiencing food-related reactions.

Lastly, as this report was being finalized a new publication appeared that assessed several different national US surveys (National Health Interview Survey, National Hospital Ambulatory Medical Case Survey, National Hospital Discharge Survey, and National Health and Nutrition Examination Survey). These surveys used self-report, utilization data, and food-specific IgE. The surveys estimated the prevalence of food allergy in the US at 3.3 percent in 1997 and 3.9 percent in 2007, and in 2005-2006 9.3 percent, 6.7 percent, 12.2 percent, and 5.2 percent of children had serum IgE to peanut, egg, milk, and shrimp, respectively. The author concludes that there are increasing reports of food allergy in the US, although data are unable to establish how much is due to increased awareness and how much to a true increase in clinical disease.

Comparison of US national studies with Prior Meta-Analyses

In Table 12, we present the data from the multinational meta-analysis with the data from the US National Studies. Some of the estimates from the two sources are similar for some foods; for example, shellfish has an estimated prevalence based on symptoms of 0.99 percent, 1.20 percent, and two percent from three different studies. For other foods, the estimated prevalence based on symptoms of allergy to cow’s milk was three percent in the meta-analysis but 0.40 percent in the US National Study. The extent to which this and other differences are due to true differences in prevalence in the US compared to other countries or due to differences in the way food allergy is measured is unknown.

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Specific Foods</th>
<th>Milk</th>
<th>Eggs</th>
<th>Peanut</th>
<th>Tree nut</th>
<th>Shellfish</th>
<th>Fish</th>
<th>Fruits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuidmeer, 2008</td>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin Prick</td>
<td></td>
<td></td>
<td></td>
<td>0-4.1%</td>
<td>0.01-4.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgE Challenge</td>
<td></td>
<td></td>
<td></td>
<td>0.1-4.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rona, 2007</td>
<td>Symptoms</td>
<td>3%</td>
<td>1%</td>
<td>0.60%</td>
<td>1.20%</td>
<td>0.60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin Prick</td>
<td>0.60%</td>
<td>0.90%</td>
<td>0.90%</td>
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<td>IgE Challenge</td>
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<tr>
<td></td>
<td>Test</td>
<td>0.90%</td>
<td></td>
<td>0.30%</td>
<td>0.90%</td>
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<tr>
<td>Sicherer, 2004</td>
<td>Symptoms</td>
<td></td>
<td>2%</td>
<td></td>
<td>0.60%</td>
<td>0.60%</td>
<td></td>
<td>0.40%</td>
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<tr>
<td></td>
<td>Skin Prick</td>
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<td></td>
<td>IgE Challenge</td>
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<td></td>
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Anaphylaxis

We next describe a discrete body of literature that assessed the incidence of anaphylaxis related to food from US representative samples. This assessment comprised seven articles, which all used administrative databases or medical record review to identify cases of anaphylaxis (Table 13).

The first study used medical records to assess all 133 persons having an anaphylactic event in Olmsted County, Minnesota (MN) from 1983 to 1987. The diagnosis of anaphylaxis was made on the basis of at least one symptom of “generalized mediator release” (flushing, pruritis, urticaria, etc) and one symptom involving the oral/gastrointestinal tract, respiratory, or cardiovascular system. The authors found a rate of 30 cases per 100,000 person-years. In 36 percent of cases, an “ingestant” was identified as the trigger. The implicated foods were fish, shellfish, tree nuts, eggs, peanuts, and seeds.

The second study was a retrospective cohort study that examined the management of food related acute allergic reactions as part of the Multicenter Airway Research Collaboration (MARC), a division of the Emergency Medicine Network (EMNet). Chart reviews of Emergency Department (ED) visits for food allergy at 21 EDs in 9 US states and four Canadian provinces were performed. Cases with ICD-9 codes specifying diagnoses of dermatitis due to food, allergy due to unspecified food, allergy due to specified foods, other anaphylactic shock, and allergy, unspecified were included. Anaphylaxis cases were further identified using specific criteria determined by the authors to define the condition. These criteria included involvement of two or more organ systems from a specified list as well as automatic inclusion of the case as anaphylaxis if hypotension (systolic blood pressure (BP) less than 100 millimeters (mm) mercury (Hg)) was present. Overall, the screening process identified and reviewed in detail the records of 678 patients from 5,296 charts identified as carrying a diagnosis of an acute allergic reaction to food.

The third study assessed cases of anaphylaxis in persons aged up to 18 years who were members of Group Health Cooperative, a health maintenance organization (HMO) in Washington state. Using an algorithm that assessed symptoms, timing, and response to treatment, the authors searched administrative databases to indentify possible cases of anaphylaxis, which they then reviewed in more detail using the medical record. The authors found 67 cases of anaphylaxis for a rate of 10.5 cases per 100,000 person-years. A food trigger was identified in 51 percent of cases.

The fourth article was a cross sectional study of patients hospitalized for anaphylaxis in Florida in 2001. Data from the Florida Agency for Health Care Administration were used, which includes almost all non-federal Florida hospitals. To be included in the study a record needed to have an ICD-9 code with a principal diagnosis of anaphylactic shock, allergic shock,
anaphylactic reaction, anaphylaxis not otherwise specified or due to the adverse effect of a correct medicinal substance that was administered properly, anaphylactic shock due to an adverse reaction to a nonpoisonous food, anaphylaxis due to anesthesia, or toxic effect of other substances (including venom). A total of 464 cases were identified in the study, 363 of which were classified as white non-Hispanic. Using this total figure and Florida’s estimated population in 2001, an incidence of 2.8 hospitalizations for anaphylaxis per 100,000 population was calculated. A rate of 19.8 cases of anaphylaxis per 100,000 patients hospitalized for all causes was also tabulated. Food-related cases made up 75 of the 464 cases of anaphylaxis (16 percent). The overall incidence of hospitalizations for anaphylaxis increased with age, although specific values were not cited.79

The fifth study was designed as a retrospective cohort to characterize anaphylaxis hospitalizations in New York State in patients younger than 20 years. The Statewide Planning and Research Cooperative System (SPARCS) database, which contains information about all New York State acute care hospitalizations, was used to extract data. Using ICD-9 codes, cases in which anaphylaxis, as well as angioedema, urticaria, or ‘allergy unspecified’ were the principal diagnoses were identified. The authors reported finding 1,972 cases of anaphylaxis in persons younger than 20 years over the study period, 22 percent of whom were black youth. The incidence of anaphylaxis increased over the study period from 1 per 100,000 person years in 1990 to 4.7 per 100,000 person years in 2006. About 66 percent or 1302 of the cases of anaphylaxis were food related.80

The last study was a retrospective cohort study attempting to identify cases of anaphylaxis occurring in patients living in Rochester, MN between 1990 and 2000. Data were extracted from the records of the Rochester Epidemiology Project, which links and indexes the records of almost all of the medical providers in Olmsted County, MN. Cases of anaphylaxis were initially identified using ICD-9 codes. These cases were then reviewed further to confirm cases of anaphylaxis using predefined criteria. There were 211 cases of anaphylaxis identified, which led to a calculated incidence of 49.8 per 100,000 person years. Of these 211 cases of anaphylaxis, 75 were determined to be food related (36 percent). Blacks accounted for six cases, and Hispanic persons accounted for one case of the 211 total cases. The incidence of adult cases of anaphylaxis was found to be 42 per 100,000 person years compared to the incidence of pediatric cases of 70 per 100,000 person years.81

The most recent study used data from the National Electronic Injury Surveillance System (NEISS) to demonstrate, in a self-described pilot study, the feasibility of estimating food allergic and anaphylactic events resulting in visits to US emergency departments.82 NEISS collects data from 98 hospital EDs that are geographically distributed throughout the US, have at least six beds, and provide 24 hour emergency services. Psychiatric and penal institutions are excluded. NEISS represents a stratified probability sample that can use weights to estimate use in EDs across the country. Two months of data (August-September 2003) were used in this pilot study. Medical records were reviewed to identify food-related adverse events. Symptom key words (flushing, rash, pruritus, wheeze) as well as voice hoarseness, congestion, sneezing, etc. were used combined with medical record indication of “food allergic reaction” and no mention of food spoilage, food poisoning, medication use, gastrointestinal infection, etc. From cases so identified, additional information was extracted. This study identified 173 visits meeting their criteria, of
which 23 were for anaphylaxis. Using their population weights, the author estimated that across
the US, during this 2 month period, there were 2,333 visits to EDs for food related anaphylaxis.
Using a US population estimate of about 300 million, this yields an incidence estimate of about
4-6 cases/100,000 person-years. Of these 23 cases, fish or shellfish were implicated in 8 and
nuts were implicated in 7. Children/teenagers accounted for 43 percent of anaphylactic events.
Interestingly, epinephrine was given in only 62 percent of anaphylactic events (antihistamines
were given in 86 percent).

Although not from a representative sample, two additional articles are noted here because of the
specific focus on severe anaphylactic reactions or death due to foods. Sampson and colleagues
reported on 13 children aged 2-17 years, six of whom died and seven who nearly died. Peanuts
were responsible in four patients, other nuts in six patients, eggs in one patient, and milk in two
patients. In a subsequent article, Bock, Munoz-Furlong and Sampson reported on an additional
32 deaths. Nearly all were caused by peanut or nuts.

In summary, seven studies found wide differences in the rates of hospitalization or ED visits for
anaphylaxis, as assessed by ICD codes or medical record review, from 1/100,000 population to
as high as 70/100,000 population. These differences may be due to differences in the study
methods or differences in the populations (Florida, New York, Washington, Minnesota). The
proportion of anaphylaxis cases thought to be due to foods also varied from 16 percent to 35
percent to 51 percent to 65 percent, depending on the study. One study reported that the number
of hospitalizations for anaphylaxis increased with increasing age, while another study reported
total cases of anaphylaxis were almost twice as high in children as in adults. We identified no
estimate of the incidence of anaphylaxis in a population that could be representative of the US
population as a whole, although a recent pilot study demonstrated the potential to estimate the
incidence of anaphylaxis that presents to US emergency departments. In case series of deaths in
the US, nearly all were attributed to peanuts or nuts.
Table 13: US Studies of the Incidence of Anaphylaxis due to Food

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design</th>
<th>Population</th>
<th>Years of Inclusion</th>
<th>Data sources</th>
<th>How Anaphylaxis Defined</th>
<th>Sample Size</th>
<th>Incidence of Anaphylaxis Overall / Food Related</th>
<th>Incidence of Anaphylaxis Adult / Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yocum, 1999</td>
<td>Cohort</td>
<td>Individuals residing in Olmstead County, Minnesota</td>
<td>1983-1987</td>
<td>medical record review</td>
<td>2 or more symptoms from a specified list</td>
<td>133</td>
<td>30 per 100,000 person-years; meal triggered</td>
<td>NS (not specified)</td>
</tr>
<tr>
<td>Clark, 2004</td>
<td>cohort</td>
<td>ED visits for acute food allergies in US and Canada</td>
<td>1999</td>
<td>medical record review</td>
<td>involvement of two or more organ systems from specified list</td>
<td>678</td>
<td>346 out of 678(51%) / 346 out of 678(51%)</td>
<td>NS (not specified)</td>
</tr>
<tr>
<td>Bohlke, 2004</td>
<td>cohort</td>
<td>children and adolescents to age 18, members of Group Health Cooperative HMO</td>
<td>1991-1997</td>
<td>medical record review</td>
<td>algorithm of organ systems involved and timing plus response to treatment</td>
<td>67</td>
<td>10.5 per 100,000 person-years; food trigger in 51%</td>
<td>All &lt; 19 years old</td>
</tr>
<tr>
<td>Mulla, 2007</td>
<td>cross sectional</td>
<td>hospitalizations for anaphylaxis in Florida</td>
<td>2001</td>
<td>hospitalized for anaphylaxis</td>
<td>ICD-9 codes</td>
<td>464</td>
<td>19.8 per 100,000 hospitalized / 75 out of 464</td>
<td>NS (not specified)</td>
</tr>
<tr>
<td>Lin, 2008</td>
<td>cohort</td>
<td>hospitalizations in NY State in patients younger than 20 years</td>
<td>1990-2006</td>
<td>administrative database</td>
<td>ICD-9 codes</td>
<td>4,341</td>
<td>1 per 100,000 person years (1990) - 4.7 per 100,000 person years (2006) / 1302 out of 1972</td>
<td>all &lt;20 years old</td>
</tr>
<tr>
<td>Decker, 2008</td>
<td>cohort</td>
<td>individuals residing in Rochester, Minnesota</td>
<td>1990-2000</td>
<td>administrative database</td>
<td>ICD-9 codes and specified list of symptoms</td>
<td>211</td>
<td>49.8 per 100,000 person-years / 75 out of 211</td>
<td>42 per 100,000 (adult) / 70 per 100,000 (pediatric)</td>
</tr>
<tr>
<td>Ross, 2008</td>
<td>cohort</td>
<td>ED visits to any of 98 hospital EDs that participate in the National Electronic Injury Surveillance System, which is a nationally representative probability sample of EDs in the US</td>
<td>August-September 2003</td>
<td>Medical Record Review</td>
<td>Specific keywords, use of phrase “food allergic reaction” no mention that symptoms were caused by food poisoning medication use, etc.</td>
<td>173 food allergic events; 23 anaphylaxis events</td>
<td>2,333 nationwide over 2 months; 4.6 per 100,000 person-years</td>
<td>44 percent of cases in children/teenagers</td>
</tr>
</tbody>
</table>

65
Key Question D/E: What are the symptoms and natural history of IgE-mediated and of immunologic but non-IgE mediated adverse reactions to food?

i. Symptoms and natural history

We identified no published studies from the US or Canada on the natural history of food allergy conditions that reported data from nationally representative or even community-based populations. The only published studies of natural history came from selected populations, usually from a single clinic or hospital. Such patient populations may not be representative of the general patient population with a specific food allergy. Nonetheless, to assist the NIAID and the Expert Panel, we summarize here the published studies we did identify, keeping in mind that their findings may not necessarily be extrapolated to all patients with the condition.

Cow’s milk allergy

We identified one US study on the natural history of IgE-mediated Cow’s Milk Allergy. All cases came from those seen between 1993 and 2004 by one of the authors. Among 1,368 patients with food allergy, 1,073 were diagnosed with milk allergy. Fifty-three patients with non-IgE mediated disease were excluded, and 213 patients were also excluded because they had only one visit. A retrospective record review and analysis was conducted for the remaining 807 patients. The diagnosis of Cow’s Milk Allergy was made on the basis of a history of symptoms clearly associated with exposure to milk, a positive oral food challenge, and/or clear improvement in eczema or other symptoms with milk avoidance. Determination of an IgE-mediated allergy was based on a skin prick test with a wheal diameter of 3 mm or greater and/or a Cow’s Milk-specific(s)IgE of 0.35 or greater kU/L (kiloUnits per liter, an arbitrary measure of reactivity in immunosorption assays for antigen-specific IgE).

The median age at the initial visit was 13 months, and patients were followed for a median of 54 months. About two-thirds of patients were male. Initial symptom presentation was as follows: skin (85 percent) including urticaria, angioedema, eczema, or other unspecific rash; gastrointestinal (46 percent) including vomiting, diarrhea, bloody stools, and/or gastroesophageal reflux; lower respiratory tract (14 percent) including wheezing, cough, stridor, or difficulty breathing; and upper respiratory tract (6 percent) including rhinitis and nasal congestion. About half of patients had one organ system affected, and half had more than one organ system affected.

Most patients had other atopic conditions: 49 percent had asthma, 40 percent had allergic rhinitis; and 71 percent had eczema. Nearly all patients (91 percent) had an allergy to another food in addition to cow’s milk (defined as having had a “clear symptomatic reaction to the food and/or having had a positive skin prick test or food-specific IgE level”): egg was most common at 79 percent, followed by peanut (73 percent), tree nut (51 percent), soy (41 percent), and wheat (35 percent).
These 807 patients underwent a total of 289 milk challenges, 68 of which were conducted at home and 221 were in the clinic. Three sets of criteria were used to define acquisition of milk tolerance: 1) passing a milk challenge, 2) passing a challenge or a Cow’s Milk sIgE level of less than 3 kU/L and no reaction in the last 12 months, and 3) a sIgE less than 15 kU/L and no reaction in the past 12 months. Using these three definitions, the proportion of patients who outgrew their allergy at 4 years was 5 percent, 19 percent, and 26 percent, respectively. The proportion who outgrew their allergy by 8 years was 21 percent, 42 percent, and 56 percent. Beyond 10 years, the number of assessed subjects dropped to under 100 (only 60 and 18 subjects were assessed at 12 and 16 years, respectively). Predictors of the acquisition of tolerance included lower peak IgE level (lower levels associated with greater acquisition of tolerance), the absence of asthma or allergic rhinitis, and never having been formula fed. Another US-based study also reported that the rate of decline of sIgE levels over time predicted the development of tolerance to cow’s milk in children with food-challenge-assessed cow’s milk allergy, albeit in a highly selected patient population.

**Tree Nut Allergy**

We identified one US study on the natural history of tree nut allergy. All cases came from a retrospective chart review of patients from a university-based pediatric allergy clinic. The diagnosis of tree nut allergy was made if the patient had a clear-cut history of an allergic reaction on ingestion and a confirmation positive test response for tree nut IgE or a history of a positive tree nut SPT or positive tree nut IgE level of greater than 0.35kU/L without a history of ingestion. Cases meeting this definition were then invited for DBPCFC if they are 4 years of age or older and had a current tree nut IgE level of less than 10kU/L and no history of an acute reaction in the past year. A total of 278 patients were enrolled, of which 65 percent of whom were males, and their allergies had been diagnosed at a median of 1.3 years. Nearly all patients (96 percent) had another atopic condition, with 66 percent having atopic dermatitis. Of the 278 patients, 4 had reported a reaction to tree nut in the prior year, and 106 had tree nut IgE levels above the threshold, and 51 had elevated IgE levels and a history of reaction to ingestion. Of the remaining 117 who were eligible for a challenge test, 78 declined (67 percent), 39 consented, and of these 23 passed the challenge. The study confirmed that some children can outgrow an allergy to tree nut over time.

**Egg Allergy**

We identified one US study on the natural history of egg allergy. All cases came from a retrospective chart review of patients from a university-based pediatric allergy clinic. Chart review was done by a single abstracter. The diagnosis of egg allergy was made if the patient had a clear clinical history of an IgE-mediated allergic reaction to egg ingestion, or if a patient had an egg IgE of greater than 2 kU/L without known tolerance to egg. A total of 881 patients were identified, of whom 68 percent were male. The median age at initial visit was 14 months and the median duration of follow-up was 59 months. Most patients had other atopic conditions: 54 percent had asthma, 55 percent had allergic rhinitis, and 81 percent had eczema. Almost all patients (93 percent) had allergies to other foods, with peanut (74 percent) and milk (72 percent) being most
common. In just over half, skin manifestations were the presenting symptoms. Over time, many patients became tolerant to egg, with tolerance values ranging from 26 percent to 55 percent at age 8 and 48 percent to 76 percent at age 12, depending on the definition used for tolerance. However, only 67 patients contributed data to the tolerance estimates at age 12.

**Wheat Allergy**

We identified one US study on the natural history of wheat allergy. All cases came from a retrospective chart review of patients from a university-based pediatric allergy clinic. Chart review was done by one of three abstractors. The diagnosis of wheat allergy was made if patients had a clinical history consistent with an IgE-mediated allergic reaction on wheat ingestion and a positive wheat IgE test. Between 1993 and 2007, 103 patients were identified. Of these, 66 percent were male, the median age at the initial visit was 19 months and the median deviation of follow-up was 31 months. Most patients had other atopic conditions: 87 percent had eczema, 67 percent had asthma, and 60 percent had allergic rhinitis. Most patients also had allergies to other foods, with milk (70 percent), egg (56 percent), and soy (50 percent) being most common. Skin reactions were the predominant symptoms, in more than half of cases. Over time, many patients became tolerant, with half or more of patients being tolerant at age 8, depending on the definition used for tolerance.

IgE-mediated wheat allergy may be indistinguishable from celiac disease based on symptomatology. Celiac disease is a non-IgE mediated condition, while wheat allergy is IgE-mediated. As guidelines for celiac disease already exist, studies of the natural history of this condition were excluded from this report.

**Peanut Allergy**

We identified five US studies of the natural history of peanut allergy. Details of the five studies are in Table 14. All five studies involved selected populations from specialist clinics. One study assessed 102 children with adverse reactions to peanuts prior to age 4. The authors reported this population was 68 percent male and they were followed for a median of 5.9 years. The authors categorized the symptoms on peanut exposure. *Non-life-threatening reactions* (experienced by 73 percent of the population) included 1) contact reactions without ingestion or skin-limited symptoms on ingestion, consisting of hives or urticaria, erythematous flushing, cutaneous pruritis, cutaneous angioedema, or atopic dermatitis; 2) respiratory, including rhinitis, sneezing, eye symptoms, and an abnormal sensation in the mouth and throat; and 3) gastrointestinal symptoms like emesis, diarrhea, and abdominal pain and cramping. *Life-threatening symptoms* (which occurred in 27 percent of the population) consisted of throat tightness and angioedema, laryngeal angioedema, angioedema in the mouth, cough, wheeze, shortness of breath, noisy breathing, tachypnea, voice change, hypotension, and loss of consciousness. Follow-up data were available for 83 patients. Of these, 50 (60 percent) reported a total of 115 accidental exposures to peanuts with adverse reactions, for a rate of 0.33 adverse reactions due to accidental exposure per year. Of the 61 patients who had initial reactions that were judged non-life-threatening, 43 had at least one subsequent reaction, and of these, 19 had potentially life-threatening symptoms (31 percent of the
original 61), while 24 continued to have non-life-threatening symptoms. Of the 22 patients who had initial life-threatening symptoms, 17 had at least one subsequent reaction, and of these reactions, 12 were considered to include life-threatening symptoms (55 percent of the original 22) and five were considered non-life-threatening. Four children were selected for a double-blind placebo controlled food challenge based on a low level of sIgE and a history suggesting they had lost their allergy to peanuts. All four passed the test; their ages were 10 years, 8 years, 6 years, and 4 years.

The second study assessed 223 patients from two university clinics and one private practice, although 95 percent of all patients came from the Johns Hopkins clinic. In this sample, 63 percent of patients were male and the median age at initial diagnosis was 1.5 years of age; the median age at the time of this evaluation was 6.5 years. In this population, the following characteristics of the initial peanut reactions were noted: rash or hives on the face only (19 percent), eczema (6 percent), hives or angioedema (19 percent), respiratory symptoms only (2 percent), gastrointestinal symptoms only (2 percent), skin and respiratory symptoms (6 percent), skin and gastrointestinal symptoms (3 percent), gastrointestinal and respiratory symptoms in (1 percent), and symptoms in all three organ systems (11 percent). Thirty percent of patients were identified on the basis of a positive skin prick test or RAST (an immunosorption test for sIgE) without symptoms. Associated allergic disorders were common: 59 percent of patients had asthma, 60 percent of patients had allergic rhinitis, and 58 percent of patients had atopic dermatitis. Concurrent allergy to another food or a history of other food allergies were present in 70 percent and 76 percent of patients, respectively. Only five percent of patients had no identifiable additional atopic disorder. Among concurrent food allergies, egg (39 percent), milk (30 percent), and tree nuts (39 percent) were most commonly reported. Among all patients, based on the history and a low level of peanut sIgE, 126 persons were deemed eligible for an oral peanut challenge. Forty one patients declined, leaving 85 patients to undergo either open peanut challenge (67 percent of cases) or DBPCFC (33 percent of cases). Of these patients, 48 passed the challenge.

The third study was drawn from the same general patient population as the prior study, and assessed 68 patients who had “outgrown” their peanut allergy. These patients were invited to undergo a DBPCFC, of whom 21 accepted. On the basis of answers to a questionnaire and the food challenges in the selected patients, the authors determined that forty seven of these patients continued to tolerate peanut ingestion. Eighteen patients were classified as “indeterminate” because they ate only limited amounts of peanuts and declined the food challenge. Three patients had recurrence of their peanut allergy: one was confirmed in the food challenge test, one was not given the food challenge test due to high peanut IgE levels, and the third case of recurrence was based on convincing history alone.

The fourth study assessed 140 children diagnosed with peanut allergy at the Duke University pediatric allergy clinic. As in the other studies, most children were male. Most patients also had other allergic disorders: 82 percent had a past or current history of atopic dermatitis, 62 percent had asthma, and 57 percent had allergic rhinitis. Accidental ingestions were common, occurring in 39 percent of patients, with a mean of 1.8
accidental ingestions per patient. Four patients (3 percent) became tolerant at a median age of 55 months; in two patients, tolerance was demonstrated by physician-supervised challenge tests.

The last study on development of tolerance to peanut was substantially older, assessing patients between 1973 and 1985. Since data come from the same center as the study by Vander Leek summarized above, and have a common author, it is not completely clear whether some of the subjects in the older study were also included in the newer study. Nonetheless, in this study, 32 children who had a positive reaction to a DBPCFC were found at two to 14 years after their original diagnosis (out of 46 sought). Of these, 16 had experienced an accidental ingestion in the year prior to contact that had resulted in symptoms, eight more had an accidental ingestion between one and five years prior to contact, and eight patients had avoided peanuts entirely since their original diagnosis. One patient was described, who, by report, was able to tolerate small amounts of peanut; however, after an accidental ingestion produced a severe reaction, the patient resumed total avoidance. No patient developed tolerance.

One US case report also described a patient who had resolution of peanut allergy at age 3 years and 4 months after being diagnosed at age 8 months on the basis of skin symptoms and a positive skin prick test.

Is the prevalence of peanut allergy increasing?

We identified two studies that assessed the change in prevalence over time of peanut allergy in children. The first report assessed prevalence in the Isle of Wight and the second study, in two reports, assessed prevalence in Montreal, Canada. Both studies were limited by low response rates—in the Isle of Wight study the response rate was 43 percent, a severe limitation, and in the Montreal the response rate in the first study was 56 percent and 64 percent in the second.

Both studies used a combination of symptoms and SPT to make the diagnosis of food allergy, and the Isle of Wight study did open oral food challenges on 24 children, while the Montreal studies used peanut-specific IgE and DBPCFC in selected children.

The Isle of Wight study found the prevalence of reported peanut allergy at 0.5 percent in 1989 and 1.0 percent in 1994-1996, a non-statistically significant difference. The prevalence of sensitization increased from 1.1 percent to 3.3 percent, a statistically significant difference. Although the authors concluded that sensitization to peanuts was rising, the very low response rate makes us unable to draw any conclusions.

The two studies from Montreal both assessed a random sample of children within a random sample of elementary schools in Montreal, in 2000-2002 and again in 2005-2007. Children reporting no difficulties eating peanuts, about 94 percent in each sample, were not assessed further. Symptoms, SPT, peanut-specific IgE levels and selected use of DBPCFC were used to classify the other children as peanut-allergic or not. The prevalence in 2000-2002 was 1.50 percent compared to 1.63 percent in 2005-2007. This
difference, and a difference based on a Bayesian sensitivity analysis, were not statistically significant, but credible set intervals varied from a 0.38 percent decrease to a 70 percent increase, meaning definitive conclusions could not be drawn.

**Risk factors for peanut allergy**

We identified no US studies using community-based sampling that assessed risk factors for peanut allergy (other than familial associations of allergic disorders). At the request of the Expert Panel, we discuss two articles from England that concern risk factors for peanut allergy. These studies are included with the caveat that they are outside the *a priori* inclusion criteria for this review.

The first study assessed patients that were part of the Avon Longitudinal Study of Parents and Children. This study used a case control design, with patients identified as having peanut allergy initially coming from responses to survey items about food avoidance and reactions to foods, previous hospitalizations, and clinical investigations. Mothers of 49 children were interviewed, and 36 of these underwent further testing (2 did not participate because they had prior anaphylactic reactions, the remainder either could not be located or their parents refused consent). Twenty-nine of these children had a positive skin test to peanut. Double blind food challenge was positive in 23 children. Both the 49 child sample and the 23 child sample were considered as "cases". Controls were 70 children who had eczema ("atopic controls") and 140 children without peanut allergy. Stored cord blood of the 23 children with peanut allergy did not contain detectible peanut-specific IgE. Based on retrospective recall of the parents, using multivariate logistic regression, the consumption of soy milk or soy formula, rashes over the joints and skin creases, and the presence of an oozing, crusted rash were all independently associated with the presence of peanut allergy (with odds ratios of 2.61, 2.60, and 5.66, respectively). An additional analysis related the use of peanut-oil containing creams to children with peanut allergy.

The second study, from some of the same investigators, used a similar case control design and assessed children attending a food allergy clinic in London. In this study, high risk controls had a diagnosis of egg allergy, and low risk controls were recruited from the general pediatric clinic. Environmental household peanut exposure (defined as peanut intake across all members of the household) was much higher in cases than in either high risk controls or low risk controls. There was no significant difference in infant intake of peanut during the first year of life between cases and controls.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Population</th>
<th>Criteria for Diagnosis</th>
<th>Sample Size</th>
<th>Years of Study</th>
<th>Population Characteristics</th>
<th>Natural History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vander Leek, 2000&lt;sup&gt;92&lt;/sup&gt;</td>
<td>Children with adverse reactions to peanuts before age 4, seen at the National Jewish Medical &amp; Research Center</td>
<td>1) Convincing history of clinical peanut hypersensitivity and/or a positive food challenge test and 2) Positive skin prick test</td>
<td>102, of which 83 contributed data to the analysis</td>
<td>Not Stated; Mean duration of follow-up = 5.9 years</td>
<td>Male = 69%; Age at beginning of study =2-4 years Initial symptoms non-life-threatening = 73%</td>
<td>Accidental exposure to peanut during follow up = 60%; Mean adverse reactions due to accidental exposure = 0-33/year 4 children selected on the basis of a low serum peanut-specific IgE had food challenges that were negative at ages 10, 8, 6 and 4 years</td>
</tr>
<tr>
<td>Skolnick, 2001&lt;sup&gt;93&lt;/sup&gt;</td>
<td>Children with a diagnosis of peanut allergy at two university clinics &amp; one private practice, age 4 years or older (95% from Johns Hopkins University)</td>
<td>History of acute reaction to peanut &amp; positive skin test, RAST, or challenge; “in some cases positive results to RAST or skin test with no history of ever ingesting peanuts”</td>
<td>223; of which 85 participated in oral peanut challenge</td>
<td>1998-2000</td>
<td>Male = 63%; Median age at diagnosis = 1.5 years Median age at evaluation =6.5 years</td>
<td>8 patients selected due to low peanut-specific IgE had negative food challenges at a median age = 6 years</td>
</tr>
<tr>
<td>Fleischer, 2004&lt;sup&gt;94&lt;/sup&gt;</td>
<td>Children with a diagnosis of peanut allergy at two university clinics &amp; one private practice, age 4 years or older (88% from Johns Hopkins University)</td>
<td>History of acute reaction to peanut &amp; positive skin test, RAST, or challenge; “in some cases positive results to RAST or skin test with no history of ever ingesting peanuts”</td>
<td>68</td>
<td>1997-2003</td>
<td>Male = 59%; Median age at diagnosis = 1.1 years Median age at evaluation =8.5 years</td>
<td>Clearly tolerate peanuts = 47/68 (6%); Indeterminate = 18/68 (26%); Recurrence = 3/38 (4%)</td>
</tr>
<tr>
<td>Green, 2007&lt;sup&gt;91&lt;/sup&gt;</td>
<td>Children diagnosed as having peanut allergy at the Duke University pediatric clinic between 2000-2006</td>
<td>Convincing clinical history and food-specific IgE or food challenge</td>
<td>140</td>
<td>2000-2006</td>
<td>Male = 66%; Median age at first visit =28 months</td>
<td>Accidental exposure to peanuts after diagnosis = 39%; Developed tolerance = 3%</td>
</tr>
<tr>
<td>Bock, 1989&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Children aged 2 to 14 years seen at the National Jewish Center for Immunology and Respiratory Medicine</td>
<td>All had symptoms and a positive double blind oral good challenge</td>
<td>32</td>
<td>1973-1985</td>
<td>Male= not stated; Median age at diagnosis = 7 Median age at evaluation = not stated</td>
<td>No patient developed tolerance</td>
</tr>
</tbody>
</table>
Asthma

We identified six US studies assessing the relationship of food allergies to asthma. In addition, two studies already discussed, both dealing with fatal or near fatal anaphylaxis to foods in US children, reported that all or almost all patients who died had co-occurring asthma. Furthermore, as already noted in numerous studies, co-occurring asthma is highly prevalent among patients diagnosed with food allergy.

The first of two studies assessed cross-sectionally the association between the presence of food allergies (based on self-report) and the severity of asthma in adults attending the general medical clinic at Mt. Sinai Hospital. Among 203 adults with asthma, 22% reported convincing symptoms to at least one food. These patients were more likely than the non-food allergic asthma patients to have had a hospitalization for asthma and increased emergency department visits for asthma.

The second study assessed the presence of food sensitization (as measured by sIgE of greater than 0.35 kU/L) in 504 random serum samples from the National Cooperative Inner City Asthma Study. This study included children between 4 and 9 years of age recruited from EDs and clinics in inner-city areas of the US. Skin prick testing was also performed. Forty-five percent of children were sensitized to at least one food, and four percent had sIgE levels that had a greater than 95% positive predictive value for food allergy. The most common sensitizations were to milk, wheat, and peanut, whereas the most common sIgEs with a 95 percent positive predictive value for food allergy were peanut and egg. Sensitized asthmatic children had a higher rate of hospitalization than non-sensitized asthmatic children and also required more steroid use.

The third study examined the medical records of 72 patients admitted to the pediatric intensive care unit of the Cleveland Clinic from 1992 to 2002. All patients had been admitted for asthma, and they were compared to 108 patients admitted for asthma but not requiring ICU admission and another 108 ambulatory care asthma patients. When compared on self-reported food allergy documented in the medical record, in a model adjusting for age, ethnicity, tobacco exposure, and other factors, the presence of food allergy was significantly much more likely in patients admitted to the ICU than in either of the comparison groups (adjusted odds ratio compared to non-ICU hospital admission 3.27 (95% CI 1.45-7.40); adjusted odds ratio compared to ambulatory asthmatic patients 7.36 (95% CI 2.54-21.39).

The fourth study assessed a convenience-sample of families with and without food allergies living in Chicago, Illinois. Food allergy was defined as typical symptoms plus an SPT or sIgE test. Asthma was assessed by parental report of a physician diagnosis. The adjusted odds ratio of having asthma was about 5.

The last study surveyed members of Kaiser Permanente Northwest who had either been hospitalized with asthma during the prior four years or who had failed at least two prescriptions for medications used to treat asthma in the prior year. Nine hundred fourteen subjects provided data, although what proportion this was of the total population was not reported. Subjects completed a survey and some had spirometry. All subjects had a physician-made diagnosis of
asthma. Among the 914 subjects, 400 reported having a reaction to food on the survey. The most commonly reported foods were milk (21.5 percent), eggs (8.5 percent), red wine (8.5 percent), chocolate (7.5 percent), and peanuts (7.2 percent). The presence of self reported food allergy was significantly associated with greater asthma severity (32 percent to 26 percent, odds ratio of 1.4), as was the odds of hospitalization for asthma (odds ratio = 1.5).

A related study reported changes in airway hyper-responsiveness to methacholine before and after DBPCFC in 26 patients with both food allergy and asthma. This study concluded that food-induced allergic reactions can increase airway reactivity.

Atopic dermatitis

We identified one US study of the natural history of food hypersensitivity in children with atopic dermatitis presented in two papers. Initially, these authors studied 113 children referred for evaluation of severe atopic dermatitis. Ninety-three of these children had at least one reaction to a standard battery of food antigens on skin prick testing. Sixty three tested children had a positive reaction to DBPCFC. Egg, peanut, and milk were the most common foods provoking a reaction. In a follow up study, seventy five children with a mean age of 8 (range 3-18) were identified, all diagnosed with a DBPCFC. In addition to atopic dermatitis, these patients had other atopic diseases: 44 percent had allergic rhinitis and asthma; 27 percent had allergic rhinitis; and four percent had asthma. Sixty percent of the patients were allergic to a single food, 28 percent were allergic to two foods, eight percent were allergic to three foods, and three children (four percent) were allergic to four foods. Milk, peanut, and egg were the most likely to produce positive food challenges. No additional data were reported about the patients (such as gender or symptoms).

After their initial diagnosis, all children were placed on allergen-restricted diets; compliance by history was 90 percent. After one or two years, patients underwent repeat food challenge tests. Twenty six percent of patients lost all evidence of symptomatic food hypersensitivity, and overall, 31 percent of the 1,221 food sensitivities were lost, or, as the authors described it, “outgrown” after one year of food avoidance. All patients who “outgrew” their reactivity to a specific food had the food reintroduced into their diets with no recurrence of symptoms and no worsening of atopic dermatitis, at a follow-up from six months to four years. Patients who developed skin and respiratory tract symptoms at the initial food challenge were much less likely to “outgrow” their food allergy than patients whose initial symptoms were limited to skin only or skin and gastrointestinal tract symptoms.

An additional article about the relationship of atopic dermatitis and food allergy assessed consecutive children presenting to a university dermatology clinic with persistent eczematous rash. Sixty-three patients were studied, with a median age of 2.8 years. Twenty two of the children had food-specific IgE levels of 0.7 kUA/L to each of milk, egg, wheat, soy, peanut and fish, and were not studied further. Of the remaining 41 patients, 10 did not undergo additional evaluation due to loss to follow up on patient preference. Of the remaining 31 patients, 19 underwent DBPCFC and 14 had open food challenges with 18 positive challenges in 11 patients. Two patients were considered food allergic based on food-specified IgE being above a threshold with 95 percent predictive value for a positive food challenge, and 6 and 5 patients were diagnosed as food allergic based on a convincing history and either a positive skin test or
elevated sIgE. In all, 23 of 63 children (37 percent) with atopic dermatitis were considered to have food allergy.  

**Chronic urticaria and angioedema**

We identified one US study of the national history of chronic urticaria and angioedema. All subjects were patients of the same allergy clinic. Eighty six patients with chronic urticaria or angioedema were identified. There was a slight preponderance of females (48 females, 38 males) and mean age of onset was 33 years of age. Eleven patients were lost to follow up. Of the remaining, 27 patients had their symptoms resolve in a 3 year period. The authors note that testing for allergies was rarely helpful.

**Eosinophilic Esophagitis**

We identified three US studies of the natural history of eosinophilic esophagitis. Details of the three studies are presented in Table 15. All studies involved selected populations from university-affiliated or referral specialty clinics. All studies used symptoms plus a positive biopsy on endoscopy to make the diagnosis. The first study assessed 71 patients, the second study assessed 89 patients, and the third study assessed 562 patients. In all three studies, the majority of patients were male, and in two of the studies, 90 percent or more white. Most children were diagnosed within the first three years of life. Symptoms in the study of 89 patients included emesis in 53, abdominal pain in 22, heartburn in 19, dysphagia in 14, diarrhea in 14, airway symptoms in 12, cough in 10 and chest pain in 6. In the study of 562 patients, symptoms were grouped into age-related categories as “refusal to eat” in toddlers, gastroesophageal reflux and vomiting symptoms in young school-age children, and dysphagia and food impaction in older children. Two of the studies differed on the report of implicated foods. The leading foods in the one study were egg, peanut, and soy (39 percent, 39 percent, and 34 percent respectively), while in the other study the leading foods were milk, egg, and wheat (17 percent, 11 percent, and 10 percent, respectively). The third study did not report specific prevalence for foods, but did note that 60 percent of tested patients had food allergies. In two studies with adequate follow-up over several years, most patients remained symptomatic, and resolution was uncommon (8/57, or 14 percent in one study, 11/562, or two percent in the other), but the two studies differed in reports of progression of eosinophilia to other parts of the gastrointestinal tract (77 percent in one study versus 0 percent in the other).

We briefly mention two additional studies here. Among 565 patients (5 percent in all, median age = 50 years) scheduled for outpatient elective upper endoscopy at Walter Reed hospital, 385 (68 percent) agreed to and received a biopsy to assess the prevalence of eosinophilic esophagitis, and completed a survey about symptoms and comorbid conditions. Of these, 25 (6.5 percent) had histologic evidence of eosinophilic esophagitis, and of these, 4 (16 percent) reported food allergies as a comorbidity. Sixty eight patients with biopsy-proven eosinophilic esophagitis at the Cleveland Clinic were identified from a registry. Of these, 28 had been referred for an allergy evaluation, and of these 26 completed the evaluation. Thirteen of these patients had a positive skin test for at least one food, with peanut, egg, soybean, and cow milk being most common.
Exercise-induced anaphylaxis

We identified one US study of the natural history of exercise-induced anaphylaxis.116 Six hundred seventy one patients were identified at a single Asthma and Allergic Diseases Center from 1980 until approximately 1993. Inclusion criteria included being age 18 or older and speaking English. A survey was mailed to all patients; 365 responded (54 percent). Of these 365, 279 (76 percent) met the criteria for exercise-induced asthma (which included report of anaphylactic symptoms, urticaria, and/or angioedema with symptoms consistent with upper respiratory obstruction) or had cardiovascular collapse during exercise. Patients with symptoms that included an elevation in core body temperature were excluded. Nearly three quarters of patients were female. The mean age was 37 years with an onset of symptoms at age 26, and the mean duration of symptoms was 10.6 years. The average number of episodes per year at the time of initial presentation was 14.5, but this frequency decreased to 8.3 at the time of the survey. Approximately one third of subjects had no attacks in the 12 months prior to the survey.

The most frequently occurring symptoms were pruritis (92 percent), urticaria (86 percent), angioedema (72 percent), flushing (70 percent), and shortness of breath (51 percent). Thirty seven percent of patients reported a food trigger. The most commonly reported food triggers were shellfish (16 percent), alcohol (11 percent), tomatoes (8 percent), cheese (8 percent), and celery (7 percent). About one half of subjects reported seasonal rhinitis or dust allergies. Asthma was reported by 19 percent, and 10 percent had eczema.
Table 15: US Studies of the Natural History of Eosinophilic Esophagitis

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Population</th>
<th>Criteria for Diagnosis</th>
<th>Sample Size</th>
<th>Years of Study</th>
<th>Population Characteristics</th>
<th>Foods with positive skin prick test or atopy patch test</th>
<th>Natural History</th>
</tr>
</thead>
</table>
| Dauer, 2005<sup>112</sup> | Pediatric patients diagnosed with eosinophilic esophagitis at the Mayo Clinic | Not specifically stated, but all but one patient underwent endoscopy with biopsy | 71 | 1992-2003 | Male: 65%  
Age at diagnosis:  
Mean = 10.5 years  
Mode = 12 year  
SPT or RAST performed in 47 patients. 60% of patients had food allergies. Most common were milk, peanuts, & soy beans. | Of 96 patients treated with swallowed fluticasone, follow up data available for only 26. 17 of these had “complete response.” |
| Assa’ad, 2007<sup>111</sup> | Pediatric patients diagnosed with eosinophilic esophagitis at Cincinnati Children’s Hospital | Symptoms; biopsy at endoscopy | 89; 57 contributed to data follow-up | 1997-2004; Mean duration of follow-up= 7.6 years | Male: 79%  
White: 94%  
Age at diagnosis:  
Mean = 6 years  
Mode = 1 year  
Egg = 39%  
Peanut = 39%  
Soy = 34%  
Beans = 29%  
Cow Milk = 29%  
Pea = 29%  
Mustard = 26% | Resolved = 8/57  
Resolved with Relapse = 30/57  
Persisted = 19/57 |
| Spergel, 2009<sup>113</sup> | Pediatric patients diagnosed with eosinophilic esophagitis at Children’s Hospital in Philadelphia | Symptoms; biopsy at endoscopy | 562 | 1996-2006; Mean duration of follow-up= 3.2 years | Male: 75%  
White: 90%  
Age at diagnosis:  
Mean = 6 years  
Mode = 0-3 years  
Milk = 17%  
Egg = 11%  
Wheat = 10%  
Soy = 8%  
Corn = 8%  
Peanut = 5% | Resolved = 11/562  
Partial Resolution = 33/562  
Progression to eosinophilia in colon or stomach = 0 |
### Table 16: Studies of Allergies to Specific Foods, Non US/Canada

<table>
<thead>
<tr>
<th>Food</th>
<th>Country</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparagus</td>
<td>Spain</td>
<td>117</td>
</tr>
<tr>
<td>Buckwheat</td>
<td>China</td>
<td>118</td>
</tr>
<tr>
<td>Celery</td>
<td>France</td>
<td>119</td>
</tr>
<tr>
<td>Cow Milk</td>
<td>Australia</td>
<td>120</td>
</tr>
<tr>
<td>Cow Milk</td>
<td>Italy</td>
<td>121</td>
</tr>
<tr>
<td>Cow Milk, Egg &amp; Atopic Dermatitis</td>
<td>Europe</td>
<td>55</td>
</tr>
<tr>
<td>Egg</td>
<td>Turkey</td>
<td>122</td>
</tr>
<tr>
<td>Egg</td>
<td>Norway</td>
<td>123</td>
</tr>
<tr>
<td>Kiwi</td>
<td>Spain</td>
<td>124</td>
</tr>
<tr>
<td>Legume</td>
<td>Spain</td>
<td>125</td>
</tr>
<tr>
<td>Melon</td>
<td>Spain</td>
<td>126</td>
</tr>
<tr>
<td>Mustard</td>
<td>France</td>
<td>127</td>
</tr>
<tr>
<td>Mustard</td>
<td>Spain</td>
<td>128</td>
</tr>
<tr>
<td>Mustard</td>
<td>France</td>
<td>129</td>
</tr>
<tr>
<td>Peanut</td>
<td>Australia</td>
<td>130</td>
</tr>
<tr>
<td>Peanut</td>
<td>UK &amp; Israel</td>
<td>131</td>
</tr>
<tr>
<td>Peanut</td>
<td>UK</td>
<td>99</td>
</tr>
<tr>
<td>Sesame</td>
<td>Israel</td>
<td>132</td>
</tr>
<tr>
<td>Sesame</td>
<td>Israel</td>
<td>133</td>
</tr>
<tr>
<td>Sesame</td>
<td>France</td>
<td>134</td>
</tr>
<tr>
<td>Sesame</td>
<td>Israel</td>
<td>135</td>
</tr>
<tr>
<td>Snail</td>
<td>Spain</td>
<td>136</td>
</tr>
<tr>
<td>Soy Bean</td>
<td>Europe</td>
<td>137</td>
</tr>
<tr>
<td>Zucchini</td>
<td>Switzerland</td>
<td>138</td>
</tr>
</tbody>
</table>
Other conditions/foods

We did not identify any US or Canadian studies of the natural history of other conditions or foods. Of note, we did identify such reports from other countries. Table 16 lists these studies.

ii. Relationship between IgE-mediated and immunologic but non-IgE-mediated food allergy and comorbid conditions.

No additional studies other than those described above in section B-D iv were found.

iii. Differences in populations related to socioeconomic status, access to health care, stress.

We did not find any US studies that specifically addressed differences in incidence, prevalence, or natural history related to socioeconomic status, access to health care, or stress. The US National Study did report data stratified by race, and some investigators use race as a proxy for socioeconomic status and access to health care. Those data are presented in tables 10 and 11 reporting the US National data. In addition, two US studies already presented (of infant feeding practices and of the NHIS/NHDS databases) reported that black males were more likely to have parent-reported food allergy and the rates of food allergy in Hispanics was lower than in non-Hispanics. One cohort study from Sweden reported that the risk of sensitization to food allergens decreased with increasing socioeconomic status, with an odds ratio of 0.65 (95% confidence interval 0.41, 1.02, p=0.03 for trend) in the highest as compared to the lowest socioeconomic group.139

Genetics

There is emerging evidence of a genetic association with food allergy. A family-based study of food allergy in Chicago reported strong familial aggregation and suggested that both genetic and environmental factors contributed to this.140 Three genetic association studies reported a relationship between certain genes (SPINK5, FOXP3, and NLRP3) and food allergy, and the NLRP3 association was reported specific for food-induced anaphylaxis.141-143

Lastly, recent studies have suggested that filaggrin mutations associated with severe atopic dermatitis may subsequently confer greater risk of allergic sensitization to foods.144 In a recent systematic review of 24 studies, filaggrin gene defects were associated with an increased odds of developing atopic eczema, allergic rhinitis, and the co-occurrence of allergic rhinitis or asthma in patients with atopic eczema. Evidence was inconclusive regarding an association between filaggrin gene mutations and asthma in patients without atopic eczema, and in this review no studies were identified assessing fillagrin gene mutations and food allergies or anaphylaxis.145
Section III. Diagnosis of Food Allergy: What tools are available and how reliable are they?

Key Questions F and G: What tools are currently used to diagnose IgE-mediated and non-IgE-mediated food allergy?

General Principles for Studies of Diagnostic Tests

Before proceeding to a description of the findings of our literature review, it will be valuable to review a few principles of how diagnostic tests are assessed. At its most fundamental level, an assessment of a diagnostic test can be depicted as shown in Table 17.

<table>
<thead>
<tr>
<th>Study Test</th>
<th>Reference Test or Gold Standard</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>True Positives (TP)</td>
<td>False Positives (FP)</td>
</tr>
<tr>
<td></td>
<td>(Type I error)</td>
<td>(Type I error)</td>
</tr>
<tr>
<td>Negative</td>
<td>False Negatives (FN)</td>
<td>True Negatives (TN)</td>
</tr>
<tr>
<td></td>
<td>(Type II error)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td></td>
<td>TP/(TP+FN)</td>
<td>TN/(FP+TN)</td>
</tr>
</tbody>
</table>

In this table, the “study test” is the diagnostic test being assessed and is compared to a reference test or “gold standard,” that is, a test that is assumed to diagnose the condition of interest with 100 percent certainty. Each participant is assessed with both the reference test and the study test. Subjects testing positive by both tests are denoted "True Positives" (TP) and those testing negative by both tests are denoted "True Negatives" (TN). Subjects who test positive by the study test but negative by the reference test are "False Positives" (FP), whereas those who test negative by the study test, but positive by the gold standard are "False Negatives" (FN). Four statistics are commonly produced from these frequencies that can be used to gauge the usefulness of a test. The sensitivity of a test is the number of true positives divided by the total number of positives as defined by the reference test or TP/(TP+FN) and is a measure of the proportion of subjects with a condition who are identified by a given test. A test with a 100-percent sensitivity is positive for all individuals with a given diagnosis. The specificity of a test is the number of true negatives divided by the total number of negatives as defined by the reference test, or TN/(FP+TN). A 100 percent specific test is negative for all people who do not have the condition by the reference standard (i.e., no false positives). The positive predictive value (PPV) of a test is the proportion of patients with a positive result by the study test who are correctly diagnosed or TP/(TP+FP). A 100% PPV means that all subjects with a positive study test result have the condition according to the reference test (i.e., no false positives). Finally, the negative predictive value (NPV) of a test is the proportion of patients with a negative test result who were correctly identified (compared to the reference test) or TN/(TN+FN). For a test with 100% NPV,
all subjects with a negative test result do not have the condition (according to the reference standard).

With an understanding of these measures, the general outline of the issues in studies of diagnostic tests can be appreciated. First, is the reference test an adequate gold standard upon which to compare the study test? Second, is the study test defined in sufficient detail that it can be replicated: the conditions used for the test and the criteria for a positive or a negative result? Third, is the interpretation of the two tests made independently, such that investigators were blinded to the results of other tests when interpreting a given test? Fourth, from what population were the subjects drawn and to whom do the study apply?

The same principles as discussed in the section introducing studies of the natural history/incidence/prevalence apply here. Studies where the patients came from a defined population, “all patients referred from primary care…” or “consecutive patients evaluated for the possibility of food allergy” give readers a better sense of whom the results apply to than vague statements like “46 patients were assessed.” The extent to which the defined population represents the kinds of patients for whom the diagnosis is uncertain increases the usefulness of the results. Likewise, performing the assessment of the study test in only those patients for whom the diagnosis is already known does not represent the real-life situation in which the study test will be used.

Search Results

Two hundred sixty-four articles were initially identified as diagnostic studies. Among the articles screened, 153 articles reported sensitivity and specificity or provided data that allowed us to calculate those values. The articles were further selected based on two criteria derived from the above discussion of principles: We chose studies that were prospective and had a defined population, at least at the level of “consecutive patients referred”. However, we also included evidence of lower quality for several conditions and tests that were specifically identified by the key questions for which no studies of higher quality were available.

In this section, we report the findings of these studies according to the type of test, the test(s) used as the gold standard (reference), and the specific food(s) involved. In general, for each study, we report the sensitivity and specificity of the test(s) compared to the reference as well as the positive predictive value and negative predictive value when provided.

Using the QUADAS criteria, we assessed the quality of all studies that met the inclusion criteria. QUADAS is a tool for the assessment of quality of studies of diagnostic methodologies. Characteristics assessed include description of the population, blinding, comparison to a gold standard, the timing of the diagnostic test compared with the gold standard, and description of the methodology. Although the complete tool includes 14 items (domains), we excluded two items that would be difficult to apply to tests of food allergy. The criteria and scoring are provided in Appendix D. The results are reported in Figure 3 below and in the evidence table in Appendix H. Two domains were almost universally satisfied by the studies: “Was the reference standard independent of the index test?” and “Was the execution of the index test described
sufficiently?” (34 of 38 studies) Two domains were satisfied in 33 out of 38 of the studies: “Is the time period between reference standard and index test short enough?” and “Did patients receive the same reference standard?” One domain satisfied 31 out of 38 of the studies: “Was the execution of the reference standard described sufficiently?” The following domains were satisfied in 30 out of 38 of the studies: “Is the reference standard likely to correctly classify the target condition?” and “Were the index test results interpreted independent of the reference standard?” One domain satisfied 26 out of 38 of the studies: “Were patients representative of those who will receive the test?” One domain satisfied 22 out of 38 of the studies: “Were selection criteria clearly described?” The domains least satisfied were the following: “Were the reference standard results interpreted independent of the index test?” (12 of 38 studies) and “Were withdrawals from the study explained?” (11 of 38 studies).

Figure 3: Numbers of Studies with a “Yes” Response to the QUADAS Domain Question

<table>
<thead>
<tr>
<th>Domain</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were patients representative of those who will receive the test?</td>
<td></td>
</tr>
<tr>
<td>Were selection criteria clearly described?</td>
<td>26</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>30</td>
</tr>
<tr>
<td>Is the time period between reference standard and index test short enough?</td>
<td>33</td>
</tr>
<tr>
<td>Did the whole sample receive a verification?</td>
<td></td>
</tr>
<tr>
<td>Did patients receive the same reference standard?</td>
<td>32</td>
</tr>
<tr>
<td>Was the reference standard independent of the index test?</td>
<td>33</td>
</tr>
<tr>
<td>Was the execution of the index test described sufficiently?</td>
<td>34</td>
</tr>
<tr>
<td>Was the execution of the reference standard described sufficiently?</td>
<td>34</td>
</tr>
<tr>
<td>Were the index test results interpreted independent of the reference standard?</td>
<td>31</td>
</tr>
<tr>
<td>Were the reference standard results interpreted independent of the index test?</td>
<td>30</td>
</tr>
<tr>
<td>Were withdrawals from the study explained?</td>
<td>12</td>
</tr>
</tbody>
</table>

History and Physical Examination

It is generally accepted that the diagnosis of food allergy must begin with a careful history and physical exam, the results of which guide the use of any further diagnostic tests; however, only one study on this topic met our inclusion criteria. This study investigated the use of umbilical erythema as an indication of cow’s milk protein intolerance (CMPi) in 796 children (aged 1 month to 10 years) consecutively referred to the gastroenterology clinic at an Italian hospital with suspected CMPi. Of these children, 384 were diagnosed with CMPi via elimination diet and subsequent DBPCFC, and of these, 36 children had umbilical erythema, yielding a sensitivity of 0.09. There were no cases of children with umbilical erythema and without CMPi, resulting in a specificity of 1.0 (this study satisfied 10 of the 12 QUADAS domains assessed).146
The quality of evidence for the history and physical examination is very low, meaning any estimate of effect is very uncertain, due to a near total absence of data, but we discuss it here at the request of the NIAID and Expert Panel.

**Food Challenge Tests**

Oral food challenge tests, in which individuals with suspected food allergies are administered increasing amounts of the suspect foods (usually following a period of prescribed avoidance) under controlled conditions, are widely used as the gold standard for food allergy diagnosis (at least when implemented under double blind conditions with placebo controls). However, several issues remain to be clarified about food challenge tests: the need for blinding, the effect of the form of food used (e.g., raw vs. cooked, fresh vs. freeze-dried, whole vs. extracts), whether the test is truly a gold standard, and when the tests are needed (given the expense, time, and potential risks involved).\(^{147}\)

Five studies that assessed various aspects of food challenge tests satisfied the inclusion criteria (four of these five studies are described in Table 18; the fifth is described in more detail later in this section).

**Double-blind versus Open Challenge**

Isolauri (1996) placed 183 Finnish children (2-36 months of age) on cows’ milk elimination diets (substituting cow’s milk with breast milk or special formula) and then randomly assigned them to open or double-blind placebo controlled cow’s milk challenge.\(^{148}\) The placebo consisted of Neocate® formula, and the challenge formula consisted of 10gm skimmed cow milk powder per milliliter (ml) of the placebo formula (beta-lactoglobulin concentration in the placebo compared with cow’s milk was 0.24 \(\mu\)g/L vs. 4x10^6 \(\mu\)g/L). The challenge involved administering increasing doses of the milk, beginning with 10 ml, and continuing for a week (day one in the clinic, the remainder at home) or until a clinical reaction occurred. Children were examined at the time of reaction and/or at 7 and 14 days. The open challenge used a commercial formula that contained 124,000\(\mu\)g/L beta-lactoglobulin. A positive challenge was defined as an unequivocal adverse reaction. The rate of positive reactions was identical between the blinded and open challenge groups (54 percent, 99 children). No differences were seen between blinded and open tests in the time to acute or delayed reaction or in the doses required to elicit their respective reactions. Although all placebo challenges were negative, one child subsequently showed a positive clinical reaction to open cow’s milk feeding, resulting in a one percent false negative challenge (this study satisfied 10 of the 12 QUADAS domains assessed).

Mehl (2006) conducted DBPCFC in 437 children (referred to an allergy department in Germany for suspected allergy to milk, egg, wheat, or soy) as a standard for assessing the utility of the atopy patch test (APT) compared with tests of immediate (IgE-mediated) reactivity. Although this study is described in much greater detail below, it seems worth noting that 10 of 341 (three percent) placebo challenges gave positive reactions (this study satisfied 9 of the 12 QUADAS domains assessed).\(^{149}\)
A 2007 study found that of 123 DBPCFC administered to 105 children, nearly 13 percent of positive reactions were reactions to placebo. Of these reactions, 65% actually involved objective symptoms (e.g., urticaria). A variety of reasons were suggested for positive placebo reactions, including hypersensitivity due to recent withdrawal from allergy medication and inadvertent exposure to the allergen. The authors cited the rate of positive placebo reactions as supportive of the need for DBPCFC. Another study published in 2007 compared open food challenges with DBPCFC in those children with a positive open challenge. Among 41 children who received both, 11 children had a positive response during a one-day open food challenge and 8 of these had a positive response on DBPCFC. Two of the three children with a positive open challenge but a negative DBPCFC had reported subjective symptoms on the open challenge. Thirty children had positive reactions to 35 open challenges of one week’s duration, and of these 20 were also positive on DBPCFC. All those with a negative DBPCFC had reported subjective symptoms. This study, like others of its kind, was limited by the refusal, of about one third of the children with a positive open challenge to receive a DBPCFC. A 2009 case report described a 15-month old child referred for assessment of egg allergy who had a positive reaction to placebo presentation during a DBPCFC. Subsequent investigation revealed that the child was inadvertently exposed to egg during the placebo portion of the test because the accompanying parent kissed the child immediately after having eaten an egg sandwich. Lastly, a research letter reported on 5 cases (out of 242 children) who had passed an open food challenge or DBPCFC but who had symptoms when consuming the food at home, with all 5 children subsequently having a positive DBPCFC. These cases were interpreted as “false negative” initial challenges.

Use of Alternative Outcomes to Improve Assessment of Reactivity.

Positive reactions to food challenges are typically some combination of signs or symptoms indicative of an adverse reaction to that food and condition. Two studies meeting the inclusion criteria investigated subjective measure of food challenge outcome.

Clark (2007) examined the use of facial thermography to improve the objective assessment of clinical symptoms in response to challenge among 24 children with confirmed egg allergy. The children were administered increasing amounts of egg (cooked egg to children with confirmed allergy to cooked egg; uncooked egg to all others) at 10-minute intervals. Thermography was performed in a temperature-controlled room by a technician blinded to other responses to the challenge. The sensitivity was 0.92 for the test (no specificity could be calculated, as the entire sample had the disease). The median time of onset to the rise in nasal temperature was 20 minutes, compared with a median 67-minute time to onset for gastrointestinal symptoms (this study satisfied 7 of the 12 QUADAS domains).

Hwang (2008) tested the use of a gastric juice leukocyte counts and several other assessments as a more rapid, reliable response to cow’s milk challenge (than vomiting and diarrhea) among 16 Korean infants with suspected cow’s milk-protein-induced enterocolitis (CMPIE). Prior to beginning the challenge, other possible causes of the symptoms were ruled out, infants were switched to hydrolyzed protein formula and/or breast milk, and weight was stabilized. Among the children, 15 had elevated levels of leukocytes in their gastric juice in response to the
challenge, compared with 14 who exhibited vomiting. Results of other tests (shown in Table 18) were considered less reliable (this study satisfied 8 of the 12 QUADAS domains assessed).

Endoscopic Allergen Provocation

Bischoff (1996) assessed 375 adults seen in a university gastroenterology clinic, 275 of whom had Crohn’s disease, 82 of whom had ulcerative colitis, and 38 of whom had other diseases. Patients were classified as “suspected intestinal food allergy” if they met at least three of the following: symptoms related to food, elevated total serum IgE, sIgE for specific foods, peripheral or tissue eosinophilia, improvement of symptoms after treatment with disodium cromoglycate or presence of an atopic disorder in a first degree relative of the patient. In 13 such patients, in whom an elimination diet did not produce a clean result, investigators performed colonoscopic allergen provocation by administering allergens and observing the mucosa for 20 minutes and then taking a biopsy. In 50 percent of provocations, the provocation test and the history were both positive, and in 6 percent of provocations, tests were negative. In 41 percent of provocations a positive history could not be confirmed by provocation. (see Table 18). The routine use of such a test was not discussed (this study satisfied 4 of the 12 QUADAS domains assessed).

Risks and Pitfalls of Food Challenges

Several studies that did not meet the initial inclusion criteria examined problems involved with food challenges. Niggemann and Beyer have reviewed the pitfalls in double-blind, placebo-controlled oral food challenges, which, in addition to those mentioned above, include the problem of determining what constitutes a reaction (short of anaphylaxis) and the time interval between administration of the test food and the clinical reaction; they conclude more standardization is needed. In a study of food challenges for adult patients with subjective symptoms (mainly abdominal), Gellerstedt reported that changing the method used for interpreting patient symptom diaries to assess a positive reaction resulted in four of 25 patients previously classified as “negative” now being classified as “positive”. No other studies of variability in interpretation were identified.

The 2009 Work Group Report on Oral Food Challenge Testing reviewed the literature on factors that can affect the outcomes of food challenge tests. The report found that reactivity to a food can depend on how the food is presented. For suspected milk, egg, and peanut/legume allergy, reactivity can depend on whether the food is left in its natural state, cooked, or baked, as well as the fat content of the food or vehicle. For suspected fruit or vegetable allergy, method of preparation as well as variety, ripeness, and storage time affect reactivity.

As described, concerns exist regarding the safety of conducting oral food challenges. The actual risks involved in DBPCFC have been investigated in several studies. A 1994 study in which 320 children with atopic dermatitis underwent DBPCFC found that 59 percent of the children with positive food challenges developed respiratory symptoms; however, only 7 percent had a decrease in forced expiratory volume of more than 20 percent. Likewise, a 2004 study that retrospectively assessed the results of DBPCFC among 584 challenges found that of the foods tested, all produced comparable reactions; all reactions were reversible with short-acting
antihistamines with or without epinephrine, β-agonists, and/or corticosteroids; and no child had cardiovascular symptoms or required hospitalization.161

Summary
A small number of studies that satisfied our inclusion criteria examined issues related to the use of DBPCFC. One study found no difference in the prevalence of positive responses between double-blind- and open tests. Other studies reported positive reactions to placebo in up to 13 percent of patients. In an effort to overcome problems in assessing outcomes of food challenges, two studies assessed the performance of alternative outcome measures, facial thermography and gastric juice analysis, with good results. Finally, another study examined the use of intestinal, rather than oral, challenge for persons with GI complaints. This test had high specificity but low sensitivity; its practicality was not discussed. The quality of these studies varied widely: QUADAS domains satisfied ranged from 4 to 10 out of 12.

A number of studies and reviews have discussed the potential pitfalls and safety issues involved in administering DBPCFC. Pitfalls include the rate of positive reactions to placebo and the many factors that can affect reactivity to a suspected allergen. The quality of evidence regarding DBCFC is judged moderate, meaning further research is likely to have an important impact on our confidence in the estimate of effect. While this test is the gold standard at present, there are numerous issues about its standardization that need attention.
Table 18: Studies of Food Challenge Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Test and Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolauri, 1996(^{148})</td>
<td>183 Finnish children (age 2-36 months) referred to a specialist for evaluation of atopic dermatitis (AD) randomized to open or DBPC cow’s milk challenge (following 4 weeks milk elimination)</td>
<td>DBPCFC</td>
<td>Open food challenge: 54% positive tests for both open and DBPC challenges (99+), 49 immediate and 50 delayed</td>
</tr>
<tr>
<td>Clark, 2007(^{154})</td>
<td>24 UK children (2.6-14 years) with history of egg allergy (positive history, SPT, and sIgE) challenged with cooked (CE) or uncooked egg (UE)</td>
<td>Objective symptoms of DBPCFC</td>
<td>Facial Thermography at 10-min. intervals: Sensitivity: 0.92 Specificity: 1 based on comparison to objective symptoms of DBPCFC</td>
</tr>
<tr>
<td>Hwang, 2008(^{155})</td>
<td>16 Korean children (14-44 days) admitted to hospital with suspected CMPIE (vomiting, diarrhea, failure to thrive, lethargy). Infants switched to protein hydrolysate formula and/or breast milk, other factors ruled out (e.g., infection), and weight stabilized prior to challenge</td>
<td>Objective symptoms of DBPCFC</td>
<td>Gastric Juice Analysis: 15/16 GJA+ (&gt;10 leukocytes/field) 14/16 vomiting+ 5/16+ Peripheral absolute neutrophil count 12/16+ Fecal white blood cells 0/16+ C-reactive protein (&gt;1mg/dL)</td>
</tr>
<tr>
<td>Bischoff, 1996(^{156})</td>
<td>375 randomly selected patients in GI clinic (Germany) with clinical criteria of intestinal food allergy (3 of the following 6 (clinical history): Hx of food-related GI symptoms, increased total sIgE, food sIgE, eosinophilia, improvement w/ cromoglycate, clinical atopy; and 1 of the following 2: +response to provocation or + response to elimination)</td>
<td>Clinical history and + elimination response</td>
<td>Colonoscopic Provocation 13 patients underwent a total of 34 tests. Provocation and history both positive: 50% Provocation and history both negative: 6% Provocation positive, history negative: 3% Provocation negative, history positive: 41%</td>
</tr>
</tbody>
</table>
Skin Prick Tests

Skin prick testing (SPT) is the preferred method of skin testing as recommended by the AAAAI\textsuperscript{162} and EAACI.\textsuperscript{163} Both organizations recommend against intracutaneous testing for food allergies, citing increased risk of serious reaction and no increase in sensitivity or specificity. Additionally, both the AAAAI and EAACI recommend against using skin scratch tests due to their low specificity compared to skin prick tests. A 2005 systematic review of systemic reactions to skin testing found that five of seven fatal reactions were from intracutaneous testing and recommended against it for that reason.\textsuperscript{164} This section reviews the evidence on the use of SPT for diagnosis of food allergy.

Administration and Interpretation of SPTs

There is no standard for administering or interpreting skin prick tests\textsuperscript{162} indeed, the studies utilizing skin prick tests that met our inclusion criteria used several different methods to define a positive test. The most common approaches either measured the absolute wheal size or measured the wheal size relative to the negative control.

Types of Allergens

Heterogeneity is also seen in the type of allergen used for SPTs: Both fresh foods and commercial preparations are used. Two studies that specifically addressed the comparability of these tests met our inclusion criteria. For milk preparation, a study of 183 children with AD and suspected CMA reported a high degree of concordance of SPT results between a commercial cow milk allergen (ALK) and milk powder with Cohen's Kappa of 0.86, 95% CI 0.77-0.95 (this study satisfied 10 of the 12 QUADAS domains assessed).\textsuperscript{148} In comparison, a study of peanut preparations in 393 children with suspected food allergy reported a high false negative rate with a commercial peanut extract (Allerbio) compared to fresh peanut, which was 100 percent sensitive (this study satisfied 10 of the 12 QUADAS domains assessed).\textsuperscript{165}

Cow's Milk Allergy

Twelve studies of the use of skin prick tests in cow’s milk allergy met our inclusion criteria and are described in Table 19 (although two, Roehr, 2001 and Mehl, 2006, may share all or some participants); all of these used food challenge as the reference test.

A small 1988 study of 26 children (aged 1-48 months) consecutively referred to a Danish hospital allergy clinic diagnosed 20 of the 26 children with cow’s milk allergy via open food challenge to compare the sensitivity and specificity of skin prick tests with those of sIgE and a novel basophil histamine release assay.\textsuperscript{166} The skin prick test was performed with raw cow’s milk extract, and any wheal size greater than that of the histamine control was considered positive; sensitivity was 0.80, specificity was 0.66, PPV was 0.89, and NPV was 0.5 (this study satisfied 8 of the 12 QUADAS domains assessed).

A 2001 study of 170 children (aged 1-12 months) consecutively seen at a Madrid university hospital allergy clinic diagnosed 67 of the 170 children with cow’s milk allergy (161 based on DBPCFC and 9 based on history of severe reaction to exposure) to compare the sensitivity and
specificity of skin prick tests using whole milk as well as three of its component proteins (α-lactalbumin[ALA], β-lactoglobulin[BLG], and casein) with that of sIgE to test immediate hypersensitivity. When at least one of the four skin prick tests was positive, the sensitivity (0.99) and NPV (0.97) were highest. Specificity and PPV were highest for casein (0.87) (this study satisfied 8 of the 12 QUADAS domains assessed).

In a 2003 study, 151 children consecutively referred to a Bologna university hospital pediatric allergy clinic with multiple atopic symptoms received a food challenge, skin prick tests, and two different commercial sIgE tests to compare the results. Among the challenges, 27 responded positively to cow’s milk A positive skin prick test, defined as a wheal diameter of 3mm or greater, was obtained in 17 of 22 children. The test had a sensitivity of 0.77, a specificity of 0.88, a PPV of 0.63 and a NPV of 0.94 (this study satisfied 10 of the 12 QUADAS domains assessed).

In a 2004 study of a 3-year-old birth cohort of 495 children in Denmark, parents completed a questionnaire that included questions about food hypersensitivities. Based on the responses, children were given open food challenges and skin prick tests (as well as APT, sIgE, and basophil histamine release assessments). Three of 8 children had positive challenge responses to cow’s milk; 2 of the 3 had positive skin prick tests, defined as a wheal diameter 3mm or larger. The test had a sensitivity of 0.66, a specificity of 0.80, a PPV of 0.66 and a NPV of 0.80 (this study satisfied 8 of the 12 QUADAS domains assessed).

In another 2004 study of 48 children (3-29 months) consecutively recruited to a French pediatric hospital allergy clinic with AD, open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Skin prick tests were performed with fresh milk; positive tests were defined as wheal diameters ≥3mm greater than negative control and at least 50% greater than positive control. The test had a sensitivity of 0.59, a specificity of 0.50, a PPV of 0.91 and a NPV of 0.56 (this study satisfied 10 of the 12 QUADAS domains assessed).

In a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis, 71 received a DBPCFC for cow’s milk and a skin prick test with fresh milk to compare the results of skin prick test with that of atopy patch test, sIgE, and combinations of the tests. Among the challenges, 45 of 71 were positive. A positive skin prick test, defined as a wheal diameter of 3mm or greater with no reaction to the negative control, was obtained in 43 of 98 children. The test had a sensitivity of 0.78, a specificity of 0.69, a PPV of 0.81 and a NPV of 0.64 (this study satisfied 9 of the 12 QUADAS domains assessed).

Among a cohort of 6209 infants recruited for a study of the effects of various infant formulae on the development of cow’s milk allergy, 239 (ages 6-7 months) showed symptoms that subsided with elimination of cow’s milk and received a milk challenge, skin prick tests, and sIgE measurements; 118 reacted positively to the challenge. The sensitivity and specificity of the skin prick test was assessed at three different wheal diameter cutoff points: ≥3, 6, and 8mm. The maximum sensitivity (0.61) and NPV (0.67) were found at a cutoff of 3mm; The maximum specificity (0.98) and PPV (0.92) were found at a cutoff of 8mm (this study satisfied 11 of the 12 QUADAS domains assessed).
In a study of 437 children (aged 3 months to 17 years) consecutively referred to a German allergy clinic with suspected food allergy, 168/437 were diagnosed with cow’s milk allergy via DBPCFC. This study used fresh milk samples, but did not report the definition of a positive test used. They report sensitivity of the test of 0.85, specificity of 0.70, PPV of 0.73, and NPV of 0.83. They also report the decision points (wheal sizes) necessary for achieving 0.95 PPV (9.2 mm) and 0.99 PPV (14.5 mm) (this study satisfied 9 of the 12 QUADAS domains assessed). This study appears to share at least some participants with reference 176, described above.

A study of 183 children with atopic dermatitis referred to a Finnish allergy clinic with suspected cow’s milk allergy used a mix of open and double blind food challenges to establish 99/183 cases of cow’s milk allergy. This study reported the following results with respect to DBPCFC (and open food challenge): sensitivity 0.48 (0.47), specificity 0.86 (0.83), likelihood ratio of positive test 3.46 (2.70), likelihood ratio of negative test 0.60 (0.64). Skin testing was not performed during the elimination period in 40 cases due to persistent atopic dermatitis, but these participants appear to have been included in the calculation of sensitivity and specificity as negative test results (this study satisfied 10 of the 12 QUADAS domains assessed).

A study of 37 children (aged 1.5-84 months) consecutively referred to a Turkish allergy clinic with suspected cow’s milk allergy found 23/37 cases of cow’s milk allergy via DBPCFC (or history of anaphylaxis due to milk in 6/23 patients). This study used a commercial milk allergen (ALK) and reported the sensitivity and specificity of SPT with respect to early reactions (occurring within two hours of food challenge) and late reactions (occurring two hours after food challenge). The study reported 100 percent sensitivity of the SPT to patients with early reactions to food challenge (19/19) compared to 50 percent sensitivity of the SPT to patients with late reactions (2/4). The SPT was 50 percent specific to both early and late reactions (this study satisfied 10 of the 12 QUADAS domains assessed).

A study of 104 children consecutively referred to an Italian pediatric allergy clinic for evaluation of suspected CMA (mean age 3.6, with standard deviation of 2.9, 71 percent male) compared the effectiveness of three milk proteins (lactalbumin, beta-lactoglobulin, and casein) with fresh milk for the detection of CMA using SPT. The study reported that fresh milk produced the largest mean wheal diameters and highest sensitivity (96.4 percent) whereas casein had the highest specificity (96 percent). When a positive test was defined as a positive reaction to any of the three milk proteins, the sensitivity was 89.3 percent, which rose to 96.4 percent if milk was included. This study also reported optimal decision points for each milk protein to achieve a 95% PPV: 5 mm for lactalbumin, 3 mm for casein, 4 mm for beta-lactoglobulin, and 8 mm for fresh milk (this study satisfied 7 of the 12 QUADAS domains assessed).174

A 2007 study that included all children (3-48 months of age) referred to a Naples pediatric gastroenterology clinic for suspected food-allergy related symptoms performed open food challenges with fresh CM based on the results of skin prick tests, APT, and sIgE. Among 55 children challenged with CM, 31 had positive reactions (10 early and 21 late reactions). Skin prick tests with wheal diameters of ≥3mm were defined as positive if participants had no reactions to the control substance. The test had a sensitivity of 0.45, a specificity of 0.70, a PPV of 0.67 and a NPV of 0.51 (this study satisfied 11 of the 12 QUADAS domains assessed).
Hen's Egg Allergy

Eight studies of the use of skin prick tests in hen's egg allergy met our inclusion criteria and are described in Table 20.

In a 2003 study, 151 children consecutively referred to a Bologna university hospital pediatric allergy clinic with multiple atopic symptoms received a food challenge, skin prick tests, and two different commercial sIgE tests to compare the results. Among the challenges, 40 responded positively to hen’s egg. A positive skin prick test, defined as a wheal diameter of 3mm or greater, was obtained in 31 of 34 children. The test had a sensitivity of 0.91, a specificity of 0.77, a PPV of 0.65 and a NPV of 0.95 (this study satisfied 10 of the 12 QUADAS domains assessed).

In a 2004 study of a 3-year-old birth cohort of 495 children in Denmark, parents completed a questionnaire that included questions about food hypersensitivities. Based on the responses, children were given open food challenges and skin prick tests (as well as APT, sIgE, and basophil histamine release assessments). Eight of 14 children had positive challenge responses to hen’s egg; 9 of 14 had positive skin prick tests, defined as a wheal diameter 3mm or larger. The test had a sensitivity of 0.88, a specificity of 0.83, a PPV of 0.88 and a NPV of 0.83 (this study satisfied 8 of the 12 QUADAS domains assessed).

In another 2004 study of 48 children (3-29 months) consecutively recruited to a French pediatric hospital allergy clinic with AD, open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Skin prick tests were performed with fresh egg; positive tests were defined as wheal diameters ≥3mm greater than negative control and at least 50% greater than positive control. The test had a sensitivity of 0.93, a specificity of 0.50, a PPV of 0.97, and a NPV of 0.66 (this study satisfied 10 of the 12 QUADAS domains assessed).

In a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis, 42 received a DBPCFC for hen’s egg and a skin prick test with whisked egg white and yolk to compare the results of skin prick test with that of atopy patch test, sIgE, and combinations of the tests. Of the 42 challenges, 28 were positive. A positive skin prick test, defined as a wheal diameter of 3mm or greater with no reaction to the negative control, was obtained in 31 of 98 children. The test had a sensitivity of 0.89, a specificity of 0.57, a PPV of 0.81 and a NPV of 0.73 (this study satisfied 9 of the 12 QUADAS domains assessed).

In a study of 437 children (aged 3 months to 17 years) consecutively referred to a German allergy clinic with suspected food allergy, 193/437 were diagnosed with hen's egg allergy via DBPCFC. This study used fresh egg samples (yolk and white), but did not report the definition of a positive test used. They report sensitivity of the test of 0.93, specificity of 0.54, PPV of 0.79, and NPV of 0.81. They also report the decision points (wheal sizes) necessary for achieving 0.95 PPV (9.0 mm) and 0.99 PPV (11.9 mm) (this study satisfied 9 of the 12 QUADAS domains assessed).

A study of 107 children (ages 1-19 months) with AD and no prior egg exposure referred to an Italian allergy clinic for management of AD used open egg challenge to find a 72/107 children with egg allergy. The SPT used a commercial extract of albumin and yolk and reported sensitivities for a range of wheal sizes (though they do not describe whether they use an absolute
wheal size, or one relative to the negative control) (this study satisfied 8 of the 12 QUADAS domains assessed). Data are shown in Table 20.

A study of 104 patients (ages 12-15 months) with IgE-mediated cow’s milk allergy (by history and SPT/sIgE) with no prior egg exposure consecutively seen at a Spanish hospital found 38/104 children with egg allergies. They performed skin prick tests with commercial extracts of six egg allergens: egg white, yolk, ovalbumin, ovomucoid, ovotransferrin, and lysozyme (this study satisfied 11 of the 12 QUADAS domains assessed). Results are reported in Table 20. This study also reported receiver-operating characteristic (ROC) curves, which were used to generate the area under the curve and optimal decision points (the diagnostic cutoff points that optimize sensitivity and/or specificity of the test).

A 2007 study that included all children (3-48 months of age) referred to a Naples pediatric gastroenterology clinic for suspected food-allergy related symptoms performed open food challenges with fresh HE based on the results of skin prick tests, APT, and sIgE. Among 28 children challenged with HE, 19 had positive reactions (5 early and 14 late reactions). Skin prick tests with wheal diameters of $\geq 3\text{mm}$ were defined as positive if participants had no reactions to the control substance. The test had a sensitivity of 0.58, a specificity of 0.67, a PPV of 0.79 and a NPV of 0.43 (this study satisfied 11 of the 12 QUADAS domains assessed).

Peanut Allergy

Three studies of the use of skin prick tests in suspected peanut allergy met our inclusion criteria and are described in Table 21.

A 2002 study of 393 children referred to a French allergy clinic with suspected food allergy found a rate of 177/393 peanut allergic children with DBPCFC. This study used a fresh peanut mix for the skin prick tests and defined a positive test as a wheal greater than 3 mm larger than the negative control. The study reported a sensitivity/specificity for two wheal sizes. For wheals $3\text{mm}$ larger than negative control, sensitivity was 1.00, specificity was 0.66, PPV was 0.74, and NPV was 1.00. For wheal diameter $16\text{mm}$ larger than the negative control, sensitivity was 14.7, specificity was 1.00, PPV was 1.00, and NPV was 0.55. This study did not monitor for late reactions to food challenge. The study reported ROC curves for both commercial and raw peanut extracts (this study satisfied 10 of the 12 QUADAS domains assessed).

A 2004 study consecutively recruited 48 children (3-29 months of age) with AD and suspected food allergy to a French pediatric hospital allergy clinic to compare the performance of skin prick tests, APT, and sIgE. Open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Oral challenges and skin prick tests were performed with fresh ground peanut; positive skin prick tests were defined as wheal diameters $\geq 3\text{mm}$ greater than negative control and at least 50% greater than positive control. The test had a sensitivity of 0.70, a specificity of 0.50, a PPV of 0.60, and a NPV of 0.55 (this study satisfied 10 of the 12 QUADAS domains assessed).

A study was conducted among 84 children who were consecutively recruited from children attending a Sydney pediatric hospital allergy clinic based on positive skin prick test for peanut
allergy using a commercial extract and a wheal size cutoff of 3 mm larger than the saline control. All participants without a history of having ingested peanut in the preceding 3 months were given an open in-hospital challenge along with sIgE measures and an immediate skin application food test (I-SAFT, a rapid topical test used to assess sensitivity to very small quantities of allergen). The purpose of the study was to assess the clinical usefulness of available *in vitro* and *in vivo* tests, alone or in combination, compared with food challenge. The sensitivity and specificity of the skin prick test were assessed at two different wheal diameter cutoffs: 8 mm and 15 mm. For wheal diameter 8 mm larger than the negative control, sensitivity was 0.75, specificity was 0.67, PPV was 0.78, and NPV was 0.63. For wheal diameter 15 mm larger than the negative control, sensitivity was 0.06, specificity was 1.00, PPV was 1.00, and NPV was 0.40 (this study satisfied 9 of the 12 QUADAS domains assessed).

A fourth study for which only 44 percent of the participants had their allergy confirmed by food challenge or history (and no data were provided to assess the performance characteristics of the index test) also assessed the use of skin prick test to diagnose peanut allergy. The results of the skin prick test alone were not considered predictive of reaction to peanuts.

### Soy Allergy

Two studies of the use of skin prick tests in soy allergy met our inclusion criteria and are described in Table 22.

In a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis, 25 received a DBPCFC for soy milk and a skin prick test to compare the results of skin prick test with that of atopy patch test, sIgE, and combinations of the tests. Of the 25 food challenges, 4 were positive. A positive skin prick test was defined as a wheal diameter of 3 mm or greater with no reaction to the negative control. Four of 98 children had positive skin prick tests to soy milk. The test had a sensitivity of 0.67, a specificity of 0.53, a PPV of 0.60 and a NPV of 0.60 (this study satisfied 9 of the 12 QUADAS domains assessed).

In a study of 437 children (aged 3 months to 17 years) consecutively referred to a German allergy clinic with suspected food allergy, 37/437 were diagnosed with soy allergy via DBPCFC. This study used fresh soy samples, but did not report the definition of a positive test. They reported a sensitivity for the test of 0.29, specificity of 0.85, PPV of 0.33, and NPV of 0.82 (this study satisfied 9 of the 12 QUADAS domains assessed).

### Wheat Allergy

Three studies of the use of skin prick tests in wheat allergy met our inclusion criteria and is described in Table 23.

In a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis, 35 received a DBPCFC for wheat and a skin prick test with wheat powder dissolved in water to compare the results of skin prick test with that of atopy patch test, sIgE, and combinations of the tests. Of the 35 challenges, 18 were positive. A positive test, defined as a wheal diameter of 3 mm or greater with no reaction to the negative control, was
obtained in 20 of the 98 children. The test had a sensitivity of 0.67, a specificity of 0.53, a PPV of 0.60 and a NPV of 0.60 (this study satisfied 9 of the 12 QUADAS domains assessed).

In a study of 437 children (aged 3 months to 17 years) consecutively referred to a German allergy clinic with suspected food allergy, 159/437 were diagnosed with wheat allergy via DBPCFC. This study used wheat samples, but did not report the definition of a positive test used. They report a sensitivity for the skin prick test of 0.75, specificity of 0.64, PPV of 0.49, and NPV of 0.85 (this study satisfied 9 of the 12 QUADAS domains assessed).

A 2004 study consecutively recruited 48 children (3-29 months of age) with AD and suspected food allergy to a French pediatric hospital allergy clinic to compare the performance of skin prick tests, APT, and sIgE. Open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Oral challenges and skin prick tests were performed with fresh wheat powder; positive skin prick tests were defined as wheal diameters ≥3mm greater than negative control and at least 50% greater than positive control. The test had a sensitivity of 0.75, a specificity of 0.50, a PPV of 0.75, and a NPV of 0.50 (this study satisfied 10 of the 12 QUADAS domains assessed).

IgE-mediated wheat allergy may be indistinguishable from celiac disease based on history and symptomatology alone. In particular, individuals with gastrointestinal symptoms consistent with for food allergy and negative work up for IgE-mediated food allergy may benefit from evaluation for celiac disease. The tests used commonly for the evaluation of celiac disease (CD) differ from those used for other allergic diseases. The diagnosis of celiac disease is suggested when biopsy of the small intestine reveals the presence of villous atrophy and crypt hyperplasia (scoring systems for intestinal biopsy include the Alexander's classification and the ESPGAN criteria; no studies validating these criteria satisfied our screening criteria) with the diagnosis confirmed by resolution of symptoms and histological abnormalities following removal of wheat from the diet and recurrence of either on rechallenge with wheat. No studies examining the reliability of this standard met our inclusion criteria. Additionally, no studies were identified that directly compared the diagnosis of IgE-mediated wheat allergy to celiac disease in individuals presenting with suspected wheat allergy (of either type).

Other Food Allergies
Two other studies that examined the performance characteristics of the skin prick test met the inclusion criteria.

A 2000 study enrolled 53 consecutive adults (15-69 years) who were referred to a Madrid university hospital allergy clinic complaining of reaction to melon. Allergy to melon as well as related foods was confirmed by open food challenge followed by DBPCFC using fresh foods unless the patient had a history of anaphylaxis associated with the food(s). Nineteen patients had positive DBPCFC or history of anaphylaxis in response to melon. Thirty six had positive skin prick tests, defined as wheal diameter ≥3mm. They reported a sensitivity for the test of 0.79,
specificity of 0.38, PPV of 0.42, and NPV of 0.77 (this study satisfied 9 of the 12 QUADAS domains assessed).

A 2005 study enrolled 100 consecutive patients who presented to a Bangkok university pediatric allergy clinic with urticaria over a 2-year period. Among 36 with suspected food hypersensitivity (to CM, HE, wheat, or shrimp), DBPCFC was performed on 22, and another 5 had a history of anaphylaxis in response to one of the foods. Skin prick tests were performed with one or more of the fresh foods in question. The definition of a positive skin prick test was not provided. The test (for all four foods combined) had a sensitivity of 0.83, a specificity of 0.38, a PPV of 0.28 and a negative predictive value of 0.89 (this study satisfied 8 of the 12 QUADAS domains assessed).

**Risks and Pitfalls to Skin Prick Testing**

A systematic review of systemic reactions from skin testing from 2006 found that while skin prick testing is generally safe, testing with fresh foods was not without risk, particularly for patients with prior history of anaphylaxis, small children, pregnant women, uncontrolled asthmatics, and high degree of reactivity. The authors concluded that while the risk of fatality from skin prick testing was "extremely remote," physicians performing such tests should be aware of this risk and prepared to deal with potentially fatal reactions.

A critique of the studies included in the analysis is that none actually confirmed the concentrations of the suspected allergen proteins in the foods or extracts. Of thirteen studies, five relied on commercial extracts only, six used only fresh foods (although preparation was not always specified), and two used both commercial extracts and fresh.

**Summary**

The reported sensitivity and specificity of skin prick testing varies greatly. There also are important issues regarding the standardization of the procedure in terms of the test allergen used and the interpretation of the wheal. Due to inconsistency of results and limitations in study design and execution, the overall quality of evidence is judged to be low, meaning further research is likely to have an important impact in our confidence in the estimate of effect. The studies of SPT included in this report satisfied 7 to 11 of the 12 QUADAS domains assessed.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Assay</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prahl, 1988&lt;sup&gt;166&lt;/sup&gt;</td>
<td>26 children (aged 1-63 months) consecutively referred to a Danish university hospital allergy clinic for suspected cow milk allergy</td>
<td>Open food challenge</td>
<td>Skin prick test with raw cow’s milk, positive test defined as wheal diameter ≥ histamine (positive) control</td>
<td>Se 0.8  Sp 0.66  PPV 0.89  NPV 0.50</td>
</tr>
<tr>
<td>Garcia-Ara, 2000&lt;sup&gt;167&lt;/sup&gt;</td>
<td>170 infants (aged 1-12 months) consecutively seen at a Madrid children’s hospital allergy service for suspected cow milk allergy</td>
<td>Open controlled challenge tests performed in 161 infants; remaining 9 had history of severe allergic reaction to cow’s milk protein and evidence of milk sIgE</td>
<td>Skin prick test with alpha-lactalbumin (ALA), beta-lactoglobulin (BLG), whole milk, and casein; positive test defined as a net wheal diameter ≥3mm≥negative control</td>
<td>Se Milk 0.72  Sp 0.62  PPV 0.60  NPV 0.73  ALA 0.66  Sp 0.64  PPV 0.59  NPV 0.70  BLG 0.84  Sp 0.53  PPV 0.59  NPV 0.81  Casein 0.55  Sp 0.87  PPV 0.78  NPV 0.71  ≥1 0.99  Sp 0.38  PPV 0.56  NPV 0.97</td>
</tr>
<tr>
<td>Roehr, 2001&lt;sup&gt;171&lt;/sup&gt;</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>71 DBPCFC with cow milk based on history 45/71 diagnosed with milk allergy</td>
<td>Skin prick test with fresh milk; positive test defined as a net wheal diameter ≥3mm with no reaction to negative control; 43/98 positive reactions</td>
<td>Se Milk 0.72  Sp 0.62  PPV 0.60  NPV 0.73  ALA 0.66  Sp 0.64  PPV 0.59  NPV 0.70  BLG 0.84  Sp 0.53  PPV 0.59  NPV 0.81  Casein 0.55  Sp 0.87  PPV 0.78  NPV 0.71  ≥1 0.99  Sp 0.38  PPV 0.56  NPV 0.97</td>
</tr>
<tr>
<td>Saarinen, 2001&lt;sup&gt;172&lt;/sup&gt;</td>
<td>239 infants (6-7 months) from a prospective Finnish birth cohort study on the effect of infant formulae on development of cow’s milk allergy with symptoms that disappeared on withdrawal of milk</td>
<td>239 open challenges 118/239 positive</td>
<td>Skin prick test with Cow’s milk formula, whole milk, or protein fractions; a positive test was defined as a wheal diameter of ≥3</td>
<td>CM ≥3 0.61  Sp 0.76  PPV 0.71  NPV 0.67  ≥6 0.37  Sp 0.93  PPV 0.83  NPV 0.60  ≥8 0.19  Sp 0.98  PPV 0.92  NPV 0.55</td>
</tr>
<tr>
<td>Ricci, 2003&lt;sup&gt;168&lt;/sup&gt;</td>
<td>151 children consecutively referred to a university hospital pediatric allergy clinic in Bologna for suspected food allergy (CM and HE)</td>
<td>FC (blinding not specified) 27 positive for CM</td>
<td>SPT with foods, preparation not specified Cutoff: wheal diameter≥3mm</td>
<td>Cow’s milk: 17/22 positive  Se 0.77  Sp 0.6  PPV 0.9  NPV 8 3 4</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Reference Test</td>
<td>Assay</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Osterball, 2004169</td>
<td>495 children 3 years of age with and without AD (members of a Danish birth cohort) whose parents responded to a questionnaire about food hypersensitivity</td>
<td>OFC to assess both early and late reactions: 3/8 positive for CM</td>
<td>Skin prick test performed with fresh CM Cutoff: ≥3mm</td>
<td>2/8 positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Se   Sp   PPV   NPV</td>
</tr>
<tr>
<td>Rancé, 2004170</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic with AD</td>
<td>OFC (based on results of APT, SPT, or slgE) or slgE</td>
<td>Skin prick test performed with fresh CM Cutoff: ≥3mm larger than negative control and ≥50% larger than positive control</td>
<td>Se   Sp   PP   NP V</td>
</tr>
<tr>
<td>Mehl, 2006149*</td>
<td>437 German children (aged 3 mos to 17 years) consecutively referred to a specialist for suspected food allergy (excluding those with a clear history of food related symptoms). 391 patients had history of AD.</td>
<td>DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, slgE, and clinical history. 168/437 diagnosed with cow’s milk allergy by DBPCFC</td>
<td>Skin prick test with fresh food samples, definition of positive tests not reported.</td>
<td>Se   Sp   PPV   NPV</td>
</tr>
<tr>
<td>Decision Points</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canani, 2007175</td>
<td>All children 3-48 months referred to Pediatric gastroenterology center in Naples for suspected FA-related symptoms</td>
<td>OFC with fresh CM, based on reactions to SPT, APT, and slgE: 89 challenges performed in 60 patients CM: 31/55 positive (10 early reax, 21 late reax)</td>
<td>SPT with fresh CM Positive reaction: ≥3mm with no reaction to control</td>
<td>Se   Sp   PP   NP V</td>
</tr>
</tbody>
</table>
### Study Population Reference Test Assay Results

**Isolauri, 1996**

183 Finnish children (ages 2-36 months) with AD and suspected CMA

Patients randomized to DBPCFC (n=118) and open FC (n=65)

99/183 confirmed with CMA by oral challenge.

Commercial cow milk allergen (ALK) and milk powder. Reactions read at 15 minutes with wheals greater than half the histamine reactions size were considered positive.

<table>
<thead>
<tr>
<th>DBPCFC (Open)</th>
<th>SPT positive %</th>
<th>negative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=64 (35)</td>
<td>48 (47)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>n=54 (30)</td>
<td>52 (53)</td>
<td>86 (83)</td>
</tr>
</tbody>
</table>

**Keskin, 2005**

37 consecutive children (age 1.5-84 months) with suspected CMA referred to Turkish allergy clinic at a tertiary care center excluding children with chronic disease.

DBPCFC preceded by at least 2 weeks of elimination of CM (except in 6 patients with history of anaphylactic reaction to cow's milk).

Reactions were categorized as early (within 2 hours of test) or late.

23/37 had positive challenges or history of anaphylactic reaction

Skin prick test with commercial allergen (ALK) wheal greater than or equal to 3mm larger than negative control was considered positive.

<table>
<thead>
<tr>
<th>FC</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blind</td>
<td>0.48</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>0.47</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Also reports concordance of SPT with ALK and milk powder: Cohen's kappa=0.86 with 95% CI=[0.77, 0.95].

<table>
<thead>
<tr>
<th>SPT positive</th>
<th>neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>early</td>
<td>late</td>
</tr>
<tr>
<td>positive</td>
<td>19</td>
</tr>
<tr>
<td>negative</td>
<td>0</td>
</tr>
</tbody>
</table>

**Calvani, 2007**

104 children consecutively referred to an Italian pediatric allergy clinic for evaluation of suspected CMA

Food challenge (70 open and 34 DBPCFC)

28/104 tests were positive

SPT with:
- lactalbumin
- casein
- beta-lactoglobulin
- fresh milk
- with positive tests defined as mean wheal diameters 3mm ≥ the negative control.

<table>
<thead>
<tr>
<th>Test</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactalbumin</td>
<td>75</td>
<td>80</td>
<td>58</td>
<td>90</td>
</tr>
<tr>
<td>casein</td>
<td>61</td>
<td>96</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>beta-lactoglobulin</td>
<td>75</td>
<td>82</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>fresh milk</td>
<td>96</td>
<td>65</td>
<td>50</td>
<td>98</td>
</tr>
<tr>
<td>≥1 protein positive</td>
<td>89</td>
<td>71</td>
<td>53</td>
<td>95</td>
</tr>
<tr>
<td>≥1 SPT positive</td>
<td>96</td>
<td>61</td>
<td>47</td>
<td>98</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; APT atopy patch test; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; Se sensitivity; Sp specificity; SPT skin prick test; *these two studies appear to share some participants

98
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Assay</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roehr, 2001</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>DBPCFC on 42 children based on history 28/42 diagnosed with egg allergy</td>
<td>Skin prick test with raw egg white and yolk; positive test defined as a net wheel diameter $\geq$ 3mm with no reaction to negative control; 31/98 positive reactions</td>
<td>Se</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Ricci, 2003</td>
<td>151 children consecutively referred to a university hospital pediatric allergy clinic in Bologna for suspected food allergy (CM and HE)</td>
<td>FC (blinding not specified) 40 positive for HE</td>
<td>SPT with foods, preparation not specified Cutoff: wheal diameter $\geq$3mm</td>
<td>31/34 positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Osterballe, 2004</td>
<td>495 children 3 years of age with and without AD (members of a Danish birth cohort) whose parents responded to a questionnaire about food hypersensitivity</td>
<td>OFC to assess both early and late reactions: 8/14 positive for HE</td>
<td>Skin prick test performed with fresh HE Cutoff: $\geq$3mm</td>
<td>9/14 positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Rancé, 2004</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic with AD</td>
<td>OFC (based on results of APT, SPT, or sIgE) or sIgE</td>
<td>Skin prick test performed with fresh whole HE Cutoff: $\geq$3mm larger than negative control and $\geq$50% larger than positive control</td>
<td>Se</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>Canani, 2007</td>
<td>All children 3-48 months referred to Pediatric gastroenterology center in Naples for suspected FA-related symptoms</td>
<td>OFC with fresh HE, based on reactions to SPT, APT, and sIgE: 89 challenges performed in 60 patients 19/28 positive for HE (5 early, 14 late reactions)</td>
<td>SPT with fresh HE Positive reaction: $\geq$3mm with no reaction to control</td>
<td>Se</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
</tbody>
</table>
### Study Population Reference Test Assay Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Assay</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehl, 2006&lt;sup&gt;149&lt;/sup&gt;</td>
<td>437 German children (aged 3mos to 17 years) consecutively referred to specialist for suspected food allergy (excluding those with a clear history of food related symptoms). 391 patients had history of AD.</td>
<td>DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, sIgE, and clinical history.</td>
<td>Skin prick test with fresh food samples, definition of positive tests not reported.</td>
<td>Se 0.93, Sp 0.54, PPV 0.79, NPV 0.81, Eff 0.79</td>
</tr>
<tr>
<td>Monti, 2002&lt;sup&gt;176&lt;/sup&gt;</td>
<td>107 children (age 1-19 months) with atopic dermatitis and no prior egg exposure referred to an Italian allergy clinic for management of AD.</td>
<td>Open egg challenge, monitoring for early and late reactions (up to 8 days)</td>
<td>SPTs were performed with commercial extracts of albumin and yolk; they reported the absolute measure of the wheal diameter.</td>
<td>PPV wheal 0.95, 9.0 mm, n 68/437</td>
</tr>
<tr>
<td>Diéguez, 2008&lt;sup&gt;177&lt;/sup&gt;</td>
<td>104 patients (ages 12-15 months) with IgE mediated CMA (by history and SPT/sIgE) with no prior egg exposure consecutively seen in the allergy clinic of a Spanish hospital</td>
<td>Open oral challenge with egg components.</td>
<td>SPTs with egg white, yolk, ovalbumin (OVA), ovomucoid (OVM), ovotransferrin (OVT), and lysozyme commercial extracts (Bial-Aristegui laboratories). Wheal of 3 mm or larger was regarded as positive.</td>
<td>SPT w/Yolk wheal Se 66.6, 88.6, Sp 92.3, PPV 56.3, NPV 77</td>
</tr>
</tbody>
</table>

### Table Notes
- AD atopic dermatitis; APT atopy patch test; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; NPV negative predictive value; Ova ovalbumin; Ovm ovomucoid; OVT ovotransferrin; OFC open food challenge; PPV positive predictive value; Se sensitivity; slgE antigen-specific immunoglobulin E; Sp specificity; SPT skin prick test
### Table 21: Summary of Peanut Allergy Assessments with Skin Prick Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Assay</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wainstein, 2007&lt;sup&gt;178&lt;/sup&gt;</td>
<td>84 children consecutively recruited in a Sydney pediatric hospital allergy clinic with positive SPT (defined as a wheal 3x3mm&gt; control)</td>
<td>DBPCFC or documented recent reaction to peanut</td>
<td>SPT performed with commercial whole peanut extract; geometric mean of wheal calculated; two wheal diameter cutoffs used to calculate sensitivity and specificity: ≥8mm and ≥15mm</td>
<td>Wheal (mm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51/84 peanut allergic by FC</td>
<td></td>
<td>≥ 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Rancé, 2004&lt;sup&gt;170&lt;/sup&gt;</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic with AD</td>
<td>OFC (based on results of APT, SPT, or sIgE) or sIgE</td>
<td>Skin prick test performed with raw peanut, crushed to powder and mixed with vehicle Cutoff: ≥3mm larger than negative control and ≥50% larger than positive control</td>
<td>Se</td>
</tr>
<tr>
<td>Rancé, 2002&lt;sup&gt;165&lt;/sup&gt;</td>
<td>393 children consecutively referred to a French hospital with suspected peanut allergy</td>
<td>DBPCFC preceded by elimination diet. Patients monitored for reactions for 4 hours following test. 177/393 peanut allergic by FC</td>
<td>SPT performed with commercial extract (Allerbio) and fresh peanut mix with wheals 3 mm greater than negative control defined as positive tests. The commercial extract was falsely negative in 32/171 patients, whereas the raw extract yielded a 100% sensitivity, so only data from the raw extracts was reported</td>
<td>Wheal (mm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥ 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; APT atopy patch test; DBPCFC double blind placebo-controlled food challenge; FC food challenge; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp specificity; SPT skin prick test
Table 22: Summary of Soy Allergy Assessments with Skin Prick Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Assay</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roehr, 2001</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>DBPCFC on 25 children for soy based on history</td>
<td>Skin prick test with soy milk; positive test defined as a net wheel diameter $\geq 3$mm with no reaction to negative control; 4/98 positive reactions to soy milk</td>
<td><strong>Se</strong> 0.50  <strong>Sp</strong> 0.90  <strong>PPV</strong> 0.50  <strong>NPV</strong> 0.90</td>
</tr>
<tr>
<td>Mehl, 2006</td>
<td>437 German children (aged 3mos to 17 years) consecutively referred to specialist for suspected food allergy (excluding those with a clear history of food related symptoms). 391 patients had history of AD.</td>
<td>DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, sIgE, and clinical history. 37/437 diagnosed with wheat allergy</td>
<td>Skin prick test with fresh food samples, definition of positive tests not reported.</td>
<td><strong>Se</strong> 0.29  <strong>Sp</strong> 0.85  <strong>PPV</strong> 0.33  <strong>NPV</strong> 0.82</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; APT atopy patch test; DBPCFC double blind placebo-controlled food challenge; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp specificity; SPT skin prick test
Table 23: Summary of Wheat Allergy assessments with Skin Prick Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Assay</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roehr, 2001</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>DBPCFC on 35 children for wheat based on history 18/35 diagnosed with wheat allergy</td>
<td>Skin prick test with wheat powder dissolved in water; positive test defined as a net wheel diameter $\geq$ 3mm with no reaction to negative control; 20/98 positive reactions to wheat</td>
<td>Se 0.67  Sp 0.53  PPV 0.60  NPV 0.60</td>
</tr>
<tr>
<td>Rancé, 2004</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic with AD</td>
<td>OFC (based on results of APT, SPT, or sIgE) or sIgE</td>
<td>Skin prick test performed with wheat powder dissolved in water Cutoff: $\geq$3mm larger than negative control and $\geq$50% larger than positive control</td>
<td>Se 0.75  Sp 0.50  PPV 0.75  NPV 0.50</td>
</tr>
<tr>
<td>Mehl, 2006</td>
<td>437 German children (aged 3mos to 17 years) consecutively referred to specialist for suspected food allergy (excluding those with a clear history of food related symptoms). 391 patients had history of AD.</td>
<td>DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, sIgE, and clinical history. 159/437 diagnosed with wheat allergy.</td>
<td>Skin prick test with fresh food samples, definition of positive tests not reported.</td>
<td>Se 0.75  Sp 0.64  PPV 0.49  NPV 0.85</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; DBPCFC double blind placebo-controlled food challenge; NPV negative predictive value; PPV positive predictive value; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp specificity; SPT skin prick test

**In Vitro (Immune) Tests**

A variety of in vitro tests of immune response have been developed because such tests are safe, relatively non-invasive, simple, and have the potential to provide rapid through-put at relatively low cost. Tests that measure total or allergen-specific IgE are generally used for suspected IgE-mediated reactions. This section describes studies that have assessed the use of these tests.

**Total IgE**

The most general in vitro test of atopy is that of total IgE. Two studies that met our inclusion criteria included measures of total IgE. In one study, which enrolled 34 children (3-51 months of age) suspected of having cow’s milk allergy and used elimination and food challenge as the reference, total IgE had a sensitivity of 0.58 and a specificity of 0.73 (this study satisfied 8 of the 12 QUADAS domains assessed).
In the other study, which enrolled 49 patients (1-51 years of age) with strong initial SPT response to whole spices and used SPT as the reference test to assess allergy to various spices, fruits, and vegetables, no correlation was found between total IgE levels and results of SPT.182 Neither of these studies found a difference in total IgE levels between allergic and non-allergic individuals (this study satisfied 7 of the 12 QUADAS domains assessed). The quality of this evidence is considered to be very low due to sparseness of data.

**Allergen-Specific IgE**

Assays to measure antigen-specific IgE (sIgE) have undergone several improvements since their first use in the early 1990s. The “first generation” of sIgE assays used a radioallergosorbic test (RAST) in which a patient’s serum was incubated with a quantity of the antigen in question. After removing unbound serum, the researcher would then add radio labeled antibody (IgG) that specifically recognizes the IgE in antigen-bound IgE complexes, separate unbound IgG after some incubation period, and count the radioactivity bound to the plates. Levels of reactivity are expressed as kilo-units of antibody per liter (kUA/L). Newer, more sensitive, variations of the test – the second and third generation - have since been developed. The second generation of test is referred to as the fluorescent enzyme immunoassay (FEIA) (e.g., UniCAP®), and the third generation is referred to as the chemiluminescent enzyme immunoassay (CLEIA) (e.g., Immulite 2000®). The major innovations consist of the chemical reaction (signal) used to detect the bound IgG-IgE-antigen complexes and automation involving application of the test antigens to solid surfaces. Although the threshold of sensitivity for these tests is advertised as 0.35 kU/L for the CAP and 0.1 for the Immulite, published studies establish their own cutoff levels of sIgE considered indicative of a positive test, and a number of studies have aimed to establish the level that optimized sensitivity and/or specificity of the test.

Twenty-five studies that met our inclusion criteria assessed the use of measures of sIgE or compared various automated systems for measuring sIgE for the diagnosis of allergy to specific foods. Among the studies that employed sIgE assays, 20 used a food challenge alone or combined with strong clinical history as the reference, three used the immediate SPT as the reference, and two used another measure of sIgE or another test as the reference. The studies are summarized according to the specific food for which reactivity was assessed. Studies aimed at determining whether combining sIgE with another test (e.g., SPT) is superior to using one test alone are described in a subsequent section.

**Food challenge/history as reference test**

**Cow’s Milk Allergy**

Fifteen studies that met the inclusion criteria assessed the use of sIgE to diagnose cow’s milk allergy with food challenge/history as a reference and are summarized in Table 24 (three of these studies—Roehr, 2001, Celik-Bilgili, 2005, and Mehl, 2006—may share at least some participants).
A small 1988 study of 26 children (aged 1-48 months) consecutively referred to a Danish hospital allergy clinic diagnosed 20 of the 26 children with cow’s milk allergy via open food challenge to compare the sensitivity and specificity of skin prick tests, sIgE, and a novel basophil histamine release assay. The sIgE was measured using a commercial extract of raw cow’s milk in the RAST assay; sensitivity was 0.80, specificity was 0.66, PPV was 0.89, and NPV was 0.5 (this study satisfied 8 of the 12 QUADAS domains assessed).

A 1990 study enrolled 34 children with suspected cow’s milk allergy (3-51 months). Allergies were confirmed in 19 with food challenge: 14 showed immediate response and five showed delayed response. Cow’s milk-sIgE determination with the RAST demonstrated a sensitivity of 0.63 and specificity of 0.80 (this study satisfied 8 of the 12 QUADAS domains assessed).

In a 2001 study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis, 71 received a DBPCFC with fresh milk to compare the results of skin prick test, atopy patch test, sIgE, and combinations of the tests. Among the challenges, 45 of 71 were positive. sIgE was determined using the Pharmacia CAP FEIA; a positive test was considered any value above the detection limit of 0.35 kU/L. Among the 98 children tested, 54 expressed CM sIgE. The test had a sensitivity of 0.84, a specificity of 0.38, a PPV of 0.70 and a NPV of 0.59 (this study satisfied 9 of the 12 QUADAS domains assessed).

The 2001 cohort study that identified infants who appeared to react to cow’s milk formula compared the sensitivity and specificity of sIgE using three different cutoff points as well as sIgE levels in response to three different forms of milk. The maximum sensitivity (0.72) and NPV (0.61) were found at a cutoff of ≥0.35kU/ml; the maximum specificity (0.98) and PPV (0.94) were found at a cutoff of ≥3.5kU/ml (this study satisfied 11 of the 12 QUADAS domains assessed).

A 2001 study of 170 children (aged 1-12 months) consecutively seen at a Madrid university hospital allergy clinic diagnosed 67 of the 170 children with cow’s milk allergy (161 based on DBPCFC and 9 based on history of severe reaction to exposure) to compare the sensitivity and specificity of sIgE using whole milk as well as three of its component proteins (α-lactalbumin[ALA], β-lactoglobulin[BLG], and casein) with that of the SPT to test immediate hypersensitivity. When at least one of the four sIgE levels was positive, the sensitivity (0.85) and NPV (0.83) were highest. Specificity and PPV were highest for ALA (0.84 and 0.74, respectively) (this study satisfied 8 of the 12 QUADAS domains assessed).

A 2003 study enrolled 35 children (2-57 months) referred for persistent, non-specific digestive symptoms to compare the utility of sIgE and APT in these children. Using food challenge (open, or if equivocal, blinded), they determined that 24 children had cow’s milk allergy and 11 did not. Cow’s milk-sIgE was positive in three of the 24 with CMA (0.6 kUI/L, 0.36 kUI/L, and 0.49 kUI/L) and negative in all 11 without evidence of cow’s milk allergy (sensitivity: 0.13; specificity: 1) (this study satisfied 8 of the 12 QUADAS domains assessed).

A 2006 study measured cow’s milk sIgE in 437 children (3 mos-14 years) using the CAP system. Sensitivity was 0.87, specificity was 0.49; PPV was 0.62; NPV was 0.79; and efficiency was 0.68 (this study satisfied 8 of the 12 QUADAS domains assessed).
A 2005 study enrolled 501 children with suspected food allergy (1 mo-16.1 years) to assess the predictive value of specific sIgE for cow’s milk and other foods using the CAP system.\textsuperscript{185} Food challenge was used to confirm allergy in children older than 1 year. Sensitivity for cow’s milk was 0.83, specificity was 0.53; PPV was 0.63; NPV was 0.76. The 90 percent predictive decision point was 88.8kU/L. The patient population may possibly be the same patient population as or may overlap with that of Mehl and coworkers (this study satisfied 9 of the 12 QUADAS domains assessed).

A second 2005 study enrolled 37 children (1.5-84 mos) with suspected cow’s milk allergy referred to a Turkish hospital clinic and measured cow’s milk sIgE, using a cutoff of 0.7kU/L.\textsuperscript{173} The sensitivity was 0.74, specificity was 0.79, PPV was 0.85, and NPV was 0.65. Subgroup assessment of children with immediate vs. late-onset reactions showed that the sensitivity and PPV for sIgE, like those of the SPT, were much lower for late-onset reactions than for early-onset, consistent with a non-IgE-mediated mechanism for late-onset reactions (this study satisfied 10 of the 12 QUADAS domains assessed).

A 2001 study enrolled 100 children (3 mos-14 years) with suspected IgE-mediated food allergy to assess the performance characteristics of the Pharmacia CAP System FEIA for six different foods, including milk.\textsuperscript{186} Sixty-two children were diagnosed with milk allergy (1/3 based on positive challenge, the remainder based on clinical history). They tested 95 percent predictive decision points (the serum sIgE levels above which patients had a 95 percent probability of having a positive reaction to the food on a challenge test) for sIgE determined previously with a retrospective sample. Sensitivity and specificity were assessed at the 90 percent and 95 percent predictive decision points. At the 90 percent predictive decision point (15 kUA/L the test had a sensitivity of 0.57, a specificity of 0.94, a PPV of 0.95 and a NPV of 0.53 (this study satisfied 9 of the 12 QUADAS domains assessed).

In a 2003 study, 151 children consecutively referred to a Bologna university hospital pediatric allergy clinic with multiple atopic symptoms received a food challenge, skin prick tests, and two different commercial sIgE tests to compare the results of the two commercial tests.\textsuperscript{168} Among the challenges, 27 responded positively to CM. A positive test was defined as a sIgE value \( \geq 0.35kU/L \). The Pharmacia UniCAP test was slightly more sensitive, with a sensitivity of 0.91, a specificity of 0.70, a PPV of 0.44 and a NPV of 0.97; the Centaur test had a sensitivity of 0.82, a specificity of 0.74, a PPV of 0.45 and a NPV of 0.94 (this study satisfied 10 of the 12 QUADAS domains assessed).

In a 2004 study of a 3-year-old birth cohort of 495 children in Denmark, parents completed a questionnaire that included questions about food hypersensitivities.\textsuperscript{169} Based on the responses, children were given open food challenges, skin prick tests, atopy patch tests, sIgE, and basophil histamine release assessments. Three of 8 children had positive challenge responses to cow’s milk. The test system was a Magic Lite, with a positive result being defined as a value greater than 1.43 sU/ml. The test had a sensitivity of 0.66, a specificity of 0.40, a PPV of 0.40 and a NPV of 0.66 (this study satisfied 8 of the 12 QUADAS domains assessed).
In another 2004 study of 48 children (3-29 months) consecutively recruited to a French pediatric hospital allergy clinic with AD, open food challenges for CM allergy were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Tests were performed with a Pharmacia CAP FEIA system; positive tests were defined as values ≥0.35kU/L. The test had a sensitivity of 0.31, a specificity of 0.66, a PPV of 0.83 and a NPV of 0.15 (this study satisfied 10 of the 12 QUADAS domains assessed).

A 2007 study that included all children (3-48 months of age) referred to a Naples pediatric gastroenterology clinic for suspected food-allergy related symptoms performed open food challenges with fresh CM based on the results of skin prick tests, APT, and sIgE. Among 55 children challenged with CM, 31 had positive reactions (10 early and 21 late reactions). A positive test was defined as a value ≥0.35kU/L. The test had a sensitivity of 0.23, a specificity of 0.74, a PPV of 0.54 and a NPV of 0.42 (this study satisfied 11 of the 12 QUADAS domains assessed).

Finally, a 2008 study enrolled all 1800 children (0-18 years of age) seen between 1994 and 2006 for suspected CM allergy. The aim of the study was to assess the utility of CM sIgE values in the first year of life for predicting persistent CM allergy at 3 years of age. The reference test was food challenge or positive history combined with sIgE. Based on positive challenge or history or a cutoff of ≥1kU/L, 135 children were considered CM allergic in their first year. Based on challenge, 56 children had persistent allergy after the age of 3. A sIgE value ≥3kU/L in the first year of life had the following performance characteristics for predicting persistent allergy: sensitivity: 0.68; specificity: 0.70; PPV: 0.83; NPV 0.52 (this study satisfied 8 of the 12 QUADAS domains assessed).

The sensitivity and specificity of sIgE measurement for the diagnosis of CMA varies widely among studies. In general, the sensitivity and NPV tend to be lower than the specificity and PPV. Again, this finding is consistent with an allergy that can be mediated by either IgE- or non-IgE-mediated mechanisms.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population (age range)</th>
<th>Reference Test</th>
<th>Assay System</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prahl, 1988</td>
<td>26 children (aged 1-63 months) consecutively referred to a Danish university hospital allergy clinic for suspected cow milk allergy</td>
<td>Open food challenge</td>
<td>RAST with commercial raw cow’s milk extract</td>
<td>Se  Sp  PPV  NPV</td>
</tr>
<tr>
<td></td>
<td>20/26 positive</td>
<td></td>
<td>(sIgE positive in 16/18 with CMA and 2/18 without CMA)</td>
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</tr>
<tr>
<td>Tainio, 1990</td>
<td>34 children w/ suspected CMA (3-51 mos)</td>
<td>Open challenge</td>
<td>RAST</td>
<td>Se  Sp</td>
</tr>
<tr>
<td></td>
<td>19/34 positive (14 immediate and 5 delayed)</td>
<td></td>
<td></td>
<td>0.63 0.8</td>
</tr>
<tr>
<td>Roehr, 2001*</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>71 DBPCFC with cow milk</td>
<td>CAP</td>
<td>Se  Sp  PPV  NPV</td>
</tr>
<tr>
<td></td>
<td>45/71 diagnosed with milk allergy</td>
<td>based on history</td>
<td></td>
<td>0.84 0.38 0.70 0.59</td>
</tr>
<tr>
<td>Saarinen, 2001</td>
<td>239 infants (6-7 months) from a prospective Finnish birth cohort study on the effect of infant formulae on development of cow’s milk allergy with symptoms that disappeared on withdrawal of milk</td>
<td>239 open challenges</td>
<td>CAP using whole CM and/or CM protein fractions</td>
<td>CM formula cutoff</td>
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<tr>
<td></td>
<td>118/239 positive</td>
<td></td>
<td></td>
<td>≥0.35 0.61 0.76 0.71 0.67</td>
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<td>≥0.7 0.37 0.93 0.83 0.60</td>
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<td>≥3.5 0.19 0.98 0.92 0.55</td>
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<td></td>
<td>(sIgE positive in 84/116 with CMA and 60/117 without CMA at a cutoff of 0.35)</td>
</tr>
<tr>
<td>Garcia-Ara, 2001</td>
<td>170 infants (aged 1-12 months) consecutively seen at a Madrid children’s hospital allergy service for suspected cow milk allergy</td>
<td>Open controlled challenge tests performed in 161 infants; remaining 9 had history of severe allergic reaction to cow’s milk protein and evidence of milk sIgE</td>
<td>CAP FEIA using milk, ALA, BLG, and casein; positive test defined as sIgE≥0.35</td>
<td>Antigen  Se  Sp  PPV  NPV</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>CM 0.84 0.56 0.61 0.81</td>
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<td></td>
<td></td>
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<td></td>
<td>ALA 0.55 0.84 0.74 0.70</td>
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<td>BLG 0.59 0.80 0.70 0.71</td>
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<td></td>
<td>Casein 0.71 0.75 0.70 0.76</td>
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<td>≥1 0.85 0.56 0.61 0.83</td>
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<td>CM by cutoff</td>
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<td>≥0.35 0.84 0.56 0.61 0.81</td>
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<td>≥0.7 0.74 0.71 0.67 0.83</td>
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<td>≥2.5 0.48 0.95 0.90 0.69</td>
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<td></td>
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<td>≥5 0.30 0.99 0.95 0.64</td>
</tr>
</tbody>
</table>

108
<table>
<thead>
<tr>
<th>Study</th>
<th>Population (age range)</th>
<th>Reference Test</th>
<th>Assay System</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeBoisseau, 2003</td>
<td>35 children (2-57 months) referred for diagnosis of non-specific persistent digestive symptoms.</td>
<td>Food challenge (open unless results equivocal)</td>
<td>CAP-RAST</td>
<td>sIgE positive in 3/24 with CMA, positive in 0/11 w/o CMA</td>
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<tr>
<td></td>
<td></td>
<td>24/35 positive</td>
<td></td>
<td>Se  0.89  Sp  1.00</td>
</tr>
<tr>
<td>Ricci, 2003</td>
<td>151 children consecutively referred to a university hospital pediatric allergy clinic in Bologna for suspected food allergy (CM and HE)</td>
<td>Food challenge (blinding not specified)</td>
<td>Pharmacia UniCAP vs. ADVIA Centaur cutoff=0.35kU/L</td>
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<tr>
<td></td>
<td></td>
<td>27 positive for CM</td>
<td></td>
<td>Se  0.91  Sp  0.70  PPV 0.44  NPV 0.97</td>
</tr>
<tr>
<td>Osterballe, 2004</td>
<td>495 children 3 years of age with and without AD (members of a Danish birth cohort) whose parents responded to a questionnaire about food hypersensitivity</td>
<td>OFC to assess both early and late reactions: 3/8 positive for CM</td>
<td>Magic Lite sIgE Cutoff: 1.43 sU/ml</td>
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<td></td>
<td>Se  0.66  Sp  0.40  PPV 0.40  NPV 0.66</td>
</tr>
<tr>
<td>Canani, 2007</td>
<td>All children 3-48 months referred to Pediatric gastroenterology center in Naples for suspected FA-related symptoms</td>
<td>OFC with fresh CM, based on reactions to SPT, APT, and sIgE: 89 challenges performed in 60 patients CM: 31/55 positive (10 early reax, 21 late reax)</td>
<td>Pharmacia CAP RAST Positive test ≥0.35kU/L</td>
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<td></td>
<td></td>
<td></td>
<td>Se  0.23  Sp  0.74  PPV 0.54  NPV 0.42</td>
</tr>
<tr>
<td>Rottem, 2008</td>
<td>All individuals seen between 1994 and 2006 for suspected milk allergy at an Israeli university medical center (1800 infants and children 0-18 years of age)</td>
<td>Food challenge or suggestive history</td>
<td>Immulite sIgE to whole milk and components Cutoff ≥1 kU/L 135 children considered positive; 56 children had persistent allergy past 3 years of age</td>
<td>Cutoff ≥3 kU/L at ≤1 year of age as prediction of persistent milk allergy at age 3:</td>
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<td></td>
<td>Se  0.68  Sp  0.83  PPV 0.83  NPV 0.0</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>CM sIgE ≥3 kU/L at ≤1 year of age was considered predictive of persistent CM allergy at 3 years of age</td>
</tr>
<tr>
<td>Rancé, 2004</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic with AD</td>
<td>OFC (based on results of APT, SPT, or sIgE) or sIgE</td>
<td>Pharmacia Upjohn CAP FEIA Cutoff: ≥0.35 kU/L</td>
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<td></td>
<td></td>
<td>Se  0.31  Sp  0.66  PPV 0.83  NPV 0.15</td>
</tr>
<tr>
<td>Mehl, 2006</td>
<td>437 children referred to specialist for diagnosis of suspected food allergy.</td>
<td>DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, sIgE, and clinical history. 168/437 positive</td>
<td>RAST</td>
<td></td>
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<td></td>
<td>Se  0.87  Sp  0.49  PPV 0.62  NPV 0.79</td>
</tr>
</tbody>
</table>
Celi̇k-Bilgili, 2005[185]
501 children (1 mo-16.1 yr)
Food challenge in children >1 year of age
CAP-RAST

Keskin, 2005[173]
37 children referred for suspected CMA
DBPCFC preceded by at least 2 weeks of elimination of CM (except in 6 patients with history of anaphylactic reaction to cow's milk). Reactions were categorized as early (within 2 hours of test) or late. 23/37 had positive challenges or history of anaphylactic reaction
ImmunoCAP FEIA

Sampson, 2001[186]
100 consecutive children (0.4-14.3 yrs)
Food challenge or strong history
62/100 positive, 1/3 based on food challenge
ImmunoCAP FEIA

Predictive decision points: 90%: 88.8 kU/L

Hen’s Egg Allergy

Ten studies attempted to assess the value of sIgE for diagnosing allergy to hen’s egg; however, one did not report study characteristics for specific foods.[188] Of the remaining four studies, one assessed sIgE for both egg white protein (albumin) and yolk, and three assessed sIgE for total egg protein. These studies are summarized in Table 25.

A 2001 study used the CAP system to assess the 90-percent predictive decision points for egg sIgE in 75 children (0.14-14.3 years) (1/3 diagnosed by positive challenge, the remainder by strong history).[186] At a cutoff of 7kU/L, the sensitivity was 0.61, specificity was 0.95, PPV was 0.98, and NPV was 0.38 (this study satisfied 9 of the 12 QUADAS domains assessed).

In another 2001 study, 98 children were admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis; 71 received a DBPCFC with hen’s egg to compare the results of skin prick test, atopy patch test, sIgE, and combinations of the tests.[171] Among the challenges, 28 of 42 were positive. sIgE was determined using the Pharmacia CAP FEIA; a positive test was considered any value above the detection limit of 0.35 kU/L. Among the 98 children tested, 36 expressed hen’s egg sIgE. The test had a sensitivity of 0.96, a specificity of

Table Notes: AD atopic dermatitis;; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test; Roehr, 2001, Mehl, 2006, and Celi̇k-Bilgili, 2005 may share some participants.
0.36, a PPV of 0.75 and a NPV of 0.83 (this study satisfied 9 of the 12 QUADAS domains assessed).

A 2002 study in 107 children (1-19 months) with atopic dermatitis and with no known previous exposure to egg used the RAST to measure both albumin- and yolk sIgEs. Using a cutoff of greater than 99kU/L for albumin sIgE, the test had a specificity of 1, a sensitivity of 16.6 percent, PPV of 100 percent and NPV of 36.8 percent. Using a cutoff of ≥17.5 kU/L for yolk sIgE, the test had a specificity of 1, sensitivity of 23.6 percent, PPV of 100 percent and NPV of 39 percent (this study satisfied 7 of the 12 QUADAS domains assessed).

A 2005 study of 501 children (1 mo-16.1 yr) with suspected egg allergy used the CAP system to assess the predictive value of sIgE levels for egg. The sensitivity was 0.97, specificity was 0.51, PPV was 0.80, and NPV was 0.89. The predicted probabilities (of a positive challenge) were 90 percent for a cutoff of 6.3, 95 percent for a cutoff of 12.6, and 99 percent for a cutoff of 59.2 kU/L for all children. Dividing children into those less than 1 year and those 1 year or older, the predictive probabilities were different. In children less than 1 year, the decision point using a 95 percent predicted probability was 10.9 kU/L, while it was 13.2kU/L for children over 1 year of age. Choosing a 90 percent predicted probability, this difference was 4.2 and 6.7kU/L, respectively (i.e., the titer was higher in older children) (this study satisfied 10 of the 12 QUADAS domains assessed).

A study of 437 children used the CAP system to assess the predictive value of sIgE for egg. They reported a sensitivity of 0.96, specificity of 0.48, PPV 0.79, and NPV 0.85 (this study satisfied 9 of the 12 QUADAS domains assessed).

In a 2003 study, 151 children consecutively referred to a Bologna university hospital pediatric allergy clinic with multiple atopic symptoms received a food challenge, skin prick tests, and two different commercial sIgE tests to compare the results of the two commercial tests. Among the challenges, 40 responded positively to HE. A positive test was defined as a sIgE value ≥0.35 kU/L. The Pharmacia UniCAP test was slightly more sensitive, with a sensitivity of 0.94, a specificity of 0.64, a PPV of 0.55 and a NPV of 0.96; the Centaur test had a sensitivity of 0.88, a specificity of 0.52, a PPV of 0.46, and a NPV of 0.90 (this study satisfied 10 of the 12 QUADAS domains assessed).

In a 2004 study of a 3-year-old birth cohort of 495 children in Denmark, parents completed a questionnaire that included questions about food hypersensitivities. Based on the responses, children were given open food challenges, skin prick tests, atopy patch tests, sIgE, and basophil histamine release assessments. Eight of 14 children had positive challenge responses to hen’s egg. The test system was a Magic Lite, with a positive result being defined as a value greater than 1.43 sU/ml. The test had a sensitivity of 0.63, a specificity of 0.66, a PPV of 0.71 and a NPV of 0.57 (this study satisfied 8 of the 12 QUADAS domains assessed).

In another 2004 study of 48 children (3-29 months) consecutively recruited to a French pediatric hospital allergy clinic with AD, open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Tests were performed with a Pharmacia CAP FEIA system; positive tests were defined as values ≥0.35kU/L. The test had a
sensitivity of 0.65, a specificity of 0.75, a PPV of 0.96 and a NPV of 0.21 (this study satisfied 10 of the 12 QUADAS domains assessed).

A 2007 study that included all children (3-48 months of age) referred to a Naples pediatric gastroenterology clinic for suspected food-allergy related symptoms performed open food challenges with fresh hen’s egg, based on the results of skin prick tests, APT, and sIgE. Among 28 children challenged with hen’s egg, 19 had positive reactions (5 early and 14 late reactions). A positive test was defined as a value ≥0.35kU/L. The test had a sensitivity of 0.32, a specificity of 0.67, a PPV of 0.67 and a NPV of 0.32 (this study satisfied 11 of the 12 QUADAS domains assessed).

Thus, four studies found high sensitivity and NPV but relatively low specificity for egg sIgE, whereas two other studies observed a lower sensitivity but high specificity. The aim of at least two of the studies was to identify threshold values that would maximize the positive predictive value (specificity), in order to minimize the proportion of individuals who might needlessly be consigned to avoidance of egg.
<table>
<thead>
<tr>
<th>ID/Author, Yr.</th>
<th>Population (age range)</th>
<th>Reference Test</th>
<th>Assay System</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampson, 2001&lt;sup&gt;186&lt;/sup&gt;</td>
<td>75 consecutive children (0.4-14.3 yrs)</td>
<td>Food challenge or strong history</td>
<td>Pharmacia CAP FEIA</td>
<td>Decision Point (kU/L) 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Se Sp PPV NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.61 0.95 0.98 0.38</td>
</tr>
<tr>
<td>Roehr, 2001&lt;sup&gt;171&lt;/sup&gt;</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>DBPCFC</td>
<td>Pharmacia CAP FEIA</td>
<td>Decision Point (kU/L) 0.35</td>
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<td></td>
<td></td>
<td>Se Sp PPV NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.96 0.36 0.75 0.83</td>
</tr>
<tr>
<td>Monti, 2002&lt;sup&gt;176&lt;/sup&gt;</td>
<td>107 children (1-19 mos)</td>
<td>Open egg challenge, monitoring for early and late reactions (up to 8 days)</td>
<td>RAST</td>
<td>Albumin&gt;99kU/L</td>
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<tr>
<td></td>
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<td>Yolk ≥17.5 kU/L</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Specificity: 1</td>
</tr>
<tr>
<td>Celik-Bilgili, 2005&lt;sup&gt;185&lt;/sup&gt;</td>
<td>501 children (1 mo-16.1 yr)</td>
<td>Food challenge in children &gt;1 year of age</td>
<td>CAP system</td>
<td>Se Sp PPV NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.97 0.51 0.80 0.89</td>
</tr>
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<td></td>
<td></td>
<td>Predictive decision points:</td>
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<td></td>
<td>All ages:</td>
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<td>90%: 6.3 kU/L</td>
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<td></td>
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<td>95%: 12.6</td>
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<td></td>
<td></td>
<td>99%: 59.2</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>&lt; 1 year:</td>
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<tr>
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<td>95%: 10.9 kU/L</td>
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<td>90%: 4.2</td>
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<td></td>
<td>≥1 year:</td>
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<td>95%: 13.2kU/L</td>
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<td>90%: 6.7kU/L</td>
</tr>
<tr>
<td>Ricci, 2003&lt;sup&gt;168&lt;/sup&gt;</td>
<td>151 children consecutively referred to a university hospital pediatric allergy clinic in Bologna for suspected food allergy (CM and HE)</td>
<td>FC (blinding not specified) 40 positive for HE</td>
<td>Pharmacia UniCAP vs. ADVIA Centaur cutoff&gt;0.35kU/L</td>
<td>UniCAP</td>
</tr>
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<td></td>
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<td>Se Sp PPV NPV</td>
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<td></td>
<td>0.94 0.64 0.55 0.96</td>
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<td></td>
<td>ADVIA Centaur</td>
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<td></td>
<td>Se Sp PPV NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.88 0.52 0.46 0.90</td>
</tr>
<tr>
<td>Osterballe, 2004&lt;sup&gt;169&lt;/sup&gt;</td>
<td>495 children 3 years of age with and without AD (members of a Danish OFC to assess both early</td>
<td>Magic Lite sIgE Cutoff: 1.43 sU/ml</td>
<td>Se Sp PPV NPV</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>0.63 0.66 0.71 0.57</td>
</tr>
</tbody>
</table>
| ID/Author, Yr. | Population (age range) | Reference Test | Assay System | Results
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Canani, 2007&lt;sup&gt;175&lt;/sup&gt;</td>
<td>All children 3-48 months referred to Pediatric gastroenterology center in Naples for suspected FA-related symptoms</td>
<td>OFC with fresh CM, based on reactions to SPT, APT, and sIgE: 89 challenges performed in 60 patients</td>
<td>Pharmacia CAP RAST</td>
<td>Positive test ≥0.35kU/L</td>
</tr>
<tr>
<td>Rancé, 2004&lt;sup&gt;170&lt;/sup&gt;</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic with AD</td>
<td>OFC (based on results of APT, SPT, or sIgE) or sIgE</td>
<td>Pharmacia Upjohn CAP FEIA</td>
<td>Cutoff: ≥0.35 kU/L</td>
</tr>
<tr>
<td>Mehl, 2006&lt;sup&gt;149&lt;/sup&gt;</td>
<td>437 children referred to specialist for diagnosis of suspected food allergy.</td>
<td>DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, sIgE, and clinical history.</td>
<td>RAST</td>
<td></td>
</tr>
</tbody>
</table>

**Table Notes:** AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test
Peanut Allergy

Five studies assessed the performance of peanut sIgE in children with positive challenge or strong suggestive clinical history. These studies are summarized in Table 26.

The first, a 2001 study, measured peanut sIgE in 68 children (2 percent diagnosed by positive challenge; the remainder by strong history).\(^{186}\) Using a cutoff of 14 kU/L gave a sensitivity of 0.57 and a specificity of 1 (this study satisfied 9 of the 12 QUADAS domains assessed).

The second study measured sIgE among 363 children with suspected peanut allergy (177 with positive challenges, 186 with negative challenge).\(^{165}\) The median peanut sIgE was 10 in children with a positive challenge (range 0-100) and 0 in children with negative challenge (range 0-56). The area under the ROC curve was 0.87 9(5% CI, 0.84, 0.91). The cutoff for a specificity and PPV of 1 was 57 kU/L, a cutoff that would have avoided the need for challenge in 27 children. However, no threshold provided 100 percent sensitivity (the lower limit of detection, 0.35kU/L, provided a sensitivity of 96.6%). At a cutoff of 15 kU/L, the specificity was 95 percent and the sensitivity was 44 percent. Levels of sIgE were not associated with severity of challenge reaction (this study satisfied 10 of the 12 QUADAS domains assessed).

The third study was a 2004 study of 48 children (3-29 months) consecutively recruited to a French pediatric hospital allergy clinic with AD; open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures.\(^{170}\) Tests were performed with a Pharmacia CAP FEIA system; positive tests were defined as values \(\geq 0.35\text{kU/L}.\) The test had a sensitivity of 0.53, a specificity of 0.66, a PPV of 0.89 and a NPV of 0.21 (this study satisfied 10 of the 12 QUADAS domains assessed).

The fourth study was conducted among 84 children who were consecutively recruited from children attending a Sydney pediatric hospital allergy clinic based on positive skin prick test for peanut allergy using a commercial extract and a wheal size cutoff of 3mm larger than the saline control.\(^{178}\) All participants without a history of having ingested peanut in the preceding 3 months were given an open in-hospital challenge along with sIgE measures and an immediate skin application food test (I-SAFT, a rapid topical test used to assess sensitivity to very small quantities of allergen). The purpose of the study was to assess the clinical usefulness of available \textit{in vitro} and \textit{in vivo} tests, alone or in combination, compared with food challenge. The sensitivity and specificity of the UniCAP FEIA test were measured using cutoffs of 0.35 and 10 kU/ml. At a cutoff of 0.37 kU/ml, the sensitivity was 0.98, with a specificity of 0.33. At a cutoff of 10 kU/ml, the sensitivity dropped to 0.54, and the specificity rose to 1.00 (this study satisfied 9 of the 12 QUADAS domains assessed).

The fifth study was a 2008 study of 324 consecutive children referred to a pediatric allergy clinic in Boulder CO for suspected allergy to peanuts, tree nuts, or seeds (age range 2.4 months-40.2 years).\(^{189}\) The reference test consisted of clinical history, a questionnaire, and the results of SPT or sIgE; 72 percent had a convincing history of peanut allergy. When a positive test was defined as a sIgE value \(\geq 0.13\text{kU/L},\) the test had a sensitivity of 0.60, a specificity of 0.96, a PPV of 0.99 and a NPV of 0.35 (this study satisfied 5 of the 12 QUADAS domains assessed).
Finally, an additional study for which only 44 percent of the participants had their allergy confirmed by food challenge or history (and no data were provided to assess the performance characteristics of the index test) also assessed the use of sIgE levels to diagnose peanut allergy.\textsuperscript{179} sIgE levels alone were not considered predictive of reaction to peanuts in this study.

Table 26: sIgE Measures of Peanut Allergy Using Food Challenge as Reference

<table>
<thead>
<tr>
<th>ID/Author, Yr.</th>
<th>Population (age range)</th>
<th>Reference Test</th>
<th>Assay System</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampson, 2001\textsuperscript{186}</td>
<td>68 consecutive children 93 mos-14 yrs)</td>
<td>Food challenge or strong history</td>
<td>Pharmacia CAP FEIA</td>
<td>Decision Point (kU\textsubscript{A}/L) 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Se Sp PPV NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.57 1.00 1.00 0.36</td>
<td></td>
</tr>
<tr>
<td>Rancé, 2002\textsuperscript{165}</td>
<td>363 children, 177 with positive challenge, 186 with negative challenge</td>
<td>DBPCFC preceded by elimination diet. Patients monitored for reactions for 4 hours following test. 177/363 peanut allergic by FC</td>
<td>Pharmacia CAP FEIA</td>
<td>Decision Point (kU kU\textsubscript{A}/L) 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Se Sp PPV NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.44 0.95 ND ND</td>
<td></td>
</tr>
<tr>
<td>Maloney, 2008\textsuperscript{189}</td>
<td>All individuals referred to pediatric allergy clinic in Boulder CO for suspected allergy to peanut, tree nut, seeds; 324 patients (2.4 months – 40.2 years)</td>
<td>Clinical history, questionnaire, and/or SPT or sIgE 72% had convincing history of peanut allergy</td>
<td>ImunoCAP sIgE</td>
<td>Decision Point: ≥13 kU/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Se Sp PPV NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.60 0.96 0.99 0.35</td>
<td></td>
</tr>
<tr>
<td>Rancé, 2004\textsuperscript{170}</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic</td>
<td>OFC (based on results of APT, SPT, or sIgE) or sIgE</td>
<td>Pharmacia Upjohn CAP FEIA</td>
<td>Decision Point: ≥0.35kU/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Se Sp PPV NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.53 0.66 0.89 0.21</td>
<td></td>
</tr>
<tr>
<td>Wainstein, 2007\textsuperscript{178}</td>
<td>84 children consecutively recruited in a Sydney pediatric hospital allergy clinic with positive SPT (defined as a wheal 3x3mm&gt; control)</td>
<td>DBPCFC or documented recent reaction to peanut 51/84 peanut allergic by FC</td>
<td>Pharmacia CAP FEIA</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Se Sp PPV NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.37 0.98 0.33 0.70 0.92</td>
<td></td>
</tr>
</tbody>
</table>
| | | | CI 0.9- 0.18-
| | | | 1.0 .52 |
| | | | 10 0.54 1.00 1.00 0.58 |
| | | | CI 0.39- 0.89-
| | | | 0.67 1.00 |

Table Notes: AD atopic dermatitis; CM cow’s milk; ALA α-lactalbumin; APT atopy patch test; BLA β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test
Soy Allergy

Four studies assessed the performance of soy sIgE as an assessment of allergy to soy.

The first study assessed soybean sIgE in 100 children, 25 of whom were diagnosed with soy allergy (84 percent by food challenge, the remainder by strong history). Using the 95% decision point determined in a previous retrospective study (65 kUA/L), they found a sensitivity of 0.24, a specificity of 0.99, PPV 0.86, and NPV of 0.78. Using the 90% cutoff point (30 kUA/L) produced a sensitivity of 0.44, specificity of 0.94, PPV of 0.73 and NPV of 0.82 (this study satisfied 6 of the 12 QUADAS domains assessed).186

In the second study, 98 children were admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis; 25 received a DBPCFC with soy milk to compare the results of skin prick test, atopy patch test, sIgE, and combinations of the tests.171 Among the challenges, 4 of the 25 were positive. sIgE was determined using the Pharmacia CAP FEIA; a positive test was considered any value above the detection limit of 0.35 kU/L. Among the 98 children tested, 12 expressed sIgE in response to soy milk. The test had a sensitivity of 0.75, a specificity of 0.52, a PPV of 0.23 and a NPV of 0.92 (this study satisfied 9 of the 12 QUADAS domains assessed).

In the third study, soy sIgE was assessed using the CAP system in 501 children, 189 of whom underwent challenge for suspected soy allergy (confirmed in 38 children). The sensitivity was 0.69, specificity was 0.50, PPV was 0.22, and NPV was 0.88.185 However, the relationship between sIgE titer and positive food challenge was highly variable (this study satisfied 10 of the 12 QUADAS domains assessed).

The fourth study assessed the performance of soy sIgE compared with food challenge in 425 children (180 challenged with soy; 37 positive challenges). The test had a sensitivity of 0.65, a specificity of 0.50, PPV of 0.22, and NPV of 0.86 (this study satisfied 9 of the 12 QUADAS domains assessed).149

Table 27: sIgE Measures of Soy Allergy Using Food Challenge as Reference

<table>
<thead>
<tr>
<th>ID/Author, Yr.</th>
<th>Population (age range)</th>
<th>Assay System</th>
<th>Results</th>
</tr>
</thead>
</table>
| Sampson, 2001186 | 100 children (3 mos-14 yrs): 21 with positive food challenge and 4 with strong history | Pharmacia CAP FEIA | 95% Decision Point (kUA/L): 65  
Se  Sp  PPV  NPV  
0.24  0.99  0.86  0.78  
90% Decision Point (kUA/L): 30  
Se  Sp  PPV  NPV  
0.44  0.94  0.73  0.82 |
| Roehr, 2001171 | 98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis; 4 of 25 with a positive DBPCFC to soy | Pharmacia CAP FEIA | Cutoff: 0.35 kUA/L  
Se  Sp  PPV  NPV  
0.75  0.52  0.23  0.92 |
| Celik-Bilgili, 2005185 | 501 children (1 mo-16.1 yrs), 189 administered food challenge, | Pharmacia CAP FEIA | Cutoff: 0.35 kUA/L |

117
of which 38 were positive

<table>
<thead>
<tr>
<th>Mehl, 2006(^{149})</th>
<th>425 children (3 mos-14 yrs), 37 with positive challenge to soy</th>
<th>Se, Sp, PPV, NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pharmacia CAP FEIA</td>
<td>Se, Sp, PPV, NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.69 0.50 0.22 0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.65 0.50 0.22 0.86</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test

Wheat Allergy

Five studies assessed the performance of wheat sIgE in patients with positive food challenges.

The first assessed wheat sIgE in 100 children, 23 diagnosed with wheat allergy (74 percent by food challenge, the remainder by strong history). Using the 95% decision point determined in a previous retrospective study, they found a sensitivity of 0.13, a specificity of 1, PPV 1, and NPV of 0.76 for a cutoff point of 100 kUA/L. Using the 90% cutoff point (26 kUA/L) produced a sensitivity of 0.61, specificity of 0.92, PPV of 0.74 and NPV of 0.87 (this study satisfied 9 of the 12 QUADAS domains assessed).\(^{186}\)

In the second study, 98 children were admitted consecutively to a Berlin pediatric hospital pneumology ward with atopic dermatitis; 35 received a DBPCFC with wheat powder to compare the results of skin prick test, atopy patch test, sIgE, and combinations of the tests.\(^{171}\) Among the challenges, 18 of the 35 were positive. sIgE was determined using the Pharmacia CAP FEIA; a positive test was considered any value above the detection limit of 0.35 kU/L. Among the 98 children tested, 21 expressed sIgE in response to wheat. The test had a sensitivity of 0.67, a specificity of 0.53, a PPV of 0.57 and a NPV of 0.57 (this study satisfied 9 of the 12 QUADAS domains assessed).

The third study assessed wheat sIgE using the CAP system in 501 children, 178 of whom underwent challenge for suspected wheat allergy (confirmed by challenge in 62). The sensitivity was 0.79, specificity was 0.38, PPV was 0.41, and NPV was 0.77.\(^{185}\) However, at no level of antibody titer was the proportion with positive food challenge greater than 75 percent (this study satisfied 10 of the 12 QUADAS domains assessed).

The fourth assessed the performance of wheat sIgE compared with food challenge in 423 children, of whom 159 underwent challenge for suspected wheat allergy (confirmed in 57). The test had a sensitivity of 0.82, a specificity of 0.34, PPV of 0.41, and NPV of 0.77 (this study satisfied 9 of the 12 QUADAS domains assessed).\(^{149}\)

The fifth study was a 2004 study of 48 children (3-29 months) consecutively recruited to a French pediatric hospital allergy clinic with AD; open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures.\(^{170}\) Tests were performed with a Pharmacia CAP FEIA system; positive tests were defined as values ≥0.35kU/L. The test had a sensitivity for wheat of 0.40, a specificity of 0.50, a PPV of 0.66 and a NPV of 0.25 (this study satisfied 10 of the 12 QUADAS domains assessed).
<table>
<thead>
<tr>
<th>ID/Author, Yr.</th>
<th>Population (age range)</th>
<th>Reference Test</th>
<th>Assay System</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampson, 2001(^1)(^8)</td>
<td>100 children (3 mos-14 yrs), 17 with positive food challenge and 6 with strong history</td>
<td>Food challenge or strong history</td>
<td>Pharmacia CAP FEIA</td>
<td>95% Decision Point (kUA/L): 100 &lt;br&gt; Se  Sp  PPV  NPV &lt;br&gt; 0.13 1.00 1.00 0.76 &lt;br&gt; 90% Decision Point (kUA/L): 26 &lt;br&gt; Se  Sp  PPV  NPV &lt;br&gt; 0.61 0.92 0.74 0.87</td>
</tr>
<tr>
<td>Roehr, 2001(^1)(^7)(^1)</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis; 18/35 with a positive DBPCFC to soy</td>
<td>DBPCFC</td>
<td>Pharmacia CAP FEIA</td>
<td>Se  Sp  PPV  NPV &lt;br&gt; 0.67 0.47 0.57 0.57</td>
</tr>
<tr>
<td>Rancé, 2004(^1)(^7)(^0)</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic</td>
<td>OFC (based on results of APT, SPT, or sIgE) or sIgE</td>
<td>Pharmacia Upjohn CAP FEIA</td>
<td>Se  Sp  PPV  NPV &lt;br&gt; 0.40 0.50 0.66 0.25</td>
</tr>
<tr>
<td>Celik-Bilgili, 2005(^1)(^8)(^5)</td>
<td>501 children (1 mo-16.1 yrs), 178 administered wheat challenge, of which 62 were positive</td>
<td>Food challenge in children &gt;1 year of age</td>
<td>Pharmacia CAP FEIA</td>
<td>Cutoff: 0.35 kUA/L &lt;br&gt; Se  Sp  PPV  NPV &lt;br&gt; 0.79 0.38 0.41 0.77</td>
</tr>
<tr>
<td>Mehl, 2006(^1)(^8)(^9)</td>
<td>423 children (3 mos-14 yrs), 159 administered wheat challenge; 57 positive</td>
<td>DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, sIgE, and clinical history.</td>
<td>Pharmacia CAP FEIA</td>
<td>Se  Sp  PPV  NPV &lt;br&gt; 0.82 0.34 0.41 0.77</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test
**Allergy to Other Foods**

Two studies that met the inclusion criteria assessed the use of sIgE measurement to diagnose allergy to other foods.

A 2000 study enrolled 53 consecutive adults (15-69 years) who were referred to a Madrid university hospital allergy clinic complaining of reaction to melon.\(^{180}\) Allergy to melon as well as related foods was confirmed by OFC followed by DBPCFC using fresh foods unless the patient had a history of anaphylaxis associated with the food(s). Nineteen patients had positive DBPCFC or history of anaphylaxis in response to melon. Twenty three patients had positive reactions based on sIgE levels (a positive test was defined as a sIgE level $\geq 0.35$ kU/L). They reported a sensitivity for the test of 0.53, specificity of 0.62, PPV of 0.44, and NPV of 0.70 (this study satisfied 9 of the 12 QUADAS domains assessed).

A 2008 study of 324 consecutive children referred to a pediatric allergy clinic in Boulder CO for suspected allergy to peanuts, tree nuts, or seeds (age range 2.4 months-40.2 years) assessed the efficacy of the skin prick test and sIgE.\(^{189}\) The reference test consisted of clinical history, a questionnaire, and the results of SPT or sIgE. When a positive test was defined as a sIgE value $\geq 18.5$ kU/L, the test for walnut allergy had a sensitivity of 0.17, a specificity of 0.98, a PPV of 0.99 and a NPV of 0.56 (this study satisfied 5 of the 12 QUADAS domains assessed).

**Skin Prick Test as Reference Test**

Three studies examined the performance of antigen sIgE measurements in patients with food allergy diagnosed using skin prick test (SPT) (or SPT and history).\(^{188,190,191}\) Although these studies included patients with positive SPT results to common food allergens, including cow’s milk, hen’s egg, peanut and other tree nuts, wheat, soy, and finfish or shellfish, each used a mixed panel for sIgE assays; thus, no study reported sensitivity or specificity by specific food.

One study compared the performance of several different sIgE assay systems in diagnosing food or inhalant allergy in a group of 193 5-year-old children, 20 of whom had at least one positive SPT to a food allergen (17 of these children also had clinical signs of atopy).\(^{190}\) Among the 20 children with positive SPT, 15 had a positive reaction in the Phadiatop Pediatric® (PP) test (a test designed primarily for children under 7) and the RAST mixed food panel, and 18 had a positive Phadiatop® test (a test designed primarily for children over 7). Among the 17 clinically atopic children with positive SPT, all had a positive Phadiatop® test; however two had a negative PP test, and three had a negative RAST mixed food test. P had a sensitivity of 0.86, a specificity of 0.94, and an efficacy of 0.92 (this study satisfied 8 of the 12 QUADAS domains assessed).

The performance of the Phadiatop Infant sIgE test was examined among 147 children, 61 of whom had SPT+ tests for a food or aeroallergen.\(^{188}\) Of these 61, 56 had a positive sIgE test, and 64 of 78 without an IgE-mediated allergy had negative results, for a sensitivity of 0.92, specificity of 0.82, PPV of 0.8 and NPV of 0.93. Thirteen children with a negative SPT and
positive sIgE were retested after two years: 12 of the 13 were diagnosed with an IgE-mediated allergy in blinded testing (this study satisfied 3 of the 12 QUADAS domains assessed).

The performance of two sIgE systems (the second generation Pharmacia UniCAP® and the third generation Immulite 2000) was compared using a population of 118 whites, 15 years and older who were referred for workup of suspected allergy. Of the 118, 63 were diagnosed as allergy-positive (for food, inhalants, or both) based on SPT and clinical symptoms/history; the remainder were diagnosed as allergy-negative. Isolated food allergy was diagnosed in seven patients, and combined inhalant and food allergy was diagnosed in two additional patients. The two sIgE food panels were positive in six and seven of the nine patients with food allergy. Of note, two patients with peanut allergy were missed by the second generation sIgE system. Compared with the SPT, the 3rd generation system had 94 percent total agreement, 0.571 relative sensitivity, and 1.0 relative specificity. The 2nd generation system had a total agreement (with SPT) of 0.924, relative sensitivity of 0.643, and relative specificity of 0.967 percent. When the results of single food sIgE tests were compared to SPTs, negative sIgE tests for egg white, cow’s milk, codfish, wheat, peanut, and soy agreed with negative SPTs for 0.95-1.0 of patients and 0.89-0.99 of patients for 3rd and 2nd generation tests respectively. Sensitivity data are inconclusive because of the small number of patients (this study satisfied 7 of the 12 QUADAS domains assessed).

**Other sIgE Test(s) as Reference Test**

Two recent studies compared the performance of sIgE assay systems against each other.

One study compared the performance of three different systems (as well as clinical data) on 50 patients (2.92-18 years)-the Phadia ImmunoCAP, Turbo-MP, and the Immulite 2000-for assessment of allergy to cow’s milk, hen’s egg, peanut, as well as three aeroallergens. Each system used slightly different forms of the antigens (e.g., skimmed cow’s milk vs. freeze-dried cow’s milk vs. whole cow’s milk). Of the 50 patients, 42 had diagnosed food allergies. Each system provided significantly different measurements of sIgE for the same serum samples. Immulite 2000 showed higher sIgE for all antigens compared with ImmunoCAP. Turbo-MP overestimated egg. Differences were also seen for cow’s milk and peanut. Thus the predictive values associated with clinical evidence of allergy for the 2nd generation ImmunoCAP cannot be applied to the 3rd generation instruments (this study satisfied 7 of the 12 QUADAS domains assessed).

A second study also compared the Immulite 2000 with the UniCAP system among 283 Korean patients (1-76 years) (645 paired tests). sIgE for cow’s milk, egg white, peanut, and shrimp were compared. Correlations between the two systems were good (0.85 or greater) for cow’s milk, egg, and peanut, but not for shrimp. However agreement about whether a particular result was positive or negative for a particular food was slightly different (0.946 for egg, 0.889 for cow’s milk, 0.75 for peanut, and 0.563 for shrimp). Sensitivity and specificity were not compared for food allergens (this study satisfied 9 of the 12 QUADAS domains assessed).

Differences in the determination of sIgE between the different assays were also reported on a study of serum samples assessing Immunocap turbo RAST and Immulite.
Summary

The reported sensitivity and specificity of sIgE assays for food allergies varied by food, assay system, and study. Studies that compared the performance of several assay systems found discrepancies, especially for particular foods (wheat and soy), such that one assay might diagnose a particular patient as being allergic whereas another test might find the same patient not to be allergic to the food.

The quality of evidence regarding sIgE is judged as low, meaning further research is likely to have an important impact on our confidence in the estimate of effect, due to important inconsistencies in study results and limitation of the studies in terms of patient populations, standardization of the test, and in some cases the gold standard test.

Immunoglobulin G(IgG)4

One study that met the inclusion criteria assessed the use of levels of serum IgG4 to common foods in diagnosing food allergy among 68 patients with a history suggestive of food allergy (age range 10-71 years) and 22 controls in an Italian academic hospital allergy clinic. Based on history and elimination diet as the reference standard, the use of food-specific IgG levels had a sensitivity of 0.81 and a specificity of 0.87, with a NPV of 0.99 (this study satisfied 10 of the 12 QUADAS criteria assessed).

In Vitro Basophil Histamine Release

A small 1988 study of 26 children (aged 1-48 months) consecutively referred to a Danish hospital allergy clinic diagnosed 20 of the 26 children with cow’s milk allergy via open food challenge to compare the sensitivity and specificity of skin prick tests and sIgE with a novel basophil histamine release assay. The tests were performed with raw cow’s milk extract. Histamine release was measured both from basophils and from leukocytes. Histamine release was considered positive in 17 of 26 children tested, 15 with a positive challenge test and 2 with a negative challenge; sensitivity was 0.75, specificity was 0.66, PPV was 0.88, and NPV was 0.44, in fair agreement with the SPT and RAST (this study satisfied 8 of the 12 QUADAS domains assessed).

In a 2004 study of a 3-year-old birth cohort of 495 children in Denmark, parents completed a questionnaire that included questions about food hypersensitivities. Based on the responses, children were given open food challenges and basophil histamine release assays (as well as APT, sIgE, and skin prick tests). Three of 8 children had positive challenge responses to cow’s milk and 8 of 14 had positive challenge responses to hen’s egg. The test for cow’s milk had a sensitivity of 0.66, a specificity of 0.80, a PPV of 0.66 and a NPV of 0.80; the test for hen’s egg had a sensitivity of 0.71, a specificity of 0.80, a PPV of 0.71 and a NPV of 0.80 (this study satisfied 8 of the 12 QUADAS domains assessed).
Serum Eosinophil Cationic Protein

One study that met the inclusion criteria compared the measurement of serum eosinophil cationic protein (SCEP) with that of other in vitro and in vivo tests to diagnose cow’s milk allergy. Among a cohort of 6209 Finnish infants recruited for a study of the effects of various infant formulae on the development of cow’s milk allergy, 239 (ages 6-7 months) showed symptoms that subsided with elimination of cow’s milk and received a milk challenge, skin prick tests, sIgE measurements, and the SCEP; 118 reacted positively to the challenge. The SCEP was measured using the Pharmacia CAP system on day 4 of the challenge. Three different cutoff values were tested: 15.0, 20.0, and 24.7 micrograms (µg)/L. At a cutoff of ≥15.9µg/L, the sensitivity was 0.27 (specificity 0.74; PPV 0.67; NPV 0.34); at a cutoff value of 24.7µg/L, the sensitivity was 0.13 (specificity 0.98; PPV 0.93; NPV 0.37).

Atopy Patch Tests

The atopy patch test is regarded as useful for assessing suspected non-IgE-mediated (delayed hypersensitivity) reactions to an allergen. Seven studies addressing the specificity and sensitivity of atopy patch tests (APT) alone met our selection criteria, all using food challenge as a reference test. These studies applied foods (fresh or from powders) with aluminum cups, with occlusion times of 48 hours, and final results read 72 hours after application of the food. Additionally, six studies checked for immediate reactions 15-30 minutes after the initial application of the food. Two studies of APT methodology met our criteria; one compared different occlusion times and one compared the use of different allergen preparations.

APT Test Performance by Food

Cow's Milk

Eight studies of APT in the diagnosis of food allergy to cow's milk met our inclusion criteria, the results of these studies are reported in Table 29 and described below.

In a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis, 71 received a DBPCFC for cow’s milk and an APT with fresh milk to compare the results of the APT with that of the skin prick test, sIgE, and combinations of the tests. Among the challenges, 45 of 71 were positive. A positive APT, defined as erythema with infiltration after 48 and 72 hours, was obtained in 22 of 98 children. The test had a sensitivity of 0.47, a specificity of 0.96, a PPV of 0.95 and a NPV of 0.51 (this study satisfied 9 of the 12 QUADAS domains assessed).

Among a cohort of 6209 Finnish infants recruited for a study of the effects of various infant formulae on the development of cow’s milk allergy, 239 (ages 6-7 months) showed symptoms that subsided with elimination of cow’s milk and received a milk challenge, skin prick tests, and sIgE measurements; 118 reacted positively to the challenge. The sensitivity and specificity of the APT were assessed for three different antigens: whole cow’s milk (0.37, 0.77), cow’s milk
protein fractions (0.26, 0.92), and either one or a mixture of both (0.43, 0.72). All three antigens had relatively low PPVs (0.60-0.77) and NPVs (0.56-0.57) (this study satisfied 11 of the 12 QUADAS domains assessed).

A study of 183 Finnish children (ages 2-36 months) with AD and suspected CMA using a mix of double blind placebo controlled and open food challenges (with 99/183 confirmed allergic) reported sensitivity and specificity of 0.61 and 0.81 respectively for the DBPCFCs and 0.59 and 0.83 respectively for the open food challenges (this study satisfied 10 of the 12 QUADAS domains assessed).  

A study of 437 German children (aged 3 mos to 17 years) consecutively referred to a specialist for suspected food allergy (excluding those with a clear history of food related symptoms) using DBPCFC as a reference (except in patients under 1 year of age or those with clear history of immediate reactions) confirmed 168/437 cases of milk allergy. The overall sensitivity and specificity of the APT were 0.31 and 0.95, with a PPV and NPV of 0.86 and 0.60 respectively. This study also reported the sensitivity of the test according to the timing of the reaction to challenge, with sensitivities of 0.27, 0.45, and 0.36 for immediate, late, and combined reactions to food challenge respectively. This study reported results stratifying by atopic dermatitis (391/437) finding sensitivity and specificity of 0.32 and 0.93 respectively in children with AD, and 0.30 and 1.0 in children without. The study also reported that the sensitivity of APT increased with age, and was 1.0 for children 3-6 years of age (this study satisfied 9 of the 12 QUADAS domains assessed).

A study of 37 children referred to a Turkish allergy clinic with suspected CMA used DBPCFC (except in the case of six patients with clear history of anaphylaxis to milk) to confirm 23 cases of allergy to cow's milk. This study reported the overall sensitivity and specificity of the APT in the diagnosis of milk allergy was 0.73 and 0.86 respectively with a PPV of 0.89 and NPV of 0.67. Comparing immediate and late reactions to milk challenge, the sensitivities were 0.72 and 0.75, specificities were both 0.86, PPVs were 0.87 and 0.60, and NPVs were 0.71 and 0.92 (this study satisfied 10 of the 12 QUADAS domains assessed).

In a 2004 study of a 3-year-old birth cohort of 495 children in Denmark, parents completed a questionnaire that included questions about food hypersensitivities. Based on the responses, children were given open food challenges and APT (as well as skin prick tests, sIgE, and basophil histamine release assessments). Three of 8 children had positive challenge responses to cow’s milk. A positive APT was defined as any erythema or slight infiltration after 72 hours. The APT had a sensitivity of 0.00, a specificity of 1.00, a PPV of 1.00 and a NPV of 0.00 (this study satisfied 8 of the 12 QUADAS domains assessed).

A 2007 study that included all children (3-48 months of age) referred to a Naples pediatric gastroenterology clinic for suspected food-allergy related symptoms performed open food challenges with fresh CM based on the results of skin prick tests, APT, and sIgE. The aim of the study was to compare the effect of using of fresh foods with those of commercial extracts on the diagnostic accuracy of the APT. Among 55 children challenged with CM, 31 had positive reactions (10 early and 21 late reactions). Occlusion time was 48 hours and tests were read 24
hours later. A positive test was defined as including erythema and slight infiltration or more. Using commercial extracts, the test had a sensitivity of 0.06, a specificity of 0.96, a PPV of 0.67 and a NPV of 0.43; using fresh milk, the test had a sensitivity of 0.65, a specificity of 0.96, a PPV of 0.95 and a NPV of 0.67. The study also found that accepting a positive APT or a positive SPT or sIgE test as indication of an allergic reaction maximized the performance characteristics of the tests (sensitivity 0.90; specificity 0.52; PPV 0.72; NPV 0.80) (this study satisfied 11 of the 12 QUADAS domains assessed).

A 2004 study of 48 children (3-29 months) with AD consecutively recruited to a French pediatric hospital allergy clinic aimed to determine the optimal occlusion time for the APT in children with AD. As a reference standard, open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Tests were performed in duplicate on either side of children’s backs and read after occlusion times of 24 and 48 hours. The results comparing occlusion times are reported below. At 48 hours, the test had a sensitivity of 0.89, a specificity of 0.96, PPV of 0.94, and NPV of 0.92 (this study satisfied 10 of the 12 QUADAS domains assessed).

Hen's Egg Allergy

Five studies of atopy patch tests in the diagnosis of hen's egg allergy met our criteria and are summarized in Table 30.

In a 2004 study of a 3-year-old birth cohort of 495 children in Denmark, parents completed a questionnaire that included questions about food hypersensitivities. Based on the responses, children were given open food challenges and APT (as well as skin prick tests, sIgE, and basophil histamine release assessments). Eight of 14 children had positive challenge responses to hen’s egg. A positive APT was defined as any erythema or slight infiltration after 72 hours. The APT had a sensitivity of 0.63, a specificity of 0.80, a PPV of 0.83 and a NPV of 0.57 (this study satisfied 8 of the 12 QUADAS domains assessed).

A 2007 study that included all children (3-48 months of age) referred to a Naples pediatric gastroenterology clinic for suspected food-allergy related symptoms performed open food challenges with fresh egg based on the results of skin prick tests, APT, and sIgE. The aim of the study was to compare the effects of using fresh foods with those of commercial extracts on the diagnostic accuracy of the APT. Among 28 children challenged with egg, 19 had positive reactions (5 early and 14 late reactions). Occlusion time was 48 hours and tests were read 24 hours later. A positive test was defined as including erythema and slight infiltration or more. Using commercial extracts, the test had a sensitivity of 0.05, a specificity of 1.00, a PPV of 1.00 and a NPV of 0.33; using fresh HE, the test had a sensitivity of 0.84, a specificity of 1.00, a PPV of 1.00 and a NPV of 0.75. The study also found that accepting a positive APT or a positive SPT or sIgE test as indication of an allergic reaction maximized the performance characteristics of the tests (sensitivity 0.95; specificity 0.44; PPV 0.78; NPV 0.80) (this study satisfied 11 of the 12 QUADAS domains assessed).
A 2004 study of 48 children (3-29 months) with AD consecutively recruited to a French pediatric hospital allergy clinic aimed to determine the optimal occlusion time for the APT in children with AD. As a reference standard, open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Tests were performed in parallel on the children’s backs and read after occlusion times of 24 and 48 hours. The results comparing occlusion times are reported below. At 48 hours, the test had a sensitivity of 0.97, a specificity of 0.71, PPV of 0.95, and NPV of 0.83 (this study satisfied 10 of the 12 QUADAS domains assessed).

In a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis, 42 received a DBPCFC for hen’s egg and an APT with egg white and yolk to compare the results of the APT with that of the skin prick test, sIgE, and combinations of the tests. Among the challenges, 28 of 42 were positive. A positive APT, defined as erythema with infiltration after 48 and 72 hours, was obtained in 17 of 98 children. The test had a sensitivity of 0.57, a specificity of 0.93, a PPV of 0.94 and a NPV of 0.52 (this study satisfied 9 of the 12 QUADAS domains assessed).

A study of 437 German children (aged 3 mos to 17 years) consecutively referred to a specialist for suspected food allergy (excluding those with a clear history of food related symptoms) using DBPCFC as a reference (except in patients under 1 year of age or those with clear history of immediate reactions) confirmed 193/437 cases of hen's egg allergy. The overall sensitivity and specificity of the APT were 0.41 and 0.87, with a PPV and NPV of 0.86 and 0.43 respectively. This study also reported the sensitivity of the test according to the timing of the reaction to challenge, with sensitivities of 0.45, 0.17, and 0.36 for immediate, late, and combined reactions to food challenge respectively. This study reported results stratifying by atopic dermatitis (391/437) finding sensitivity and specificity of 0.40 and 0.91 respectively in children with AD, and 0.60 and 0.85 in children without. The study also reported that the sensitivity of APT was not affected by age (this study satisfied 9 of the 12 QUADAS domains assessed).

**Peanut Allergy**

One study of atopy patch tests in the diagnosis of peanut allergy met our inclusion criteria. A 2004 study of 48 children (3-29 months) with AD consecutively recruited to a French pediatric hospital allergy clinic aimed to determine the optimal occlusion time for the APT in children with AD. As a reference standard, open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Tests were performed in parallel on the children’s backs and read after occlusion times of 24 and 48 hours. At 24 and 48 hours, the test for peanut reactivity had a sensitivity of 0.13 and 0.71; a specificity of 0.97 and 0.82; PPV of 0.67 and 0.66; and NPV of 0.72 and 0.85, respectively (this study satisfied 10 of the 12 QUADAS domains assessed).
**Soy Allergy**

Two studies of atopy patch tests in the diagnosis of soy allergy met our inclusion criteria and is summarized in Table 31.

In a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis, 25 received a DBPCFC and an APT with soy milk to compare the results of the APT with that of the skin prick test, sIgE, and combinations of the tests. Among the challenges, 4 of 25 were positive. A positive APT, defined as erythema with infiltration after 48 and 72 hours, was obtained in 6 of 98 children. The test had a sensitivity of 0.75, a specificity of 0.86, a PPV of 0.50 and a NPV of 0.95 (this study satisfied 9 of the 12 QUADAS domains assessed).

A study of 437 German children (aged 3 mos to 17 years) consecutively referred to a specialist for suspected food allergy (excluding those with a clear history of food related symptoms) using DBPCFC as a reference (except in patients under 1 year of age or those with clear history of immediate reactions) confirmed 37/437 cases of soy allergy. The overall sensitivity and specificity of the APT were 0.23 and 0.86, with a PPV and NPV of 0.30 and 0.82 respectively. The sensitivity and specificity of the APT did not vary according to the timing of the reaction to food challenge. Stratifying by atopic dermatitis (391/437), sensitivity and specificity were 0.25 and 0.88 respectively in children with AD, and 0.0 and 0.86 in children without. The sensitivity of APT increased with age, and was 1.0 in children older than 6 years (this study satisfied 9 of the 12 QUADAS domains assessed).

**Wheat Allergy**

Four studies of atopy patch tests for the diagnosis of wheat allergy met our inclusion criteria and are summarized in Table 32.

In a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis, 25 received a DBPCFC and an APT with wheat to compare the results of the APT with that of the skin prick test, sIgE, and combinations of the tests. Among the challenges, 18 of 35 were positive. A positive APT, defined as erythema with infiltration after 48 and 72 hours, was obtained in 17 of 98 children. The test had a sensitivity of 0.89, a specificity of 0.94, a PPV of 0.94 and a NPV of 0.89 (this study satisfied 9 of the 12 QUADAS domains assessed).

A study of 437 German children (aged 3 mos to 17 years) consecutively referred to a specialist for suspected food allergy (excluding those with a clear history of food related symptoms) using DBPCFC as a reference (except in patients under 1 year of age or those with clear history of immediate reactions) confirmed 159/437 cases of wheat allergy. This study also reported the sensitivity of the test according to the timing of the reaction to challenge, with a sensitivities of 0.22, 0.29, and 0.50 for immediate, late, and combined reactions to food challenge respectively. The sensitivity of APT increased with age, and was 1.0 in children older than 6 years (this study satisfied 9 of the 12 QUADAS domains assessed).
A study of 90 children with food challenge confirmed cow's milk allergy, but with residual symptoms after milk elimination (and elimination of eggs, nuts, fruits, chocolate, and fish) tested for cereal (wheat, rye, barley, oats) allergy. In the 44 children tested for wheat allergy by open food challenge, 30 children had confirmed wheat allergy (66/90 children were positive for any cereal allergy). For wheat allergy, the sensitivity was 0.70, specificity was 0.71, PPV 0.84, and NPV 0.69; for any cereal allergy, the sensitivity was 0.67, specificity 0.79, PPV 0.90, and NPV 0.46 (this study satisfied 9 of the 12 QUADAS domains assessed).

A 2004 study of 48 children (3-29 months) with AD consecutively recruited to a French pediatric hospital allergy clinic aimed to determine the optimal occlusion time for the APT in children with AD. As a reference standard, open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Tests for wheat allergy were performed in parallel on the children’s backs and read after occlusion times of 24 and 48 hours. The results comparing occlusion times are reported below. At 48 hours, the test for reaction to wheat had a sensitivity of 0.83, a specificity of 0.94, PPV of 0.71, and NPV of 0.97 (this study satisfied 10 of the 12 QUADAS domains assessed).

**APT Performance Under Different Conditions**

Two studies that met the inclusion criteria examined the performance of APT under different conditions.

**Fresh Foods vs. Commercial Extracts**

A 2007 study that included all children (3-48 months of age) referred to a Naples pediatric gastroenterology clinic for suspected food-allergy related symptoms performed open food challenges with fresh foods based on the results of skin prick tests, APT, and sIgE. The aim of the study was to compare the effects of using fresh foods with those of commercial extracts on the diagnostic accuracy of the APT. Among 55 children challenged with cow’s milk, 31 had positive reactions (10 early and 21 late reactions). Occlusion time was 48 hours and tests were read 24 hours later. A positive test was defined as including erythema and slight infiltration or more. Using commercial extracts, the test had a sensitivity of 0.06, a specificity of 0.96, a PPV of 0.67 and a NPV of 0.93; using fresh cow’s milk, the test had a sensitivity of 0.65, a specificity of 0.96, a PPV of 0.95 and a NPV of 0.67. Similar results were found for hen’s egg: fresh hen’s egg had a sensitivity of 0.84, compared with 0.05 for commercial extracts (this study satisfied 11 of the 12 QUADAS domains assessed).

**Occlusion Times**

A 2004 study of 48 children (3-29 months) with AD consecutively recruited to a French pediatric hospital allergy clinic aimed to determine the optimal occlusion time for the APT in children with AD. As a reference standard, open food challenges were administered based on the results of skin prick tests, atopy patch tests, and/or sIgE measures. Tests were performed in parallel on the children’s backs and read after occlusion times of 24 and 48 hours. At 24 hours, the test for CM had a sensitivity of 0.18, a specificity of 1.00, a PPV of 1.00 and a NPV of 0.63. At 48 hours, the test had a sensitivity of 0.80, a specificity of 0.96, PPV of 0.94, and NPV of 0.92. The
tests for reactivity to HE, wheat, and peanut gave similar results (see Tables 30-32) (this study satisfied 10 of the 12 QUADAS domains assessed).

Reproducibility

Finally, one study that did not meet the inclusion criteria assessed the reproducibility of the test within the same individuals by applying duplicate test foods on the right and left side of the back. This 2008 study enrolled a cohort of 277 Italian children in two age groups. The younger children (mean age 8.7 years) underwent duplicate testing with fresh food extracts of CM, HE, tomato, and wheat flour. The older group (mean age 12.9 years) was tested with duplicate samples of commercial extracts of the same foods. For both the fresh and commercial foods, 25% to 75% of the tests were positive on one side and negative on the other (Cohen’s Kappa 0.38 for fresh tomato to 0.81 for fresh CM).

Summary

Two studies that met the inclusion criteria specifically addressed the methodology of atopy patch tests. One showed that applying a food for 48 hours (with the final reading of the test performed 72 hours after the food was first applied) provided better sensitivity and specificity than applying the food for 24 hours (with the final reading at 48 hours). Additionally, some studies reported checking for immediate reactions 15-30 minutes after the food was applied. One study compared the use of different food preparations and found that fresh foods provided superior sensitivity but not specificity. The sensitivity and specificity of the atopy patch test may vary by the timing of the reaction to oral food challenge (early vs. late), but the variation was not consistent either between foods or between studies of the same food. The sensitivity and specificity of this test may also vary by the presence of atopic dermatitis and the age of the patient. The QUADAS scores for included studies ranged from 8 to 10 out of 12. The quality of evidence is judged to be very low, meaning any estimate of effect is uncertain, due to sparseness of data, important inconsistency in study results, and limitations of the studies in terms of study populations, and lack of standardization of the test itself.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Assay</th>
<th>Result</th>
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<tbody>
<tr>
<td>Roehr, 2001</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>71 DBPCFC with cow milk based on history 45/71 diagnosed with milk allergy</td>
<td>One drop of fresh cow’s milk placed on filter paper and applied to patients’ backs using 12mm aluminum cups; occlusion time, 48 hours, read 20 minutes after removal of the cup, and then again at 72 hours; erythema with infiltration constituted positive reaction.</td>
<td>Se 0.47  Sp 0.96  PPV 0.95  NPV 0.51</td>
</tr>
<tr>
<td>Saarinen, 2001</td>
<td>239 infants (6-7 months) from a prospective Finnish birth cohort study on the effect of infant formulae on development of cow’s milk allergy with symptoms that disappeared on withdrawal of milk</td>
<td>239 open challenges 118/239 positive</td>
<td>CM formula powder, bovine serum albumin, crystallized bovine BLG, and bovine casein were each dissolved in saline, and filter papers were soaked in the solutions before being applied to the back under aluminum cup. Occlusion time, 48 hours, results read 48 hours after removal of cups; marked erythema (&gt;half the size of the cup) and erythema with induration constituted positive response.</td>
<td>Se 0.43  Sp 0.72  PPV 0.60  NPV 0.57</td>
</tr>
<tr>
<td>Isolauri, 1996</td>
<td>183 Finnish children (ages 2-36 months) with AD and suspected CMA</td>
<td>Patients randomized to DBPCFC (n=118) and open FC (n=65) 99/183 confirmed with CMA by oral challenge.</td>
<td>humidified powdered skim cow milk applied to patient's backs with aluminum cups, occlusion time of 48 hours, results read at 15 minutes after cup removal and again at 72 hours</td>
<td></td>
</tr>
<tr>
<td>Osterballe, 2004</td>
<td>495 children 3 years of age with and without AD (members of a Danish birth cohort) whose parents responded to a questionnaire about food hypersensitivity</td>
<td>OFC to assess both early and late reactions: 3/8 positive for CM</td>
<td>APT scored after 72 hours; positive test ranged from erythema and slight infiltration to papules and vesicles Cow’s milk: 0/8 positive</td>
<td>Se 0.0  Sp 1.00  PPV 0.0  NPV 0.62</td>
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<tr>
<td>Study</td>
<td>Population</td>
<td>Reference Test</td>
<td>Assay</td>
<td>Result</td>
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<tr>
<td>Rancé, 2004</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric allergy clinic</td>
<td>OFC (based on results of APT, SPT, or slgE) or slgE</td>
<td>APT scoring compared after 24- and 48-hour occlusion times; positive test required a minimum of erythema and slight infiltration</td>
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<td>48 hr</td>
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<tr>
<td>Canani, 2007</td>
<td>All children 3-48 months referred to Pediatric gastroenterology center in Naples for suspected FA-related symptoms</td>
<td>OFC with fresh CM, HE, and wheat powder based on reactions to SPT, APT, and slgE: 89 challenges performed in 60 patients CM: 31/55 positive (10 early reax, 21 late reax)</td>
<td>APT performed with fresh foods compared with commercial extracts; Occlusion time 48 hours Results read at 72 hours Positive test defined as a minimum of erythema and slight infiltration</td>
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<tr>
<td>Mehl, 2006</td>
<td>437 German children (aged 3 mos to 17 years) consecutively referred to a specialist for suspected food allergy (excluding those with a clear history of food related symptoms). 391 patients had history of AD.</td>
<td>DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, slgE, and clinical history. 168/437 diagnosed with cow’s milk allergy by DBPCFC</td>
<td>One drop fresh CM put on filter paper and applied to back with aluminum cups. Checked at 20 minutes for immediate reactions. Cups removed at 48 hours and read 20 minutes later, then again 24 hours later (72 hours after application).</td>
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<tr>
<td>Keskin, 2005</td>
<td>37 consecutive children (age 1.5-84 months) with suspected CMA referred to Turkish allergy clinic at a tertiary care center excluding children with chronic disease.</td>
<td>DBPCFC preceded by at least 2 weeks of elimination of CM (except in 6 patients with history of anaphylactic reaction to cow's milk). Reactions were categorized as early (within 2 hours of test) or late. 23/37 had positive challenges or history of anaphylactic reaction</td>
<td>cow’s milk powder mixed with saline, applied with aluminum cups to packs. Children examined after 30 minutes for immediate reactions. Cups removed after 48 hours and read 72 hours after application.</td>
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**Table Notes:** AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; slgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test.
Table 30: APT studies of hen’s egg

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Assay</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Roehr, 2001</strong> 171</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>DBPCFC in 42 children 28/42 positive</td>
<td>One drop of fresh whisked egg white and yolk placed on filter paper and applied to patients’ backs using 12mm aluminum cups; occlusion time, 48 hours, read 20 minutes after removal of the cup, and then again at 72 hours; erythema with infiltration constituted positive reaction 17/98 positive</td>
<td>Se 0.57  Sp 0.93  PPV 0.94 NPV 0.52</td>
</tr>
<tr>
<td><strong>Osterballe, 2004</strong> 169</td>
<td>495 children 3 years of age with and without AD (members of a Danish birth cohort) whose parents responded to a questionnaire about food hypersensitivity</td>
<td>OFC to assess both early and late reactions: 8/14 positive for HE Hen’s egg: 6/13 positive</td>
<td>APT scored after 72 hours; positive test ranged from erythema and slight infiltration to papules and vesicles</td>
<td>Se 0.63  Sp 0.80  PPV 0.83 NPV 0.57</td>
</tr>
<tr>
<td><strong>Rancé, 2004</strong> 170</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic</td>
<td>OFC (based on results of APT, SPT, or sIgE) or sIgE APT scoring compared after 24- and 48-hour occlusion times; positive test required a minimum of erythema and slight infiltration</td>
<td></td>
<td>Se 24 hr 0.15  Sp 0.83  PPV 0.86 NPV 0.12 48 hr 0.97  0.71  0.95  0.83</td>
</tr>
<tr>
<td><strong>Canani, 2007</strong> 175</td>
<td>All children 3-48 months referred to Pediatric gastroenterology center in Naples for suspected FA-related symptoms</td>
<td>OFC with fresh CM, HE, and wheat powder based on reactions to SPT, APT, and sIgE: 89 challenges performed in 60 patients HE: 19/28 positive (5 early, 14 late reactions) APT performed with fresh foods compared with commercial extracts; Occlusion time 48 hours Results read at 72 hours Positive test defined as a minimum of erythema and slight infiltration</td>
<td></td>
<td>Se Fresh 0.84  Sp 1.00  PPV 1.00 NPV 0.75 Extract 0.05  1.00  1.00  0.33</td>
</tr>
<tr>
<td><strong>Mehl, 2006</strong> 149</td>
<td>437 German children (aged 3mos to 17 years) consecutively referred to specialist for suspected food allergy (excluding those with a clear history of food related symptoms). 391 patients had history of AD.</td>
<td>DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, sIgE, and clinical history. 193/437 diagnosed with egg allergy</td>
<td>One drop fresh HE (white and yolk) put on filter paper and applied to back with aluminum cups. Checked at 20 minutes for immediate reactions. Cups removed at 48 hours and read 20 minutes later, then again 24 hours later.</td>
<td>Reaction Overall 41  Sp 87  PPV 86 NPV 43 Immediate 45 Late 17 Combined 36 AD+ 40  91 AD- 60  85 there was no effect of age on sensitivity.</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test
Table 31: APT studies of soy

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Assay</th>
<th>Result</th>
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</thead>
</table>
| Roehr, 2001    | 98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis | DBPCFC in 25 children               | One drop of soy milk placed on filter paper and applied to patients’ backs using 12mm aluminum cups; occlusion time, 48 hours, read 20 minutes after removal of the cup, and then again at 72 hours; erythema with infiltration constituted positive reaction. 6/98 positive | Se  Sp  PPV  NPV  
|                |                                                 | 4/25 positive                       |                                                                       | 0.75  0.86  0.50  0.95                                                  |
| Mehl, 2006     | 437 German children (aged 3mos to 17 years) consecutively referred to specialist for suspected food allergy (excluding those with a clear history of food related symptoms). 391 patients had history of AD. | DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, sIgE, and clinical history. 37/437 diagnosed with wheat allergy | One drop soy milk put on filter paper and applied to back with aluminum cups. Checked at 20 minutes for immediate reactions. Cups removed at 48 hours and read 20 minutes later, then again 24 hours later. | Reaction  Se  Sp  PPV  NPV  
|                |                                                 |                                    |                                                                       | Overall 23 86 30 82                                                   |
|                |                                                 |                                    |                                                                       | AD+ 25 88                                                           |
|                |                                                 |                                    |                                                                       | AD- 0 86                                                           |
|                |                                                 |                                    |                                                                       | No difference seen in the sensitivity of the test by reaction timing |
|                |                                                 |                                    |                                                                       | sensitivity of APT increased with age, and was 100% for children older than 6 years of age. |

Table Notes: AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference Test</th>
<th>Assay</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roehr, 2001&lt;sup&gt;171&lt;/sup&gt;</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>DBPCFC performed with wheat powder on 35 children</td>
<td>One drop of wheat powder dissolved in water placed on filter paper and applied to patients’ backs using 12mm aluminum cups; occlusion time, 48 hours, read 20 minutes after removal of the cup, and then again at 72 hours; erythema with infiltration constituted positive reaction. 17/98 positive</td>
<td>Se 0.89, Sp 0.94, PPV 0.94, NPV 0.89</td>
</tr>
<tr>
<td>Rancé, 2004&lt;sup&gt;170&lt;/sup&gt;</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic</td>
<td>OFC (based on results of APT, SPT, or sIgE) or sIgE</td>
<td>APT scoring compared after 24- and 48-hour occlusion times; positive test required a minimum of erythema and slight infiltration</td>
<td>Se 24 hr 0.25, Sp 1.00, PPV 1.00, NPV 0.94</td>
</tr>
<tr>
<td>Mehl, 2006&lt;sup&gt;149&lt;/sup&gt;</td>
<td>437 German children (aged 3mos to 17 years) consecutively referred to specialist for suspected food allergy (excluding those with a clear history of food related symptoms). 391 patients had history of AD.</td>
<td>DBPCFC (except patients under 1 year of age with clear history of immediate reactions) guided by SPT, sIgE, and clinical history. 159/437 diagnosed with wheat allergy.</td>
<td>One drop wheat powder (Kröner) dissolved in water, put on filter paper and applied to back with aluminum cups. Checked at 20 minutes for immediate reactions. Cups removed at 48 hours and read 20 minutes later, then again 24 hours later.</td>
<td>Overall 27 Se 89, Sp 58, PPV 69, NPV 69  Immediate 22 Late 29 Combined 50 sensitivity of APT increased with age, and was 100% for children older than 6 years of age.</td>
</tr>
<tr>
<td>Jarvinen, 2003&lt;sup&gt;196&lt;/sup&gt;</td>
<td>90 children (2.5-36 months) w/CMA (both IgE- and non-IgE-mediated) controlled via elimination but w/ residual symptoms that did not respond to elimination of eggs, nuts, fruits, chocolate, fish.</td>
<td>Open food challenge preceded by elimination diet. Immediate reactions were those occurring within an hour of the last dose. Each child only tested with one cereal (reason of choice not reported. 30/44 OFCs were positive for wheat 66/90 OFCs were positive for all cereals (wheat, rye, barley, oats)</td>
<td>wheat flour mixed with isotonic saline was applied to the back with aluminum cups. Cups were removed after 48 hours and reactions read 72 hours after the cups were applied. Presence of edema or eczema was considered a positive reaction.</td>
<td>Food Wheat 70 Se 71, Sp 84, PPV 53, NPV 53  All Cereals 67 79 90 46</td>
</tr>
</tbody>
</table>

**Table Notes:** AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test
Immediate Skin Application Test
Immediate skin application testing (I-SAFT) is a rapid assessment of topical allergic response to very small quantities of allergen that has been used to predict the likelihood of a strong response to oral challenge. One study compared response to I-SAFT with that of SPT, APT, and sIgE in diagnosing peanut allergy. The study was conducted among 84 children who were consecutively recruited from children attending a Sydney pediatric hospital allergy clinic based on positive skin prick test for peanut allergy using a commercial extract and a wheal size cutoff of 3mm larger than the saline control. All participants without a history of having ingested peanut in the preceding 3 months were given an open in-hospital challenge. Prior to the challenge, one gram of commercial peanut butter on a cardboard square was applied directly to the skin; the response was read after 15 minutes. A positive score consisted of the appearance of any wheal in the area. The test had a sensitivity of 0.50 (95% CI 0.36, 0.64); specificity of 0.82 (95% CI 0.65, 0.93); PPV of 0.81 and NPV of 0.51 (this study satisfied 9 of the 12 QUADAS domains assessed).
Meta-analysis comparing different diagnostic tests
To summarize and compare the results of studies of SPT, sIgE, and APT, where possible we constructed Receiver Operator Characteristic (ROC) curves for each test, both within and across food types. ROC curves plot sensitivity versus 1-specificity and are useful when assessing whether different tests reporting different results, are actually different, since simply changing the threshold for a positive test will make any data appear “different” by trading off sensitivity for specificity. Twelve studies provided data on SPT, 11 studies provided data on sIgE, and 8 studies provided data on APT.

For three foods, cow’s milk, hen’s egg, and wheat, there were sufficient data to construct ROC curves. Figure 4 shows the results for cow’s milk, figure 5 shows the results for hen’s egg. There were sufficient data to compare SPT and sIgE for diagnostic accuracy, within cow's milk and hen's egg, and across all food types. Figure 6a shows the data across all food types, with an area under the curve of 0.85 for SPT and 0.81 for sIgE, this difference is not statistically significant. Figure 6b shows the data for cow's milk, with an area under the curve of 0.84 for SPT and 0.78 for sIgE, this difference is not statistically significant. Figure 6c shows the data for hen's egg, with an area under the curve of 0.87 for SPT and 0.85 for sIgE, also a non-significant difference. Neither is there any statistically significant difference in diagnostic accuracy for the tests across foods (data not shown). In prior sections of this report, the most likely explanation for variations in reported sensitivity and specificity of SPT and sIgE across foods is differences in the criteria for a positive test. Our Receiver Operator Characteristic curves are most consistent with the hypothesis that all IgE-based tests are operating on the same curve.

The quality of this evidence is considered moderate meaning future research may change our confidence in the estimate of effect.
Figure 4: ROC curve for SPT, sIgE, APT for Cow’s Milk
Figure 5: ROC curve for SPT and sIgE for Hen's egg
Figure 6: Figures 6a, 6b, and 6c

Figure 6a: All food: SPT, slgE with sens/spec pairs from studies

- Sensitivity
- 1 - Specificity
- AUC SPT: 0.85 (0.79, 0.91)
- AUC slgE: 0.81 (0.74, 0.87)
- Diff: 0.04 (-0.05, 0.13)

Figure 6b: Cow’s Milk: SPT, slgE with sens/spec pairs from studies

- Sensitivity
- 1 - Specificity
- AUC SPT: 0.84 (0.75, 0.92)
- AUC slgE: 0.78 (0.70, 0.86)
- Diff: 0.06 (-0.05, 0.18)

Figure 6c: Hen’s Egg: SPT, slgE with sens/spec pairs from studies

- Sensitivity
- 1 - Specificity
- AUC SPT: 0.87 (0.76, 0.97)
- AUC slgE: 0.85 (0.62, 1.09)
- Diff: 0.01 (-0.25, 0.27)
Use of Combined Tests

Eleven studies compared the diagnostic value of combining two or more types of tests with using only one test. Combining test results could be accomplished in one of two ways: 1) a positive result on either one test or another (others) (referred to as parallel testing in some studies); or 2) a positive result on two or more tests (referred to as serial testing in some studies). Some studies assessed parallel testing, some assessed serial testing, and some assessed both. The findings of these studies are summarized here.

Skin Prick Test and Atopy Patch Test
Six studies assessed the combination of SPT and atopy patch test (APT) (Table 33).

The combination of SPT and APT (both in serial and in parallel) was compared with that of each alone for the diagnosis of cow’s milk allergy in 183 patients (2-36 months), some with immediate onset reactions and some with delayed onset reactions to cow’s milk (reference was food challenge). The SPT tended to be positive in those with immediate responses and negative in those with delayed responses. When both tests were required to be positive, they displayed a sensitivity of 0.24 and specificity of 0.94; when one or the other was positive, the sensitivity was 0.72 and the specificity 0.86. In comparison, the SPT alone had a sensitivity of 0.48 and a specificity of 0.86; the APT alone had a sensitivity of 0.61 and specificity of 0.81. The responses to the SPT and APT were both positive in only 0.15 and both negative in only 0.38 of participants. Cohen’s κ statistic for concordance was 0.03 (95% CI -0.13, 0.19) indicating no agreement. The authors concluded that use of both tests was superior to use of only one in diagnosing cow’s milk allergy and pinpointing the type (McNemar chi square test for SPT: 8.17, p=0.004) vs. chi square test for APT 6.25, p=0.01) (this study satisfied 10 of the 12 QUADAS domains assessed).

The combined use of APT and SPT (in serial) was compared with individual tests and other combinations of tests in a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis and suspected allergy to cow’s milk, hen’s egg, wheat, or soy. All children received DBPCFC based on previous history and all received SPT, APT, and sIgE. Combining the SPT and APT did not improve the PPV or NPV over that of the individual tests (this study satisfied 9 of the 12 QUADAS domains assessed).

The use of both APT and SPT in serial was compared with individual tests in 37 children with suspected cow’s milk allergy (some with immediate and some with delayed-onset symptoms) diagnosed with food challenge. Combining both tests provided a sensitivity of 1, specificity of 0.5, PPV of 0.76 and NPV of 1. In comparison, the SPT alone had a sensitivity of 0.91 and a specificity of 0.5 and the APT had a sensitivity of 0.73 and a specificity of 0.86 (the significance of these differences was not tested statistically) (this study satisfied 10 of the 12 QUADAS domains assessed). However, the authors concluded that while the addition of APT could help rule out cow’s milk allergy in some children, positive responses to both tests was not an adequate substitute for food challenge.
The use of SPT and APT were compared with the use of both tests (in parallel and in serial) in diagnosing cereal allergy in children who had cow’s milk allergy but who had residual symptoms after cow’s milk withdrawal. As shown in Table 29, the use of both tests in serial provided greater sensitivity and NPV than either test alone, whereas the SPT alone had the best specificity and PPV. The APT was as sensitive as the SPT for immediate hypersensitivity but far more efficient for detecting delayed hypersensitivity (this study satisfied 9 of the 12 QUADAS domains assessed). The authors concluded that the APT aids in diagnosis of cereal allergy, especially if the primary test was a SPT, but that diagnosis still required food challenge for confirmation.

The performances of SPT, APT, and both tests in serial were compared in diagnosing allergy to cow’s milk, egg, wheat, and soy in 437 children (ages 3 mos to 14 years) who had received DBPCFC (this study satisfied 9 of the 12 QUADAS domains assessed). The combination of tests was superior to either test alone for all foods.

Finally, a study that enrolled all children (3-48 months) referred to an Italian pediatric gastroenterology center for evaluation of suspected food hypersensitivity compared the combination of SPT and APT in parallel to that of the individual tests for diagnosing allergy to cow’s milk and hen’s egg. The study found that accepting a positive APT or a positive SPT as indication of an allergic reaction increased the sensitivity of testing for allergy to cow’s milk and hen’s egg (sensitivity for cow’s milk 0.87; specificity 0.65; PPV 0.77; NPV 0.79; sensitivity for hen’s egg: 0.95, specificity 0.67; PPV 0.86; NPV 0.86)( this study satisfied 11 of the 12 QUADAS domains assessed).
<table>
<thead>
<tr>
<th>Study</th>
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<th>SPT</th>
<th>APT</th>
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<tr>
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<td>Results</td>
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<td>Isolauri, 1995</td>
<td>148</td>
<td>0.48 0.86</td>
<td>0.61 0.81</td>
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<td>0.72 0.86</td>
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<td>Both tests +:</td>
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<td>0.92 0.24</td>
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<tr>
<td>Roehr, 2001</td>
<td>171</td>
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<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
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<tr>
<td>Keskin, 2005</td>
<td>37 children referred for suspected CMA</td>
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<tr>
<td>Jarvinen, 2003</td>
<td>196</td>
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<td></td>
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<tr>
<td></td>
<td>90 children (2.5-36 months) w/CMA (both IgE- and non-IgE-mediated) controlled via elimination but w/residual symptoms that did not respond to elimination of eggs, nuts, fruits, chocolate, fish. DBPCFC was reference.</td>
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<tr>
<td>Mehl, 2006</td>
<td>149</td>
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<tr>
<td></td>
<td>437 children referred to specialist for diagnosis of suspected allergy to CM, egg, wheat, soy (3 mos-14 yrs), confirmed with DBPCFC</td>
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<tr>
<td>Canani, 2007</td>
<td>All children 3-48 months referred to Pediatric gastroenterology center in Naples for suspected FA-related symptoms</td>
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<td></td>
<td>Reference Test: OFC with fresh CM, HE, and wheat powder based on reactions to SPT, APT, and sIgE: 89 challenges performed in 60 patients CM: 31/55 positive (10 early reax, 21 late reax) HE: 19/28 positive (5 early reax, 14 late reax)</td>
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<tr>
<td>SPT with fresh foods Positive reaction ≥3mm with no reaction to control Cow’s milk:</td>
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<td>Hen’s Egg:</td>
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<tr>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td>0.45</td>
<td>0.70</td>
<td>0.67</td>
<td>0.51</td>
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| APT with fresh food Cow’s milk: |
| Hen’s Egg: |

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<th>Se</th>
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<td>0.84</td>
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| APT or SPT Cow’s milk: |
| Hen’s Egg: |

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<tr>
<td>0.95</td>
<td>0.67</td>
<td>0.86</td>
<td>0.86</td>
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</table>

**Table Notes:** AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test
SPT and Antigen-specific IgE

Three studies compared the performance of combining SPT with sIgE with that of the tests alone (Table 34).

One study reported that the use of RAST to measure sIgE did not improve the predictive value of SPT alone for diagnosis of cow’s milk allergy in 135 children (5 mos to 13 years), half of whom had been diagnosed as cow’s milk allergic and the other half as not allergic with food challenge (this study satisfied 9 of the 12 QUADAS domains assessed). These authors did not report the predictive value of RAST alone.

The combination of SPT and sIgE was compared with individual tests and other combinations of tests in a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis and suspected allergy to cow’s milk, hen’s egg, wheat, or soy. All children received DBPCFC based on previous history and all received SPT, APT, and sIgE. Combining the SPT and sIgE did not improve the PPV or NPV over that of the individual tests (this study satisfied 9 of the 12 QUADAS domains assessed).

The third study compared the performance of SPT (using both raw and commercial extracts), sIgE (measured by CAP FEIA), and the two tests combined for measuring peanut allergy. They reported that the performance characteristics of raw extracts were superior to those of the commercial extracts. They also found that the combination of SPT and sIgE was superior to that of either test alone, and that the predictive values of the combined tests would avoid the need for DBPCFC in patients with SPT wheal diameter <3 and sIgE<57 (indicating a negative result) or with wheal diameter ≥16 OR sIgE≥57 (indicating a positive result) (this study satisfied 10 of the 12 QUADAS domains assessed).
Table 34: Combination of SPT and sIgE compared with Individual Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>SPT Results</th>
<th>sIgE Results</th>
<th>SPT+sIgE Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill, 1988</td>
<td>135 children referred to specialist with CMA (5 mos-13 yrs); ½ CMA+ by food challenge</td>
<td>SPT≥4=positive PPV: 1 NPV: 0.65</td>
<td>RAST Predictive value not reported</td>
<td>Se 0.54  Sp 0.91  PPV 0.86  NPV 0.66</td>
</tr>
<tr>
<td>Roehr, 2001</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>Cutoff: ≥3mm (no reaction to control) Milk</td>
<td>Cutoff: ≥0.35 kU/L</td>
<td>Milk</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Se 0.78  Sp 0.69  PPV 0.81  NPV 0.64</td>
<td>Se 0.84  Sp 0.38  PPV 0.70  NPV 0.59</td>
<td>Se 0.85  Sp 0.56  PPV 0.83  NPV 0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hen’s Egg</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Se 0.89  Sp 0.57  PPV 0.81  NPV 0.73</td>
<td>Se 0.96  Sp 0.36  PPV 0.75  NPV 0.83</td>
<td>Se 0.96  Sp 0.43  PPV 0.86  NPV 0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Soy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Se 0.50  Sp 0.90  PPV 0.50  NPV 0.90</td>
<td>Se 0.75  Sp 0.52  PPV 0.23  NPV 0.92</td>
<td>Se 1.00  Sp 0.91  PPV 0.50  NPV 1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wheat</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Se 0.67  Sp 0.53  PPV 0.60  NPV 0.60</td>
<td>Se 0.67  Sp 0.47  PPV 0.57  NPV 0.57</td>
<td>Se 0.71  Sp 0.50  PPV 0.63  NPV 0.60</td>
</tr>
<tr>
<td>Rance, 2002</td>
<td>363 children referred for suspected peanut allergy</td>
<td>NPV for raw extract =1 SPT&gt;3mm: specificity 74% PPV=1 for SPT≥16mm:</td>
<td>CAP FEIA PPV=1 for kUA/L≥57 sIgE+SPT Predictive values of nearly 1 for the following cutoffs: + Dx: SPT≥16 and sIgE≥57 -Dx: SP&lt;3 and sIgE&lt;57</td>
<td></td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test

Atopy Patch Test and Antigen-specific IgE

Two studies assessed the performance of combining the results of APT and sIgE (Table 35). The combination of APT and sIgE was compared with individual tests and other combinations of tests in a 2001 study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis and suspected allergy to cow’s milk, hen’s egg, wheat, or soy (the results of combining tests were reported only for suspected milk and egg allergy). All children received DBPCFC based on previous history and all received SPT, APT, and sIgE. slgE reactions were assessed at two different cutoff points, and at two different time points (early and delayed), in an attempt to assess the utility of combining tests to distinguish IgE-mediated (early) vs. non-IgE-mediated (delayed) allergy. For cow’s milk allergy, the APT had a PPV of 0.95; combining the APT with slgE or SPT improved the PPV to 1.00. Combining APT with slgE also slightly improved the PPV for both early and late reactions to cow’s milk over that of APT, SPT, or slgE alone and improved the NPV for late reactions over that of APT, SPT, or slgE alone. For hen’s egg allergy, the combination of APT and slgE had no advantage over individual tests.
The second study assessed the effect of combining the results of APT and sIgE for the same four foods. The addition of APT to sIgE resulted in increased sensitivity and/or specificity in diagnosis over the use of either sIgE or APT alone. These authors attempted to calculate the proportion of children who could be spared a DBPCFC by the use of combined tests; they found that setting the PPV of the test at 0.99, only 0.05 -7 of children would fulfill the criteria, and setting it at 0.95, between 0.06 and 0.14 would fulfill the criteria for being able to avoid food challenge (this study satisfied 9 of the 12 QUADAS domains assessed).
Table 35: Combination of APT and Antigen-specific IgE Compared with Individual Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>APT Results</th>
<th>sIgE Results</th>
<th>APT+sIgE Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Milk-Early</td>
<td>Milk-Early</td>
<td>Milk-Early</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Se</td>
<td>Sp PPV NPV</td>
<td>Se Sp PPV NPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥0.35</td>
<td>0.38 0.59</td>
<td>≥0.35 0.64 1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥17.5</td>
<td>0.96 0.86</td>
<td>≥17.5 0.06 1.00</td>
</tr>
<tr>
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<td>0.98 0.89</td>
<td>0.78 0.96 0.84</td>
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<td>0.93 0.89</td>
<td>0.44 0.93 0.89</td>
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<tr>
<td></td>
<td></td>
<td>0.80</td>
<td>0.93 0.89</td>
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<tr>
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<td>≥0.35</td>
<td>0.94 0.65</td>
<td>≥0.35 0.92 1.00</td>
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<td></td>
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<td>≥17.5</td>
<td>1.00 1.00</td>
<td>≥17.5 0.35 1.00</td>
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<td>0.95 0.86</td>
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<td>0.41</td>
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<td>0.27</td>
<td>0.89 0.58</td>
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<td>0.23</td>
<td>0.86 0.30</td>
<td>0.23 0.86 0.30</td>
</tr>
<tr>
<td>Roehr, 2001171</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
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<tr>
<td></td>
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<td>Milk-Late</td>
<td>Milk-Late</td>
<td>Milk-Late</td>
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<td>Se</td>
<td>Sp PPV NPV</td>
<td>Se Sp PPV NPV</td>
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<td>≥0.35</td>
<td>0.38 0.48</td>
<td>≥0.35 0.92 1.00</td>
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<td>0.96 0.75</td>
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<td>0.23</td>
<td>0.86 0.30</td>
<td>0.23 0.86 0.30</td>
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<tr>
<td>Mehl, 2005149</td>
<td>437 children referred to specialist for diagnosis of suspected allergy to CM, egg, wheat, soy (3 mos-14 yrs), confirmed with DBPCFC</td>
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<td></td>
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<td>CM:</td>
<td>Egg:</td>
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<td>Se</td>
<td>Sp PPV NPV</td>
<td>Se Sp PPV NPV</td>
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<td>0.95 0.86</td>
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<td>Se</td>
<td>Sp PPV NPV</td>
<td>Se Sp PPV NPV</td>
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<td>0.89 0.58</td>
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<td>Soy:</td>
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<td></td>
<td>Se</td>
<td>Sp PPV NPV</td>
<td>Se Sp PPV NPV</td>
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<td></td>
<td></td>
<td>0.23</td>
<td>0.86 0.30</td>
<td>0.23 0.86 0.30</td>
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<td></td>
<td></td>
<td>Soy:</td>
<td>Soy:</td>
<td>Soy:</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test

Skin Prick Test and Atopy Patch Test and Antigen-specific IgE

Five studies compared the performance characteristics of combining SPT, APT, and sIgE in serial or parallel. (Table 36) The combined use of APT and SPT and sIgE (in serial) was compared with individual tests and other combinations of tests in a study of 98 children admitted consecutively to a Berlin pediatric hospital pneumonology ward with atopic dermatitis and suspected allergy to cow’s milk, hen’s egg, wheat, or soy. All children received DBPCFC.
based on previous history and all received SPT, APT, and sIgE. Combining the SPT, APT, and sIgE did not improve the PPV or NPV over that of the individual tests (this study satisfied 9 of the 12 QUADAS domains assessed).

In a second study, the performance of APT was compared with that of APT+SPT+sIgE (in parallel) in 34 children with suspected milk allergy (5 mos-16 years). Positive reactions on any of three tests improved the sensitivity and PPV of cow’s milk allergy diagnosis among children younger than 3 years (0.80 and 0.73 for APT alone vs. 0.92 and 0.85 for all three tests, respectively); however, specificity and NPV did not improve (this study satisfied 7 of the 12 QUADAS domains assessed).

A third study compared the performance of the APT+SPT+cown’s milk sIgE (in serial) with that of the individual tests and the combination of APT+SPT. The combination of the three tests had greater sensitivity and NPV than any of the tests alone but was no better than the APT+SPT on any performance parameter (this study satisfied 10 of the 12 QUADAS domains assessed).

The performance of the APT+SPT+sIgE (in serial) was compared with those of each test alone as well as with the combination of APT+SPT and APT+sIgE to assess the value of adding the APT to determination of early-phase, presumably IgE-mediated reactions. Their population comprised 437 children (3 mos-14 years) in a large German medical center who had received a DBPCFC. The use of all three tests improved the sensitivity and NPV of the cow’s milk assessment over that of the other combinations of tests and had a better NPV than the individual tests alone. The specificity and PPV were also improved over that of sIgE or SPT or APT alone for cow’s milk, egg, wheat, and soy (this study satisfied 9 of the 12 QUADAS domains assessed).

Finally, a study that enrolled all children (3-48 months) referred to an Italian pediatric gastroenterology center for evaluation of suspected food hypersensitivity compared the combination of SPT and APT and sIgE in parallel to that of the individual tests for diagnosing allergy to cow’s milk and hen’s egg. The study found that accepting a positive APT or a positive SPT or a positive sIgE as indication of an allergic reaction maximized the performance characteristics of the test for allergy to cow’s milk (sensitivity for cow’s milk 0.90; specificity 0.52; PPV 0.72; NPV 0.80) (this study satisfied 11 of the 12 QUADAS domains assessed).

**Skin Prick Test and Antigen-specific IgE and Immediate Skin Application Food Test**

One study compared response to a combination of SPT, sIgE and I-SAFT with that of the individual tests in diagnosing peanut allergy. The study was conducted among 84 children who were consecutively recruited from children attending a Sydney pediatric hospital allergy clinic based on positive skin prick test for peanut allergy using a commercial extract and a wheal size cutoff of 3mm larger than the saline control. All participants without a history of having ingested peanut in the preceding 3 months were given an open in-hospital challenge. The combination of tests did not increase the sensitivity or specificity over those of any of the individual tests (this study satisfied 9 of the 12 QUADAS domains assessed).
Table 36: Combination of SPT and APT and Antigen-specific IgE compared with Individual Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>SPT Results</th>
<th>APT Results</th>
<th>sIgE Results</th>
<th>SPT+APT+sIgE Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roehr, 2001†</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>Milk: 0.78 0.69 0.81 0.64 Hen’s Egg: 0.89 0.57 0.81 0.73 Soy: 0.50 0.90 0.50 0.90 Wheat: 0.67 0.53 0.60 0.60</td>
<td>Milk: 0.47 0.96 0.95 0.51 Hen’s Egg: 0.57 0.93 0.94 0.52 Soy: 0.75 0.86 0.50 0.95 Wheat: 0.89 0.94 0.94 0.89</td>
<td>Cutoff point≥0.35 Milk: 0.84 0.38 0.70 0.59 Hen’s Egg: 0.96 0.36 0.75 0.83 Soy: 0.75 0.52 0.23 0.92 Wheat: 0.67 0.47 0.57 0.57</td>
<td>Milk: 0.81 1.00 1.00 0.67 Hen’s Egg: 0.94 0.75 0.94 0.75 Soy: 1.00 1.00 1.00 1.00 Wheat: 0.91 0.86 0.91 0.86</td>
</tr>
<tr>
<td>Cudowska, 2005†</td>
<td>34 children (5 mos-16 yrs) 20&lt;3yrs 14≥3yrs w/suspected milk allergy</td>
<td>Age&lt;3 years: 0.80 0.79 0.73 0.22 Age ≥3 years: 0.80 0.89 0.80 0.11</td>
<td>Age&lt;3 years: 0.80 0.79 0.73 0.22 Age ≥3 years: 0.80 0.89 0.80 0.11</td>
<td>Cutoff point≥0.7kU/L Age&lt;3 years: 0.91 0.50 0.75 0.65 Age ≥3 years: 0.80 0.89 0.80 0.11</td>
<td>Cutoff point≥0.7kU/L Criterion: &gt;1 positive Se: 0.74 0.79 0.85 0.65 Se: 0.74 0.79 0.85 0.65</td>
</tr>
<tr>
<td>Keskin, 2005†</td>
<td>37 children referred for suspected CMA</td>
<td>Cutoff point≥3mm</td>
<td>Se: 0.91 0.50 0.75 0.65</td>
<td>Cutoff point≥0.7kU/L Criterion: &gt;1 positive</td>
<td>Se: 1.00 0.50 0.76 1.00</td>
</tr>
<tr>
<td>Mehl, 2006†</td>
<td>437 children referred to specialist for diagnosis of suspected allergy to CM, egg, wheat, soy (3 mos-14 yrs), confirmed with DBPCFC</td>
<td>CM: 0.85 0.70 0.73 0.83 Egg: 0.85 0.70 0.73 0.83</td>
<td>CM: 0.31 0.95 0.86 0.60 Egg: 0.31 0.95 0.86 0.60</td>
<td>CM: 0.87 0.49 0.62 0.79 Egg: 0.87 0.49 0.62 0.79</td>
<td>CM: 0.82 0.95 0.91 0.90 Egg: 0.82 0.95 0.91 0.90</td>
</tr>
<tr>
<td></td>
<td>Se</td>
<td>Sp</td>
<td>PPV</td>
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<tr>
<td>Wheat</td>
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<tr>
<td>Se</td>
<td>0.75</td>
<td>0.64</td>
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<td>Soy</td>
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<tr>
<td>Se</td>
<td>0.29</td>
<td>0.85</td>
<td>0.33</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Canani, 2007</td>
<td>All children 3-48 months referred to Pediatric gastroenterology center in Naples for suspected FA-related symptoms</td>
<td>SPT with fresh foods</td>
<td>Positive reaction ≥3mm with no reaction to control</td>
<td>Cow’s milk:</td>
<td>Se</td>
</tr>
<tr>
<td></td>
<td>Se</td>
<td>Sp</td>
<td>PPV</td>
<td>NPV</td>
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<tr>
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<td>0.45</td>
<td>0.70</td>
<td>0.67</td>
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<tr>
<td>Hen’s Egg:</td>
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</tr>
<tr>
<td>Se</td>
<td>0.58</td>
<td>0.67</td>
<td>0.70</td>
<td>0.43</td>
<td></td>
</tr>
</tbody>
</table>

**Table Notes:** AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CM cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test

Canani, 2007

**Reference Test:**
- OFC with fresh CM, HE, and wheat powder based on reactions to SPT, APT, and sIgE: 89 challenges performed in 60 patients
- CM: 31/55 positive (10 early reax, 21 late reax)
- HE: 19/28 positive (5 early reax, 14 late reax)

**SPT with fresh foods**
- Positive reaction ≥3mm with no reaction to control
- Cow’s milk:
  - Se | Sp | PPV | NPV |
  - 0.45 | 0.70 | 0.67 | 0.51 |
- Hen’s Egg:
  - Se | Sp | PPV | NPV |
  - 0.58 | 0.67 | 0.70 | 0.43 |

**APT with fresh vs. commercial food extracts**
- Cow’s milk:
  - Se | Sp | PPV | NPV |
  - 0.65 | 0.96 | 0.95 | 0.67 |
- Hen’s Egg:
  - Se | Sp | PPV | NPV |
  - 0.32 | 0.67 | 0.67 | 0.32 |

**sIgE**
- Cow’s milk:
  - Se | Sp | PPV | NPV |
  - 0.23 | 0.74 | 0.54 | 0.42 |
- Hen’s Egg:
  - Se | Sp | PPV | NPV |
  - 0.95 | 0.44 | 0.78 | 0.80 |
Antigen-specific IgE Plus Lymphocyte Stimulation with Beta Lactoglobulin

One study assessed the performance of combining cow’s milk sIgE with a relatively uncommon in vitro test that assesses the induction of lymphocyte proliferation with beta-lactoglobulin (BLG). Cow’s milk allergy was assessed in 34 children, 19 of whom had a positive DBPCFC. By itself, the BLG test showed a sensitivity of 0.40 and a specificity of 0.83. Combining the two tests had a sensitivity of 0.88 and a specificity of 0.67 (this study satisfied 8 of the 12 QUADAS domains assessed).

Summary

Of the ten studies that tried to improve diagnostic specificity or sensitivity by combining two or more tests, seven paired the APT with SPT, sIgE, or both, in an attempt to capture both immediate and delayed responses to antigen, whereas two combined SPT with sIgE to try to improve sensitivity, and one combined sIgE assessment with BLG-induced proliferation. Pairing the APT with SPT, sIgE, or both improved sensitivity and specificity over the use of individual tests in most studies; however, the small number of studies that calculated the proportion of patients for whom two or more tests could obviate the need for DBPCFC found these proportions to be quite small. Of the three studies that paired SPT with sIgE in an attempt to improve identification of IgE-mediated allergy, one found improved performance with the two tests, and the other two found no difference. These studies satisfied 7 to 10 out of 12 QUADAS domains. The quality of evidence is judged to be very low, meaning any estimate of effect is uncertain.

Diagnosis of Specific non-IgE Mediated Conditions

Diagnosis of Cow’s Milk and Other Protein-Induced Enteropathy

Several studies that attempted to establish a method to differentially diagnose IgE- and non-IgE-mediated cow’s milk allergy (using a combination of APT and SPT or sIgE) and that met the inclusion criteria were described above. A small number of studies specifically focused on the diagnosis of (non-IgE-mediated) Cow’s milk-induced or protein-induced enteropathy but none met the inclusion criteria. These studies are described here.

A study of 142 consecutive infants admitted to a Korean hospital with gastrointestinal symptoms following cow’s milk ingestion were subjected to milk elimination and open challenge as well as assessments of growth, serum albumin, acidosis, and peripheral leukocytosis. Among 16 patients diagnosed with cow’s milk protein-induced enterocolitis based on challenge, hypoalbuminemia and failure to thrive were found to be independent predictors of the diagnosis.

A retrospective record review of ten Thai children with cow’s milk sensitive enteropathy found that cow’s milk sIgE and total serum IgE levels were predictive of the course of the allergy (likelihood of recovery).

The utility of the lymphocyte proliferation (LP) assay was tested in a group of US children (9 with milk-induced enterocolitis syndrome (ME), 27 with IgE-mediated milk allergy (diagnosed with history, food challenge, and SPT), and 21 controls. Among children with ME, in vitro LP
was higher than controls in terms of total radioactivity incorporated but not in terms of the stimulation index (the ratio of incorporation by stimulated cells to incorporation by unstimulated cells). Median LP for children with IgE-mediated allergy was higher than that of control children but the ranges overlapped greatly. And probably most indicative of the lack of utility of this assay was the finding that LP was elevated in response to soy exposure in a subgroup of milk-allergic patients who had no response to soy on food challenge.

Finally, 20 US infants with proctocolitis attributed to cow’s milk, soy milk, or breast milk (by clinical history) underwent colonic mucosal biopsy at three different anatomical sites. Nineteen of the 20 infants had at least one abnormal biopsy, characterized by eosinophilic infiltration. The authors concluded that multisite colonic mucosal biopsy is useful for confirmation of this disorder.

**Diagnosis of Eosinophilic Esophagitis**

The diagnosis of eosinophilic esophagitis is defined as esophageal biopsy with the finding of greater than 20 eosinophils per high power field; the gold standard for establishing food allergy as the causal mechanism is resolution of esophageal eosinophilia and symptoms following elimination of the food from diet followed by recurrent esophageal eosinophilia with food challenge.

Three articles addressing the diagnosis of food allergy-induced eosinophilic esophagitis were discovered in our literature search: these studies were all produced by the same group and based on the same patient population. Because all three papers reported results from the same patient population, only the results of the final publication from this series are reported here. In this paper, the authors report the effectiveness of using skin prick and patch tests to identify causative foods in patients with eosinophilic esophagitis. Results are reported for a subset of patients with EE (n=316) at Children's Hospital Philadelphia in whom single causative foods were identified (note that patients had to choose to have a subsequent esophageal biopsy). Skin prick tests were performed using a commercial extract (Allergy Labs of Ohio) with a wheal of 3mm greater than the negative control being considered positive. Patch tests were performed using a mix of dry foods and isotonic saline with the patches removed at 48 hours and the results read at 72 hours. The diagnosis of food allergy as the cause of EE was made by normalization of esophageal biopsy (0 eosinophils/HPF) after elimination of that food for 1-2 months, with esophageal eosinophilia (>20 eos/HPF) recurring on challenge with that food. The authors do not report the number of subjects who test positive for APT and SPT for each food, but do report the number of individuals whose diagnosis was confirmed with elimination and challenge (this study satisfied 5 of the 12 QUADAS domains assessed). The results are reported in Table 37.
Table 37: Sensitivity and Specificity of SPT and APT in EE

<table>
<thead>
<tr>
<th>Food*</th>
<th>SPT</th>
<th></th>
<th></th>
<th></th>
<th>APT</th>
<th></th>
<th></th>
<th></th>
<th>SPT+APT</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Se</td>
<td>Sp</td>
<td>PPV</td>
<td>NPV</td>
<td>Se</td>
<td>Sp</td>
<td>PPV</td>
<td>NPV</td>
<td>Se</td>
<td>Sp</td>
<td>PPV</td>
<td>NPV</td>
</tr>
<tr>
<td>Milk (n = 46)</td>
<td>0.42</td>
<td>0.98</td>
<td>0.96</td>
<td>0.58</td>
<td>0.44</td>
<td>0.90</td>
<td>0.83</td>
<td>0.59</td>
<td>0.64</td>
<td>0.82</td>
<td>0.92</td>
<td>0.41</td>
</tr>
<tr>
<td>Egg (n = 39)</td>
<td>0.65</td>
<td>0.90</td>
<td>0.85</td>
<td>0.75</td>
<td>0.62</td>
<td>0.91</td>
<td>0.78</td>
<td>0.83</td>
<td>0.87</td>
<td>0.86</td>
<td>0.85</td>
<td>0.88</td>
</tr>
<tr>
<td>Soy (n = 28)</td>
<td>0.38</td>
<td>0.90</td>
<td>0.70</td>
<td>0.69</td>
<td>0.67</td>
<td>0.87</td>
<td>0.67</td>
<td>0.87</td>
<td>0.88</td>
<td>0.84</td>
<td>0.74</td>
<td>0.93</td>
</tr>
<tr>
<td>Wheat (n = 26)</td>
<td>0.19</td>
<td>0.97</td>
<td>0.78</td>
<td>0.65</td>
<td>0.72</td>
<td>0.86</td>
<td>0.74</td>
<td>0.84</td>
<td>0.81</td>
<td>0.87</td>
<td>0.77</td>
<td>0.90</td>
</tr>
<tr>
<td>Corn (n = 26)</td>
<td>0.14</td>
<td>0.95</td>
<td>0.57</td>
<td>0.71</td>
<td>0.89</td>
<td>0.78</td>
<td>0.66</td>
<td>0.94</td>
<td>0.87</td>
<td>0.77</td>
<td>0.63</td>
<td>0.93</td>
</tr>
<tr>
<td>Beef (n = 23)</td>
<td>0.30</td>
<td>0.97</td>
<td>0.82</td>
<td>0.75</td>
<td>0.65</td>
<td>0.98</td>
<td>0.94</td>
<td>0.87</td>
<td>0.82</td>
<td>0.94</td>
<td>0.85</td>
<td>0.93</td>
</tr>
<tr>
<td>Chicken (n = 15)</td>
<td>0.26</td>
<td>0.93</td>
<td>0.50</td>
<td>0.83</td>
<td>0.80</td>
<td>0.92</td>
<td>0.67</td>
<td>0.96</td>
<td>0.94</td>
<td>0.89</td>
<td>0.63</td>
<td>0.99</td>
</tr>
<tr>
<td>Rice (n = 14)</td>
<td>0.13</td>
<td>0.98</td>
<td>0.50</td>
<td>0.86</td>
<td>0.87</td>
<td>0.88</td>
<td>0.59</td>
<td>0.97</td>
<td>1.00</td>
<td>0.89</td>
<td>0.61</td>
<td>1.00</td>
</tr>
<tr>
<td>Potato (n = 11)</td>
<td>0.25</td>
<td>0.98</td>
<td>0.60</td>
<td>0.90</td>
<td>0.64</td>
<td>0.92</td>
<td>0.54</td>
<td>0.95</td>
<td>0.85</td>
<td>0.91</td>
<td>0.61</td>
<td>0.97</td>
</tr>
<tr>
<td>Peanut (n = 10)</td>
<td>0.78</td>
<td>0.98</td>
<td>0.78</td>
<td>0.98</td>
<td>0.60</td>
<td>0.99</td>
<td>0.75</td>
<td>0.98</td>
<td>1.00</td>
<td>0.95</td>
<td>0.71</td>
<td>1.00</td>
</tr>
<tr>
<td>Oat (n = 9)</td>
<td>0.10</td>
<td>0.98</td>
<td>0.33</td>
<td>0.90</td>
<td>0.90</td>
<td>0.87</td>
<td>0.47</td>
<td>0.99</td>
<td>1.00</td>
<td>0.89</td>
<td>0.50</td>
<td>1.00</td>
</tr>
<tr>
<td>Barley (n = 9)</td>
<td>0.27</td>
<td>0.95</td>
<td>0.43</td>
<td>0.91</td>
<td>0.90</td>
<td>0.99</td>
<td>0.90</td>
<td>0.99</td>
<td>1.00</td>
<td>0.95</td>
<td>0.73</td>
<td>1.00</td>
</tr>
<tr>
<td>Apple (n = ?)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.67</td>
<td>0.97</td>
<td>0.57</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; ALA α-lactalbumin; APT atopy patch test; BLG β-lactoglobulin; CMA cow’s milk; CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; FC food challenge; FEIA fluorescent enzyme immunoassay; HE hen’s egg; NPV negative predictive value; OFC open food challenge; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test
* number in parentheses is the number of subjects in 316 cohort in which the given food was diagnosed as the causative agent.
Diagnosis of Heiner's Syndrome (Pulmonary Hemosiderosis)

No studies addressing the diagnosis of Heiner's Syndrome met our inclusion criteria. One study that did not meet the exclusion criteria examined the utility of the LP assay (using peripheral monocytes) among 22 Japanese patients with non-IgE-mediated food allergies, including one patient with buckwheat flour-sensitive pulmonary hemosiderosis; 18 patients with IgE-mediated allergies; and 15 controls.\(^{206}\) Whereas LP for patients with IgE-mediated allergies did not differ from that of controls, response to suspect foods correlated with oral food challenge results among patients with non-IgE-mediated allergies.

Diagnostic Tools Used by Different Groups of Clinicians

Only a small number of studies have addressed the differences between allergists and non-allergists in the types of diagnostic tests used or the implications of any differences. Two studies conducted surveys of physician knowledge and practices. A third study addressed a tangential issue by comparing diagnoses made by allergists using DBPCFC with those of primary care physicians using sIgE tests. None of these studies satisfied the inclusion criteria for this review.

Krugman (2006) reported on the results of a survey mailed to a random sample of 1,130 US pediatricians (drawn from the membership roster of the American Academy of Pediatrics) that used clinical cases to assess knowledge of food-induced anaphylaxis diagnosis and management (treatment, counseling, and prevention) among primary care physicians. The response rate was approximately 40 percent (419/1,130). Of the respondents (most of whom were in private practice), 86 percent said they cared for children with food allergies; 66 percent said they felt comfortable managing food allergy patients. Some 69 percent reported having received CME credit in the prior 3 years for food allergy-related training. For a clear-cut case of food-induced anaphylaxis, 30 percent of responding pediatricians missed the diagnosis (suggesting it could be oral allergy syndrome), which resulted in their not administering epinephrine or prescribing self (parent)-injectible epinephrine. Pediatricians who managed children with food allergy had greater knowledge about food allergy management than those who did not; recent participation in CME was not a predictor of greater knowledge when the researchers controlled for caring for food allergy patients.\(^{207}\)

The AAAAI Adverse Reactions to Food Committee conducted a survey among 3,000 allergists and 4,000 non-allergists to assess differences in diagnosis and management between the two groups. This survey was prompted by reports of large discrepancies between patient/parental perceptions of allergy prevalence and the results of comprehensive diagnostic workups. The response rate was 19.5 percent for allergists and 1.9 percent for non-allergists, thus few statistical analyses were conducted. Non-allergists and allergists differed greatly in their use of the various allergy tests. No statistical differences were found between allergists and non-allergists in the use of medical history, food diaries, or elimination diets. However, allergists were significantly more likely than non-allergists to use percutaneous skin testing (SPT and APT), sIgE, and food challenge. Allergists were significantly less likely to report using intradermal tests, sIgG4, and sublingual tests than non-allergists (tests that have shown poor PPV compared with DBPCFC). Regarding food challenge, non-allergists were also more likely than allergists to regard open or
single-blinded food challenge as inadequate in infants and children under 6 years. The two groups also differed in their ranking of the most common food allergens. E.g., for infants and children under 20, non-allergists failed to consider soy as a common allergen; among adults, non-allergists considered wheat to be the third most common allergen, whereas wheat was not among the top five considered by allergists. Sucrose was viewed as a cause of food allergy by 35.1 percent of non-allergists vs. 5.2 percent of allergists. 208

Summary
A small number of studies have examined differences in the use of diagnostic tests between allergists and non-allergists. The findings of one survey suggest that PCPs who do not care for many patients with allergies lack knowledge about appropriate diagnostic criteria. Another survey suggests that allergists differ considerably from non-allergists in their choice of diagnostic tests as well as the foods they consider to be of greatest concern, with allergists relying more on DBPCFC, sIgE, and SPT/APT tests. Additional studies in more diverse metropolitan areas are clearly needed on differences in the types of allergy tests conducted among various health care settings and the value of commercial tests in the absence of confirmation by FC.

Discussion/Limitations
Although the DBPCFC is widely used as the gold standard for food allergy testing, the literature reveals same problems with the use of the DBPCFC as a gold standard (since some individuals who have a positive challenge are able to tolerate the food under different conditions, and vice versa). Related to this issue is the observation that in a number of studies that reported using DBPCFC as the gold standard, DBPCFC was not always administered to all participants, and instead, history was sometimes substituted (with no attempt to compare individual SPT or sIgE results with that of DBPCFC or history). (See below for additional discussion of concerns about DBPCFC)

A number of studies that employed SPT or sIgE failed to define the cutoff points for a positive test, and comparisons among studies often showed different cutoff points being used. Although several studies attempted to assess the effect of age or other factors on cutoff points (sensitivity and specificity of the test at various cutoff points), these findings were inconsistent.

Although a number of studies attempted to assess the incremental value of performing multiple tests, results were inconclusive.

The inclusion/exclusion criteria for study participation were not always clearly defined and differed among otherwise similar studies. For example, some studies included only patients with a history of atopic dermatitis or a personal or family history of other allergies.

Several studies assessed the effect of the form of test food used (e.g., raw vs. cooked; boiled vs. roasted) on the results of food challenges, SPTs, and APTs. Although these studies did not draw firm conclusions, the literature appears to support a difference in response to various forms of
particular foods. However, not all studies reported the form of the food used (or the amount), and those that did varied widely.

The Practice Parameter on allergy diagnosis states that actual wheal size (in response to SPT) and sIgE levels have been correlated with increasing likelihood of clinical reaction (but not with clinical manifestations of the allergy). Such a correlation is critical if the simple-to-perform SPT and sIgE are to be considered valid and reliable substitutes for food challenge tests. However, these points were not supported or refuted in any of the original studies reviewed. A 2002 review addressed the question of whether SPT wheal sizes or sIgE levels predict clinical reactivity (positive DBPCFC). Early tests with large sample sizes showed good correlation between sIgE levels and clinical reactivity as well as skin test results. False positives in young children were found to predict subsequent sensitization (i.e., sIgE appearance preceded symptoms). However, the 2009 Work Group Report on oral food challenge testing concludes that sIgE levels and wheal sizes do not predict severity of clinical reactions and that guidelines for deciding whether to perform or defer an oral food challenge based on SPT wheal diameter or sIgE levels are constantly evolving based on new evidence. Another 2009 review on this topic also asserted that determining whether and when to administer DBPCFC in adults is contentious and that the use of sIgE or SPT wheal size cutoffs to determine whether or not to administer DBPCFC is of dubious value, because the cutoffs that predict positive DBPCFC results differ by age, population, preparation of food used, and for SPT, the methods and reading times as well. Most cutoff levels have been determined in populations of children, making their value for adults even more questionable.

Finally, the diagnostic tests reviewed in this section are those for which we were able to identify studies that assessed their validity against a gold standard (usually the DBPCFC). We are aware that other tests have been used in or proposed for the diagnosis of food allergy, including tryptase assays, chymase assays, component resolution sIgE assays with purified antigens or specific epitopes, provocation-neutralization tests, applied kinesiology, hair analysis, and cytotoxic food testing; however, no literature was identified on the validation of any of these tests for food allergy.
Section IV. Management, Treatment and Prevention of Food Allergy

Overview

In the sections that follow we present the evidence on strategies for the prevention, treatment, and management of food allergies. The key questions are organized principally by intervention type (e.g., dietary avoidance, immunotherapy). We first present the results for the key questions, then present the evidence according to common foods evaluated (e.g., cow’s milk, peanut), and finally present the evidence for common clinical allergy syndromes (e.g., oral allergy syndrome, eosinophilic esophagitis).

For those key questions not well addressed by systematic reviews or RCTs, we found eleven observational studies: None included a comparison and eight had sample sizes over 100 (range of the sample sizes: 102-567). Two studies (Hoffmann et al and Narisety et al.) with fewer than 100 participants were included, given the paucity of studies and the concern for safety of immunotherapy. The study by Henriksen et al. reported nutrient intake among 34 children on cows’ milk restricted diets. The study quality of ten of these was poor. Only one study was considered to be of fair quality, given its large sample size (567 participants) and its complete reporting of dropouts.

Prevention

In general, the RCTs of food allergy prevention enrolled pregnant women with a history of allergic disease and/or their newborns, randomized them to receive special diets/formula or placebo (to be given with or without breast milk), and followed the children to compare the cumulative incidence of allergic disease in the intervention and placebo groups. We identified seven systematic reviews (Table 39) and 46 randomized controlled trials that evaluated methods to prevent food allergies (Table 40-Table 42). Twenty-one of the included RCTs were evaluated in one or more of these systematic reviews and were not analyzed further. Two studies, reporting information on identical populations were excluded because they did not report data comparing the intervention and control groups. We also excluded an RCT that evaluated the use of cetirizine for the prevention of food allergies and the publications by Chandra et al. given the published reports that seriously question the validity of his data.
Of the 19 RCTs of allergy prevention strategies that were included, 17 were performed in Europe (Figure 7) and randomized a total of 11,759 patients, (sample sizes ranged from 62 to 4753). Six studies evaluated strategies for the prevention of milk allergies either alone or in combination with other food allergies; 10 evaluated allergies to more than one food. The average follow up period was 3 years (range: 1-3 years).
The included RCTs evaluated five allergy prevention strategies: seven evaluated breastfeeding either alone or in combination with other interventions, six studied special diets for infants, two studied special diets for pregnant mothers, four evaluated probiotics, and one studied C-section delivery (Figure 8).

Quality information for each of the included prevention trials is presented in Appendix F.

**Management/Treatment**

We identified three systematic reviews (Table 43: Food allergy treatment systematic reviews and meta-analyses) and 28 randomized controlled trials (Table 44-Table 46) that evaluated methods to manage or treat food allergies. Five RCTs\(^{241-245}\) were included in one or more systematic reviews and were not analyzed further.
The 23 RCTs that were included were performed around the world, including five trials in the US (Figure 9). The RCTs of management and treatment were considerably smaller in total than the prevention trials: they included 1,371 participants (sample size ranged from 10 to 200 participants). The most commonly evaluated foods in the management/treatment RCTs were milk (11 RCTs), egg (7 RCTs), and nuts (6 RCTs)—most studies evaluated more than one type of food allergy. The duration of the management/treatment RCTs was far shorter than for the prevention trials: follow up ranged from 7 days to 3 years but 19 studies were six months or less.

The included RCTs evaluated four main types of treatment/management strategies: pharmacological management, allergen-specific immunotherapy, specific immunotherapy with cross-reactive allergies, and allergen avoidance (Figure 10).

Quality information for each of the included management/treatment trials is presented in Appendix F.

Key Question H. What methods are currently used to manage patients diagnosed with IgE-mediated food allergy?

i. Dietary avoidance (including cross-reacting allergens and issues of breast feeding and delay of solids) in the context of preventing food allergy.

i. a. What are the effects of early versus delayed introduction of certain foods into an infant’s diet?

Background

Several guidelines recommend delaying the introduction of solid foods to infants for four or six months after birth in an effort to prevent atopic disease. However, there is not a clear consensus regarding the risks and benefits of delaying introduction of solid foods in infants.
Results

We identified one systematic review on this topic. However, 12 of the 13 publications included in the review were observational studies, a study design that we excluded from our review on this key question. Therefore, we did not consider this systematic review any further. We identified two controlled trials that evaluated the effect of breastfeeding in combination with delayed introduction of solid foods in infants at high risk for all allergies (Table 40-Table 42). Halmerbauer et al. conducted an RCT on environmental procedures to reduce house dust-mites as well as an educational intervention to delay introduction of solid foods. They found a significantly reduced risk of parent-reported food intolerance (vomiting, prolonged crying, diarrhea, and swollen lips after eating) in the intervention group. However, the study findings should be interpreted with caution because the study was only of fair quality and the intervention included both breastfeeding and education regarding the delayed introduction of foods; therefore it is difficult to evaluate the independent effects of individual components of the intervention.

Kajosaari and colleagues reported results from a comparative study that evaluated the effect of exclusive breastfeeding and delayed introduction of solid foods until six months. They conducted an extended analysis and found a possible protective effect of prolonged breastfeeding; they reported a higher incidence of atopy in the control group that did not reach conventional levels of statistical significance (p=0.15), but no differences in rates of asthma, atopic eczema, or fresh fruit allergy. This study was rated as poor quality because it was not randomized, and no information was provided on the comparability of the two groups.

Summary

The quality of evidence for this key question is low given that only two controlled trials of relatively low quality address this question. While both of the included studies found some association between delayed solids and decreased incidence of atopic symptoms, their findings should be interpreted with caution given the multimodal nature of one study and the poor quality of the other. In summary, we found insufficient evidence to support the association between delayed introduction of solid foods in infants and the incidence of atopic disease.

i. b. What is the effect of maternal diets during pregnancy and lactation on the development of, and clinical course of, food allergy?

Background

Several authors have observed that maternal dietary antigens can pass into breast milk and have hypothesized a protective effect of a diet in which certain allergens are reduced or avoided during pregnancy and lactation by women at high risk of having infants who will go on to develop atopic disease.

Results

One systematic review and one non-randomized comparative study evaluated the effect of maternal diet during pregnancy and lactation on the development of food allergy. Kramer et al. conducted a systematic review (search conducted as of March 2006) that evaluated the effect of maternal dietary avoidance on either treating or preventing atopic disease in children (Table
The literature search and screening process was comprehensive and followed the methods used by the Cochrane Collaboration. Articles were selected if they were controlled trials comparing dietary avoidance or reduction of potential allergens to usual diet by pregnant women at high risk of delivering infants with atopic disease; articles where both the mothers and infants’ diets (other than breast milk) were manipulated were excluded. The review scored highly on the AMSTAR criteria for evaluating systematic reviews. Their analysis pooled data from two trials with a total of 334 pregnant women; however, they acknowledged that the two trials were of unequal methodologic quality. The authors found no significant difference in the incidence of atopic eczema (relative risk 1.01; 95% confidence interval CI 0.57-1.79), asthma (RR 2.22; 95% CI 0.39-12.67), positive skin prick tests to egg (RR 0.95; 95% CI 0.52-1.74) or milk (RR 0.86; 95% CI 0.16-4.59) during the first 18 months of life in infants whose mothers avoided dietary antigens during pregnancy. There was insufficient evidence to determine the effect on urticaria, allergic rhinitis, conjunctivitis, or both since these outcomes were reported by only one trial. One included trial evaluated the avoidance of dietary antigens during lactation on the incidence of atopic eczema and found no significant difference in the incidence of atopic eczema between the two groups (RR 0.73; 95% CI 0.32-1.64). Overall, the review concluded that a maternal allergen avoidance diet was “unlikely to reduce substantially” the risk of having a child with atopic disease but that such a diet may have “adverse effects on maternal or fetal nutritional status;” however, more data on these adverse effects were needed.

Two publications reporting on one non-randomized comparative study, evaluated the effect of restricting maternal diet during lactation for the first three months after birth, on the incidence of food allergies (Table 40-Table 42). Hattevig et al. reported study results at 18 months and Sigurs et al. reported results at four years of age. The authors found significantly reduced cumulative incidence and prevalence of atopic dermatitis at four years in children in the intervention group compared to the control group. The authors also observed this reduced incidence at three and six months of age, but not at nine, 12, and 18 months. They found no significant differences in the cumulative incidence and prevalence of respiratory allergic diseases, in adverse reactions to egg or cow’s milk, or in positive skin prick tests or positive serum specific IgE tests at any ages. This study was rated as poor quality; however, the authors report that the two groups were comparable and matched through recruitment.

Summary

We found conflicting evidence on maternal diet during pregnancy and/or lactation and its effect on atopic disease among children at high risk for atopic disease. While the systematic review reported no evidence to support a protective effect of maternal diet, the comparative study found significantly reduced incidence of atopic dermatitis in children whose mothers had a restricted diet during lactation; however, this study was of poor quality. Given these findings, we conclude that there is insufficient evidence to determine the effect of restricting maternal diet in reducing the risk of atopic disease in infants.

i. c. What is the effect of breastfeeding infants on the development of, and clinical course of, food allergy?
Background

The protective role of breastfeeding in preventing atopic disease has been uncertain, with some studies reporting favorable outcomes associated with breastfeeding and others reporting no effects. The effectiveness of combining exclusive breastfeeding with other interventions to prevent atopic disease is also unclear.

Results

We found seven studies that evaluated the effect of breastfeeding in combination with either restricted maternal or infant diet, use of hydrolyzed formulas, or delayed introduction of solid foods (Table 40-Table 42). These studies are reviewed in the relevant key questions for those topics. One study was an RCT from Spain that only reported SPT and sIgE sensitization outcomes for children but not the development of food allergies and therefore was excluded. In addition, we identified three analyses of data from the same study population that randomized participants to either exclusive breastfeeding or partial or complete cow milk formula and compared their incidence of atopic dermatitis (Table 40-Table 42). Schoetzau et al. reported results on a sub-group of infants who were part of the German Nutritional Intervention Study (GINI) cohort study and found a significantly lower risk of atopic dermatitis at one year of age in infants who were exclusively breastfed compared to infants who were not (9.5 percent versus 14.8 percent, respectively, p=0.015). Their logistic regression model found that the risk of atopic dermatitis was reduced by nearly 50 percent in the exclusively breastfed group, after adjusting for atopic risk factors and other confounders such as parent education, gender, pet keeping, and maternal smoking (adjusted OR 0.47, 95% CI 0.3-0.74). They also conducted analyses to determine the effect of delayed introduction of solid foods between the two groups but did not find a significant effect modification of either age at first introduction (Wald-Chi square p=0.58) or diversity of foods (p=0.89). The analysis conducted in this paper differed from that by Filippiak et al. using the infant population from the GINI study. Schoetzau et al. compared differences based on exclusive breastfeeding or not in only intervention group infants of the GINI study whereas the Filippiak study compared breastfeeding, use of hydrolysed formulas, and delayed introduction of solid foods in intervention group infants to a separate control group of infants whose mothers did not receive these recommendations. They concluded that there was no evidence to support a protective effect of delayed introduction of solids for eczema.

Laubereau, et al also reported on the GINI-birth cohort study and found exclusive breastfeeding was not associated with higher risk for atopic dermatitis either in the entire cohort (OR, 0.95; 95% CI, 0.79-1.14) or if stratified by family history of atopic dermatitis. In the intervention subgroup, but not in the non-intervention subgroup, exclusive breast-feeding showed a significant protective effect on atopic dermatitis if compared with conventional cow’s milk formula (OR, 0.64; 95% CI, 0.45-0.90).

Summary

The quality of evidence for this key question is low given that we found only one fair quality non-randomized comparative study addressing this question and conflicting evidence from that study.
i. d. What are the effects of special diets in infants and young children (e.g., formula, hydrolyzed formula) on the development of, and clinical course of, food allergy?

Background

Food allergies in infants and children may be associated with cow milk proteins, and various hydrolyzed or soy-based formulas have been used to treat infants with food intolerance or allergies. However, it is unclear if these formulas can be used to prevent food allergies in infants without established food allergies.

Results

We identified two systematic reviews that evaluated the effects of hydrolyzed infant formulas267,268 and one of soy formula269 on the development of food allergies in children (Table 39). The literature search and screening process was comprehensive for all three reviews and followed the methods used by the Cochrane Collaboration for two reviews. Articles were selected if they were controlled trials comparing dietary avoidance or reduction of potential allergens to usual diet by pregnant women at high risk of delivering infants with atopic disease; articles where both the mothers and infants’ diets (other than breast milk) were manipulated were excluded. Two reviews scored highly on the AMSTAR criteria for evaluating systematic reviews (9 criteria met); the third scored lower (5 criteria met).267

Soy Formulas vs Hydrolyzed Formulas vs Cow’s Milk

Osborn and Sinn269 conducted a review to determine the effect of feeding infants adapted soy formula compared to human milk, hydrolysed protein formulas, or cow milk formula. Their search (conducted as of March 2006) resulted in the inclusion of three studies that compared soy formula to cow milk formula. They reported no significant differences in incidence of childhood allergies, infant or childhood asthma, infant or childhood eczema, or infant or childhood rhinitis. The authors concluded that there was no evidence to suggest that the use of soy formula instead of cow milk formula prevented allergies in infants at high risk for food allergies, either in later infancy or childhood.

Hydrolyzed Formulas vs Cow’s Milk Formula or Breastfeeding

Osborn and Sinn also conducted a Cochrane review comparing the effect of hydrolyzed formulas to cow milk formula or human milk in preventing food allergy.268 We note that several studies on hydrolyzed formulas failed to specify the exact type/composition/brand name of the formulas provided. Also, the terms “partially” and “extensively” hydrolyzed are not well defined in this literature. They included four trials comparing short term hydrolyzed formula feeding to human milk or cow’s milk formula and found no significant differences in infant or childhood cow’s milk allergy between the groups. When assessing prolonged feeding with hydrolyzed formula compared to cow milk formula in infants at high risk, their meta-analysis of seven studies found a significant decrease in infant allergies (RR 0.79 95% CI 0.66-0.94), but no difference in the incidence of childhood allergy (two studies, RR: 0.85, 95% CI 0.68-1.04); they also found no significant differences in infant or childhood eczema or infant or childhood asthma, rhinitis and food allergy. Their subgroup analysis restricted to studies using partially hydrolyzed formulas had similar findings. There was no significant difference in outcomes when comparing
extensively hydrolyzed formulas with cow milk formula; however, when compared with partially hydrolyzed formulas, infants fed extensively hydrolyzed formulas had a significant decrease in food allergy overall (two studies, RR 0.43; 95% CI 0.19-0.99), but not in any specific food allergy. Their meta-analysis of three studies comparing extensively hydrolyzed casein formula with cow milk formula found a significant decrease in incidence of infant eczema (RR 0.71; 95% CI 0.51-0.97). The authors concluded in their review that there was limited evidence that prolonged feeding with hydrolyzed formulas in high risk infants reduced infant and childhood allergy and infant cow’s milk allergy when compared with cow milk formula; however, they reported concerns about the methodology of the included studies as well as inconsistencies in the findings.

In their review, Hays and Wood\textsuperscript{267} included controlled trials to assess the effect of hydrolyzed formulas in preventing allergies when compared with breastfeeding, cow’s milk formula, or soy formula and the difference between extensively (eHF) and partially (pHF) hydrolyzed formulas. The authors included nine trials on eHFs (all were casein hydrolysate formulas) and 11 studies on pHFs (10 whey formulas and one casein formula). Due to the heterogeneity of trial methods, the authors did not pool the data but presented a narrative synthesis and a table with each included trial. They concluded that for both eHFs and pHFs, “the data support a protective effect…but the research falls short of meeting the American Academy of Pediatrics criteria for evidence of allergy prevention.”

A related trial is the GINI study,\textsuperscript{270, 271} which randomized 2,252 infants less than 2 weeks old who had at least one parent or sibling with a history of allergic disease, and without any history of formula supplementation to receive one of three hydrolyzed formulas or to cow’s milk formula. Children were followed to six years. Children fed with partially hydrolyzed whey formula (pHF-W) and extensively hydrolyzed casein formula (eHF-C) were less likely to have “any allergy diagnosis from a physician” compared with children fed cow’s milk formula (47.1 percent, 46.1 percent, vs 56 percent respectively). However, there was no difference between extensively hydrolyzed whey formula (eHF-W) and cow’s milk formula.

An RCT by Odelram et al.\textsuperscript{272} examined whey hydrolysate and cow milk formula compared to strict breastfeeding in the prevention of atopic disease of infants. Inclusion criteria were at least two atopic family members or one atopic parent and total cord blood IgE >0.5 kU/I. Exclusion criteria were gestational age below 37 weeks, complicated delivery, neonatal illness, severe birth defects, and documented or expected noncompliance with diet prescription. Presence of atopic disease was 10/25 in the infants fed extensively hydrolyzed formula, 15/32 in the infants fed cow milk formula, and 3/13 in those who were breastfed. No statistical difference in the presence of atopic disease was found. There was no statistically significant difference in positive SPT or in serum IgE at 18 months.

Von Berg et al.\textsuperscript{270, 271} evaluated the long-term allergy-preventive effect of three hydrolyzed infant formulas compared with cow’s milk formula. Between 1995 and 1998, 2,252 newborns with atopic heredity were randomly assigned at birth to receive one of four blinded formulas: partially or extensively hydrolyzed whey formula, extensively hydrolyzed casein formula, or cow’s milk formula as milk substitute for the first four months when breast feeding was insufficient. At three years of follow-up, there was no statistically significant effect on the incidence of asthma.
In an intention to treat analysis of 2,252 children at six years of follow-up, it was found that only the extensively-hydrolyzed whey formula was associated with an increased RR of asthma of 2.16 (CI 1.02-4.58). This was not found in the per protocol analysis.

A trial by Arslanoglu et al. randomized 259 infants with a family history of atopy to receive either a hypoallergenic formula supplemented with a mixture of 90 percent short-chain galactooligosaccharides and 10 percent long-chain fructooligosaccharides (IMMUNOFORTIS) intended to mimic human milk oligosaccharides or to the same formula without this supplementation (Table 40-Table 42). The cumulative incidences of atopic dermatitis, recurrent wheezing, and allergic urticaria were lower in the treatment group than the control group (13.6 vs 27.9 percent, 7.6 vs 20.6 percent, 1.5 vs 10.3 percent respectively, p<0.05).

Szajewska et al. studied the prevention of allergic disease in preterm infants by comparing extensively and partially hydrolyzed preterm formulas with standard preterm formula. This study did not show any difference in the incidence of allergic diseases in preterm infants.

Han et al. studied the effects of partially hydrolyzed formula on development of atopic dermatitis in infants at high risk. The infants of parents with allergy symptoms and serum total IgE over 200 kU/L were divided into three groups: partially hydrolyzed formula, standard formula, and breast milk. In addition, the infants received no allergenic food for 6 months, and breastfeeding mothers avoided egg ingestion. The cumulative incidence and prevalence of atopic dermatitis at the age of 6 months were significantly less in the partially hydrolyzed formula group than in the SF group (47% vs. 78%, p<0.05; 20% vs. 59%, p<0.05). There was no statistically significant difference in comparison with the breastfed group.

**Summary**

The quality of evidence for the key question on special diets in infants and young children is moderate to high. The quality of evidence on use of soy formulas is moderate given that this was addressed by a high quality review that included only three small RCTs; the evidence suggests that there is little difference between soy formula and cow's milk formula for the prevention of allergies in high risk infants. The quality of evidence on use of hydrolyzed formulas is high given that two systematic reviews and four other RCTs address this question; there is some evidence that hydrolyzed formulas (particularly extensively and partially hydrolyzed formulas) may reduce infant and childhood allergy, asthma, and cow's milk allergy syndrome in high risk infants when compared with cow milk formula.

**i.e. What are the recommendations by professional organizations regarding the avoidance of food and non-food allergens by people with food allergy?**

Table 38 presents the recommendations found in our search of the websites of professional organizations.
<table>
<thead>
<tr>
<th>Food Allergy Expert Panel</th>
<th>Guidance Organizations</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
- Children with life-threatening food allergies should always have two doses of auto-injectable epinephrine available to treat anaphylaxis – especially if they also have asthma. Advice based on a in the Journal of Allergy and Clinical Immunology. [http://www.aanma.org/2009/05/keep-two-doses-of-epi/](http://www.aanma.org/2009/05/keep-two-doses-of-epi/)
| American Academy of Pediatrics | [http://www.aap.org/](http://www.aap.org/) | - FAQ directed at parents gives information on distinguishing food allergy from food intolerance and other conditions that can be confused with food allergy. [http://www.aap.org/publiced/BR_FoodAllergy.htm](http://www.aap.org/publiced/BR_FoodAllergy.htm)
- AAP also produces (for sale) books and pamphlets to educate parents.
- Guidelines for the administration of medication in school. American Academy of Pediatrics – Medical Specialty Society. 2003 Sep. (These cover all kinds of medications, such as insulin, and are not specific to allergy meds.) |
| American Academy of Allergy Asthma and Immunology | [http://www.aaaai.org/](http://www.aaaai.org/) | A brochure for parents, updated in 2009, includes these specific guidelines:
- Try to wait until babies are 6 months old before you give them solid foods.
- Wait until they are 1 year old before giving them milk and other dairy (like cheese and yogurt).
- Toddlers should not eat eggs until they are 2 years old.
- Children should not eat peanuts, nuts or fish until they are 3 years old.
- Talk to your doctor about a plan for introducing these foods. [http://www.aaaai.org/patients/resources/easy_reader/food.pdf](http://www.aaaai.org/patients/resources/easy_reader/food.pdf) |
| Other Web sites/Advice of Note | | - Allergic Child.com recommends parents “err on the side of caution” and use EpiPens, even if the source of a reaction has not been determined. [http://www.allergicchild.com/epipen_ana_medicalert.htm](http://www.allergicchild.com/epipen_ana_medicalert.htm)
- Food Allergy.org has a Food Allergy Action for teachers of allergic children.
- There is still no federal regulation requiring all public schools to allow students to carry their own auto-injectables (as opposed to leaving them with school nurses). This is a great concern to parents of children in “zero tolerance” school districts. The Action Plan is downloadable at: [http://www.foodallergy.org/downloads/FAAP.pdf](http://www.foodallergy.org/downloads/FAAP.pdf)
- “Common Beliefs About Peanut Allergy: Fact or Fiction?” written for FAAN by Michael C. Young, M.D., Assistant Clinical Professor of Pediatrics, Harvard Medical School for FAAN. Young’s article underscores the need to distinguish between anaphylactic shock caused by contact and shock caused by conditioned fear. [http://www.allergysafecommunities.ca/assets/common_beliefs_faan_2003.pdf](http://www.allergysafecommunities.ca/assets/common_beliefs_faan_2003.pdf) |
Additional Information Relevant to Key Question H.i.: Systematic review of the association of caesarean delivery and allergic diseases.

Background
Some authors have raised a suspicion of an association between the mode of delivery (vaginal vs. cesarean/c-section) and allergic diseases on the basis that babies born by c-section have different gut flora than babies born by vaginal delivery. Specifically, it has been hypothesized that this difference in gut flora may lead to prolonged immunologic immaturity in babies born by c-section that may increase the risk of allergic disease later in life.

Results
We identified two systematic reviews275, 276 and a prospective controlled trial of 609 patients277 that evaluated the risk of allergic diseases after c-section (Table 39 and Table 40). All studies in the review by Koplin et al.276 were listed in the review by Bager et al.275 The Bager et al review275 included six articles that specifically evaluated the association of food allergies/atopy and c-section, three of which found no statistically significant association and three of which found a significant association; although all six studies had a positive odds ratios.278-283 Overall, the review found an increased incidence of food allergies/food atopy among children delivered by c-section compared with those delivered vaginally, with a random effects odd ratio of 1.45 (95% CI 1.12-1.86, heterogeneity statistics: Q=8.99, p 0.11). However, the authors note that this result may be subject to significant publication bias. Additionally, the metrics of food allergy varied among the six included studies (e.g., IgE to food allergen, parent report of food allergy), and the ages of the children varied from 0 to 17 years. Kvenshagen et al.277 enrolled 609 children at birth and followed them for two years. Food allergy was diagnosed in 36.2% (62/171) of children delivered by c-section and in 39.8% (136/341) of children delivered vaginally. There was no statistical difference in food allergies between the two modes of delivery.

Summary
There may be an association between c-section and the development of allergic disease later in life; however, the total body of evidence on this issue is mixed and has significant methodologic concerns, necessitating further investigation; the grade of evidence for this conclusion is therefore low.

Additional Information Relevant to Key Question H.i.: Studies on the use of probiotics for the prevention of food allergies.

Background
Probiotics are live microbial food ingredients. Some authors suggest that probiotic bacteria, like other gut microflora, may affect neonatal mucosal barrier function and the digestion of protein antigens and oligosaccharides present in breast milk and formula and in doing so, prevent the development of food allergies later in life.
Results

Five high quality RCTs of similar design\textsuperscript{284-288} reported the use of probiotics prenatally and in the neonatal period for the prevention of food allergies in children considered high risk for developing them (Table 40-Table 42). Four of these studies were done in Finland and one in Sweden.

Two studies\textsuperscript{284, 285} performed by the same investigators at the University of Turku, Finland evaluated the role of probiotics in combination with breastfeeding as a means of preventing atopy in children. In their 2002 publication,\textsuperscript{285} the Turku group evaluated whether the probiotic \textit{Lactobacillus rhamnosus} given to 64 pregnant women starting four weeks before delivery and continued with breastfeeding for three months postpartum decreased the risk of atopy among their children at two years. They found that only four of the 27 children of the women who received probiotics developed chronic relapsing atopic eczema compared with 14 of the 30 whose mothers received placebo (RR 0.32, 95% CI 0.12-0.85, \textit{p}=0.0098).\textsuperscript{285} In their 2008 publication,\textsuperscript{284} the Turku group randomized 72 pregnant women to receive the probiotics \textit{L. rhamnosus} and \textit{Bifidobacterum lactis} and 68 women to receive placebo from the first trimester of pregnancy to the end of exclusive breastfeeding. There was no difference in positive reactions to SPT at one year between the children of women who received probiotics (29 percent) and those who did not (31 percent; OR: 0.92, 95% CI 0.45-1.90, \textit{p}=0.825).

Two studies\textsuperscript{286, 287} were performed by the same investigators in Helsinki and Tampere, Finland. In a similar design to the work by the Turku group, these investigators recruited pregnant women who were randomized to receive four probiotics twice daily beginning two to four weeks prenatally (\textit{L. rhamnosus GG, L. rhamnosus LC705, B. breve,} and \textit{Proprionibacterium freudenreichii}). Newborns in the treatment arm continued these probiotics for six months. At age five years, there were no significant differences in the primary end points of allergic and IgE-associated allergic disease or frequencies of eczema, asthma, allergic rhinitis, or atopic sensitization in the probiotic and placebo arms. In post-hoc secondary analyses, the authors reported a significant decrease in IgE-associated allergic diseases, particularly eczema, and less IgE sensitization in the probiotics group of children born by c-section delivery than among the placebo group. However, there were no such differences between treatment groups among children born by vaginal delivery.\textsuperscript{286}

Abrahamsson et al.\textsuperscript{288} provided the probiotic \textit{L. reuteri} to pregnant women in Sweden starting four weeks prenatally and continued by the infants for 12 months (mothers were encouraged to breast feed, and at weaning, infants were offered a hypoallergenic formula). At 24 months, the cumulative incidence of eczema was not different between the treatment (36 percent) and placebo groups (34 percent), and there was also no difference in the cumulative incidence of wheeze. However, IgE-mediated eczema was lower in the probiotics group (8 percent versus 20 percent; \textit{p}=0.02) as was the circulating IgE to egg white—although not to other food allergens.

Summary

The quality of evidence for this key question is moderate. There are five high-quality RCTs that address this question but there is some heterogeneity in the results. The use of probiotics in the prenatal and early neonatal period may be associated with mild reductions in the cumulative incidence of allergic skin disease in children. However, these results are interpreted with caution.
since the trials with the most significant results used probiotics in conjunction with breastfeeding and/or hypoallergenic formula. Therefore, the independent effects of probiotics cannot be established in these trials.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Question</th>
<th>Databases searched/ Years</th>
<th>Intervention</th>
<th>Inclusion/Exclusion</th>
<th>Total Publications Included</th>
<th>Outcomes reported</th>
<th>AMSTAR Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer, 2009&lt;sup&gt;253&lt;/sup&gt;</td>
<td>To evaluate the effect of an antigen avoidance diet during pregnancy and/or lactation on the prevention of atopic disease in children</td>
<td>Cochrane Pregnancy and Childbirth Group Trial register; Up to March 2006</td>
<td>Mothers prescribed a diet to either exclude or reduce potentially allergenic foods: cow milk, egg, peanuts, fish, chocolate during pregnancy or lactation</td>
<td>RCTs or quasi-RCTs comparing diets of different levels of antigen avoidance</td>
<td>4</td>
<td>Occurrence/severity of atopic disease in child; nutritional status of mother and fetus; other pregnancy outcomes; cord blood IgE levels</td>
<td>01. Can’t Answer 02. Yes 03. Yes 04. Yes 05. Yes 06. Yes 07. Yes 08. Yes 09. Yes 10. No 11. Yes</td>
</tr>
<tr>
<td>Osborn, 2009&lt;sup&gt;269&lt;/sup&gt;</td>
<td>To assess the effect of soy formula compared to cow milk formula, hydrolyzed protein formula or human milk in preventing food allergy in infants who do not have clinical evidence of food allergy</td>
<td>Medline (1966-March 2006); EMBASE (1980-March 2006); CINAHL (1982-March 2006); Cochrane Central (up to March 2006)</td>
<td>Use of an adapted soy formula</td>
<td>RCTs or quasi-RCTs with &gt; 80% follow up; cross-over trials excluded</td>
<td>3</td>
<td>All allergies; asthma; atopic dermatitis; allergic rhinitis; food allergy; food intolerance</td>
<td>01. Can’t Answer 02. Yes 03. Yes 04. Yes 05. Yes 06. Yes 07. Yes 08. Yes 09. Yes 10. No 11. Yes</td>
</tr>
<tr>
<td>Osborn, 2009&lt;sup&gt;268&lt;/sup&gt;</td>
<td>To assess the effect of hydrolyzed protein formulas compared to human milk or adapted cow milk in preventing food allergies in infants who do not have clinical evidence of food allergies</td>
<td>Medline (1966-March 2006); EMBASE (1980-March 2006); CINAHL (1982-March 2006); Cochrane Central (up to March 2006)</td>
<td>Use of any hydrolyzed infant formulas</td>
<td>RCTs or quasi-RCTs with &gt; 80% follow up</td>
<td>4</td>
<td>All allergies; asthma; atopic dermatitis; allergic rhinitis; food allergy; food intolerance; infant growth parameters; cost; infant feed refusal</td>
<td>01. Can’t Answer 02. Yes 03. Yes 04. Yes 05. Yes 06. Yes 07. Yes 08. Yes 09. Yes 10. No 11. Yes</td>
</tr>
<tr>
<td>Study</td>
<td>Study Question</td>
<td>Databases searched/ Years</td>
<td>Intervention</td>
<td>Inclusion Exclusion</td>
<td>Total Publications Included</td>
<td>Outcomes reported</td>
<td>AMSTAR Criteria</td>
</tr>
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<tr>
<td>Hays, 2005²⁶⁷</td>
<td>To assess the effect of hydrolyzed infant formulas in preventing food allergies</td>
<td>Medline (1985-2005)</td>
<td>Infants received extensively hydrolyzed or partially hydrolyzed formulas</td>
<td>Prospective controlled trials</td>
<td></td>
<td>Atopic dermatitis; urticaria; asthma; angioedema; GI disease; allergic rhinitis; cow’s milk allergy; conjunctivitis</td>
<td></td>
</tr>
<tr>
<td>Bager, 2008²⁷⁵</td>
<td>To evaluate whether caesarean delivery is associated with an increased risk of atopy and allergy disease</td>
<td>MEDLINE (1966-2007)</td>
<td>Caesarean delivery (c-section)</td>
<td>Studies of c-section that presented information on at least one of 6 allergic conditions including food allergy/food atopy.</td>
<td>26 total but only 6 reported on food allergy/food atopy</td>
<td>Food allergy/atopy, inhalant atopy, eczema/atopic dermatitis, allergic rhinitis, asthma, hospitalization for asthma.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 39: Food allergy prevention systematic reviews and meta-analyses (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Question</th>
<th>Databases searched/ Years</th>
<th>Intervention</th>
<th>Inclusion Exclusion</th>
<th>Total Publications Included</th>
<th>Outcomes reported</th>
<th>AMSTAR Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koplin, 2008&lt;sup&gt;276&lt;/sup&gt;</td>
<td>To determine whether there is sufficient evidence to support an association between delivery by cesarean section and the development of food allergens and IgE mediated food allergy</td>
<td>MEDLINE and PubMed (prior to July 1997)</td>
<td>Caesarean delivery (c-section)</td>
<td>Studies with mode of delivery and either IgE-mediated sensitization to food allergies or confirmed food allergy</td>
<td>4</td>
<td>Number positive for food allergy</td>
<td>01. Can’t Answer 02. Can’t Answer 03. No 04. No 05. Yes 06. Yes 07. No 08. No 09. Yes 10. No 11. Yes</td>
</tr>
<tr>
<td>Maas, 2009&lt;sup&gt;289&lt;/sup&gt;</td>
<td>To compare the effectiveness of mono- and multifaceted allergen reduction interventions in the primary prevention of asthma and asthma symptoms in children judged to be at high risk of developing asthma</td>
<td>Cochrane Airways Trials Register up to December 2008</td>
<td>Reduced exposure to allergens, either multi (inhalants and food) or mono (inhalants or food)</td>
<td>RCTs of allergen exposure for the primary prevention of asthma in children with follow up from birth or pregnancy to a minimum of 2 years</td>
<td>4</td>
<td>Physician diagnosed asthma in children &lt;5 years and asthma as defined by respiratory symptoms and lung function in children &gt; 5 years</td>
<td>01. Can’t Answer 02. Yes 03. Yes 04. Yes 05. Yes 06. Yes 07. Yes 08. Yes 09. Yes 10. No 11. Yes</td>
</tr>
</tbody>
</table>

**Table Notes:** RCTs randomized controlled trials; GI gastrointestinal; sIgE antigen-specific immunoglobulin

**AMSTAR criteria:** 01. Was an a priori study design provided? 02. Was there duplicate study selection and data extraction? 03. Was a comprehensive literature search performed? 04. Was the status of publication (gray literature) used as an inclusion criterion? 05. Was a listed of studies (included/excluded) provided? 06. Were the characteristics of the included studies provided? 07. Was the scientific quality of the included studies assessed and documented? 08. Was the scientific quality of the included studies used appropriately in formulating conclusions? 09. Were the methods used to combine the findings of studies appropriate? 10. Was the likelihood of publication bias assessed? 11. Was the conflict of interest stated?
### Table 40: Food allergy prevention controlled trials: study information

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Purpose</th>
<th>Food</th>
<th>Condition of interest</th>
<th>Study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breastfeeding and delayed introduction of solid foods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halmerbauer, 2002&lt;sup&gt;251&lt;/sup&gt;</td>
<td>Austria; Germany; UK</td>
<td>To determine if reduction in house-dust mites and prolonged breastfeeding and delayed introduction of solids reduce rates of sensitization and atopic diseases.</td>
<td>Milk, Egg</td>
<td>Food intolerance</td>
<td>Fair</td>
</tr>
<tr>
<td>Kajosaari, 1994&lt;sup&gt;252&lt;/sup&gt;</td>
<td>Finland</td>
<td>To determine the benefit of exclusive breastfeeding and delayed introduction of solid foods in children at risk for atopy</td>
<td>NS</td>
<td>Atopic eczema; asthma; food allergy</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>Maternal diets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hattevig, 1989&lt;sup&gt;254&lt;/sup&gt; and Sigurs, 1992&lt;sup&gt;255&lt;/sup&gt;</td>
<td>Sweden</td>
<td>To determine effect of maternal avoidance of eggs, cow's milk, and fish during lactation and delayed introduction of solids to infants on allergies in children</td>
<td>Multiple</td>
<td>Eczema, asthma, bronchial obstruction, rhinoconjunctivitis</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>Breastfeeding (with other interventions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filipiak, 2007&lt;sup&gt;260&lt;/sup&gt;</td>
<td>Germany</td>
<td>To assess association between solid food introduction and eczema occurrence</td>
<td>Multiple</td>
<td>Eczema</td>
<td>Poor</td>
</tr>
<tr>
<td>Bardare, 1993&lt;sup&gt;261&lt;/sup&gt;</td>
<td>Italy</td>
<td>To evaluate the effect of breastfeeding vs soy formula vs soy with dietary restrictions on the incidence of atopic disease in infants at risk of allergy</td>
<td>Multiple</td>
<td>Atopic eczema; allergic asthma; allergic rhinitis</td>
<td>Poor</td>
</tr>
<tr>
<td>Arshad, 2007&lt;sup&gt;262&lt;/sup&gt;</td>
<td>UK</td>
<td>To determine effect of breastfeeding (with mothers placed on a low allergen diet) or hydrolyzed formula and house dust mite exposure prevention on the development of atopic dermatitis, asthma, and atopy</td>
<td>Multiple</td>
<td>Asthma, AD, food allergy</td>
<td>Fair</td>
</tr>
<tr>
<td>Schoetzau, 2009&lt;sup&gt;265&lt;/sup&gt;</td>
<td>Germany</td>
<td>To evaluate the effect of exclusive breast-feeding and early solid food avoidance on atopic dermatitis</td>
<td>Multiple</td>
<td>Atopic dermatitis</td>
<td>Fair</td>
</tr>
<tr>
<td>Laubereau, 2004&lt;sup&gt;266&lt;/sup&gt;</td>
<td>Germany</td>
<td>To investigate if exclusive breast-feeding for 4 months is associated with atopic dermatitis during the first 3 years of life.</td>
<td>Multiple</td>
<td>Atopic dermatitis</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Special diets for infants and young children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Von Berg, 2008, 2007&lt;sup&gt;270&lt;/sup&gt;</td>
<td>Germany</td>
<td>To assess the effect of hydrolyzed formulas in preventing allergy development (GINI trial)</td>
<td>Milk</td>
<td>Multiple</td>
<td>Good</td>
</tr>
<tr>
<td>Odelram, 1996&lt;sup&gt;272&lt;/sup&gt;</td>
<td>Denmark</td>
<td>To examine whey hydrolysate compared with cow milk based formula on atopic disease</td>
<td>Milk</td>
<td>Atopic diseases (including urticaria, atopic dermatitis, and cow’s milk allergy)</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Table 40: Food allergy prevention controlled trials: study information (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Objective</th>
<th>Major Allergen</th>
<th>Other Allergens</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szajewska, 2004</td>
<td>Poland</td>
<td>To evaluate extensively and partially hydrolysed preterm formulas in the prevention of allergic disease in preterm infants</td>
<td>Milk</td>
<td>Atopic diseases (atopic dermatitis, gastrointestinal symptoms, wheezing, and cow’s milk allergy)</td>
<td>Good</td>
</tr>
<tr>
<td>Han, 2003</td>
<td>Korea</td>
<td>To assess the effects of partially hydrolyzed formula on the prevention of atopic dermatitis in high risk infants</td>
<td>Milk</td>
<td>Atopic dermatitis</td>
<td>Poor</td>
</tr>
<tr>
<td>Arslanoglu, 2008</td>
<td>Multiple European countries</td>
<td>To determine the effect of prebiotic oligosaccharides in formula-fed infants on the incidence of allergies and infections</td>
<td>Milk</td>
<td>Allergies, infections</td>
<td>Good</td>
</tr>
<tr>
<td>Rautava, 2002</td>
<td>Finland</td>
<td>To determine the effect of probiotic supplementation in pregnant and lactating women on reducing the risk of allergies in their infants</td>
<td>Milk, other</td>
<td>Allergy, not specified</td>
<td>Good</td>
</tr>
<tr>
<td>Huurre, 2008</td>
<td>Finland</td>
<td>To evaluate the effect of probiotics for allergy prevention in infants.</td>
<td>Milk, other</td>
<td>Allergy, not specified</td>
<td>Good</td>
</tr>
<tr>
<td>Kuitunen, 2009</td>
<td>Finland</td>
<td>To assess probiotic supplementation in pregnant women and infants in reducing the risk of allergies in children</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Good</td>
</tr>
<tr>
<td>Kvenshagen, 2009</td>
<td>Norway</td>
<td>To investigate whether children delivered by cesarean section were more prone to develop food allergy</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; GINI German Infant Nutritional Intervention; sIgE antigen-specific immunoglobulin
Table 41: Food allergy prevention controlled trials: patient characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention Group Selection Criteria</th>
<th>Control Selection Criteria</th>
<th>Subject Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion/exclusion criteria</strong></td>
<td>IgE</td>
<td>Skin Test</td>
<td>Clinical reaction</td>
</tr>
<tr>
<td>Halmerbauer, 2002251</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kajosaari, 1994252</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Maternal diets</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hattevig254 and Sigurs255</td>
<td>cord blood IgE = 0.9 ku/L</td>
<td>No</td>
<td>Same as intervention group</td>
</tr>
<tr>
<td>Bardare, 1993261</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention Group Selection Criteria</td>
<td>Control Selection Criteria</td>
<td>Subject Demographics</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------------</td>
<td>----------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Inclusion/exclusion criteria</td>
<td>IgE</td>
<td>Skin Test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arshad, 2007&lt;sup&gt;262&lt;/sup&gt;</td>
<td>Inclusion: infants at high risk for atopic disease plus cord blood serum IgE &gt; 0.5 kilo units/L; high risk defined as two or more members of immediate family with allergic disease (asthma, AD or allergic rhinitis) or either parent or sibling with allergic disease;</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Schoetzau, 2002&lt;sup&gt;265&lt;/sup&gt;</td>
<td>Inclusion: infants with family history of atopy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Laubereau, 2004&lt;sup&gt;266&lt;/sup&gt;</td>
<td>Inclusion: infants with family history of atopy</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 41: Food allergy prevention controlled trials: patient characteristics (Continued)

<table>
<thead>
<tr>
<th>Study Authors, Year</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Grouping</th>
<th>Diet Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Berg, 2008 (271)</td>
<td>Infants with at least 1 parent or sibling with a history of allergic disease, less than 2 weeks old, and without any history of formula supplementation</td>
<td>NR</td>
<td>Same as intervention group</td>
<td></td>
</tr>
<tr>
<td>Odelram, 1996 (272)</td>
<td>Inclusion: at least 2 atopic family members or one atopic parent, total cord blood IgE was &gt;0.5 kU/L. Exclusion: gestational age below 37 weeks, complicated delivery, neonatal illness, severe birth defects, documented or expected noncompliance with diet prescriptions</td>
<td>NR</td>
<td>Exclusively fed breast milk for &gt;9 months: 6 males; 14 females</td>
<td></td>
</tr>
<tr>
<td>Szajewska, 2004 (274)</td>
<td>Inclusion: birth weight &lt; 2500 grams but appropriate for gestational age, had not received a non-study formula before randomization and had at least one first degree relative with allergic disease</td>
<td>NR</td>
<td>Same as intervention group</td>
<td></td>
</tr>
<tr>
<td>Han, 2003 (263)</td>
<td>Infants of parents with allergy symptoms and serum total IgE over 200 kU/L. Excluded if birth defects, severe chronic diseases, or gestational age less than 36 weeks.</td>
<td>NR</td>
<td>Same as intervention group</td>
<td></td>
</tr>
<tr>
<td>Arslanoglu, 2008 (273)</td>
<td>Inclusion: term infants with a parental history of atopy; birth weight appropriate for gestational age, and start of formula feeding within the first 2 weeks of life.</td>
<td>NR</td>
<td>Same as intervention group</td>
<td></td>
</tr>
<tr>
<td>Probiotics</td>
<td>Rautava, 2002 (285)</td>
<td>Inclusion: pregnant women from atopic families; included breast-feeding women and the maternal use of probiotics until age 3 months</td>
<td>NR</td>
<td>Same as intervention group</td>
</tr>
</tbody>
</table>

NR: Not reported
<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Intervention</th>
<th>Maternal Atopic Disease (%)</th>
<th>Maternal Allergy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huurre, 2008</td>
<td>Inclusion: enrolled in the nutrition modulation by dietary counseling for allergic families; no chronic or metabolic disease in the mother before or during early pregnancy, and completed follow-up and SPT of the infant at age 1 year.</td>
<td></td>
<td>No</td>
<td>Same as intervention</td>
<td>Maternal atopic disease 81%</td>
</tr>
<tr>
<td>Kuitunen, 2009</td>
<td>Inclusion: pregnant mothers carrying children at increased risk for allergy defined as at least one parent having physician-diagnosed allergic disease. Exclusion: Infants born before 37 weeks, with major malformations, and B-twins</td>
<td></td>
<td>NS</td>
<td>Same as intervention</td>
<td>Males 50%; Maternal allergy: 80%</td>
</tr>
<tr>
<td>Abrahamsson, 2007</td>
<td>Families with allergic disease (1 or more family members with eczema, asthma, gastrointestinal allergy, allergic urticaria, or allergic rhinoconjunctivitis) were recruited at antenatal clinics; diagnosis made by family history.</td>
<td></td>
<td>NS</td>
<td>Same as intervention</td>
<td>100% infants; 56% boys; Family history of 54% eczema; 47% asthma; 91% food allergy</td>
</tr>
<tr>
<td>Kvenshagen, 2009</td>
<td>One hundred and ninety-three premature infants born consecutively at the maternity clinic of Ostfold Hospital Trust and the two following children born at term</td>
<td></td>
<td>No</td>
<td>Same as intervention</td>
<td>48% premature; 52% full-term</td>
</tr>
</tbody>
</table>

Table Notes: AD atopic dermatitis; CMF cow milk formula; EHF=extensively hydrolysed formula; GA gestational age; GI gastrointestinal; NICU neonatal intensive care unit; PHF=partially hydrolysed formula; SD standard deviation; sIgE antigen-specific immunoglobulin; SPT skin prick test
<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Description</th>
<th>Timing</th>
<th>Sample Size</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halmerbauer, 2002&lt;sup&gt;251&lt;/sup&gt;</td>
<td>Exclusive breastfeeding for as long as possible and at least until 3 months of age; Introduction of solids and soy milk delayed until 6 months; hypoallergenic formula used if supplementation required prior to 6 months (except for UK infants); Cow milk, egg and fish after 12 months; peanut or tree nuts after 3 years; Environmental measures for anti-dust-mite procedures; all beds in child's room had special dust-mite protection covers</td>
<td>Same recommendations made as those to intervention group; no protective mattress cover provided</td>
<td>12 months</td>
<td>349</td>
</tr>
<tr>
<td>Kajosaari, 1994&lt;sup&gt;252&lt;/sup&gt;</td>
<td>Exclusive breastfeeding until 6 months of age; no introduction of solid foods until 6 months of age</td>
<td>Exclusive breastfeeding until 3 months of age at which time solid feeding was started</td>
<td>5 years</td>
<td>51</td>
</tr>
<tr>
<td>Maternal diets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hattevig, 1989&lt;sup&gt;254&lt;/sup&gt; and Sigurs, 1992&lt;sup&gt;255&lt;/sup&gt;</td>
<td>Lactating mothers diet up to 3 months post-partum to be free from eggs, cow milk and fish product. After 3 months all returned to normal diet. Infants: cow milk after 6 months and fish after 9 months; during first 6 months breastfeeding or hydrolyzed casein formula</td>
<td>Mothers: no restriction on diet. Infants: same as intervention group</td>
<td>Infant seen at neonatology and at 3, 6, 9, 12, 18 months; again at 4 years</td>
<td>65</td>
</tr>
<tr>
<td>Breastfeeding (with other interventions)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filipiak, 2007&lt;sup&gt;260&lt;/sup&gt;</td>
<td>Mothers encouraged to breastfeed for at least 4 months; if this was not possible then they were to use one of four hydrolyzed formulas; delayed introduction of solids until 4 months and potentially allergenic food to be delayed until 1st year</td>
<td>Did not receive any dietary recommendations</td>
<td>4 years</td>
<td>1939</td>
</tr>
</tbody>
</table>
Table 42: Food allergy prevention controlled trials: intervention characteristics and outcomes reported (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Description</th>
<th>Timing Info</th>
<th>Sample Size</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardare, 1993</td>
<td>Infants: soy formula supplementation if required; gluten after 8th month; cow milk and dairy products after 10th month; lamb, turkey rabbit, pear, pineapple allowed before 1 year; avoidance of tobacco smoke and animal dander recommended; Mother during breastfeeding: no more than 200 dL of milk and only one egg per week; completely avoid tomato, fish, shellfish, nuts and foods mother was allergic to;</td>
<td>No diet prescribed; parents informed of infant's atopy risk</td>
<td>158 218</td>
<td>Atopic symptoms; IgE levels based on symptoms; atopic eczema</td>
</tr>
<tr>
<td>Arshad, 2007</td>
<td>Infants: Elimination of dairy products, eggs, wheat, nuts, fish and soy until 12 months of age. Extensively hydrolyzed formula supplementation if breast-feeding discontinued before 9 months; reduction in exposure to house dust mite allergens. Mothers: elimination of same foods as infants except wheat, during lactation</td>
<td>Infants followed standard recommendations at that time</td>
<td>58 62</td>
<td>Clinical asthma diagnosed at least once during the first 8 years</td>
</tr>
<tr>
<td>Schoetzau, 2002</td>
<td>Infants were exclusively breastfed for at least 4 months</td>
<td>Partially or exclusively received cow milk formula</td>
<td>865 256</td>
<td>AD incidence; sensitization to egg and milk</td>
</tr>
</tbody>
</table>
### Table 42: Food allergy prevention controlled trials: intervention characteristics and outcomes reported (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Follow-up duration</th>
<th>Outcomes</th>
<th>Atopic dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laubereau, 2004 266</td>
<td>Mothers encouraged to breastfeed for at least 4 months; if this was not possible then they were to use one of four hydrolyzed formulas; delayed introduction of solids until 4 months and potentially allergenic food to be delayed until 1st year</td>
<td>3 years</td>
<td>I—900 NI—1131</td>
<td>1—684 NI—1188</td>
</tr>
<tr>
<td>Von Berg, 2008 270 2007 271</td>
<td>Received one of three hydrolyzed formulas: partially hydrolyzed whey formula (pHF-W); extensively hydrolyzed casein formula eHF-W; extensively hydrolyzed casein formula (eHF-C)</td>
<td>6 years</td>
<td>pHFW—557; eHFW—559; eHFC—580</td>
<td>556</td>
</tr>
<tr>
<td>Odelram, 1996 272</td>
<td>EHF was a whey hydrolysate. Lactating mothers and infants were on elimination diets for cow milk, egg, and fish</td>
<td>18 months</td>
<td>Group 1 (EHF): 32. Group 2 (CMF): 39</td>
<td>20</td>
</tr>
<tr>
<td>Szajewska, 2004 274</td>
<td>Preterm infants were assigned an extensively hydrolyzed formula or a partially hydrolyzed formula or fortified breast milk (with extensively hydrolyzed mixture) for 4-5 months</td>
<td>Evaluated 4-5 months after intervention and then again at 12 months</td>
<td>EHF—20, PHF—22, fortified breast milk (BMF)</td>
<td>26</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Comparison</td>
<td>Follow-up</td>
<td>Outcomes</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Han, 2003</td>
<td>All encouraged to be fed with breast milk. During the nursing period, lactating mothers eliminated all sources of egg from their diet.</td>
<td>When the parents did not want to feed their babies with breast milk or breast milk was not available, partially hydrolyzed formula was recommended as substitution. Standard formula was given in cases when the parents did not want partially hydrolyzed formula.</td>
<td>Evaluated every 2 months for 6 months</td>
<td>PHF—15 SF—32 22 Incidence, prevalence, and severity of atopic dermatitis</td>
</tr>
<tr>
<td>Arslanoglu, 2008</td>
<td>Formula supplemented with a mixture of 90% short-chain galactooligosaccharides and 10% long-chain fructooligosaccharides (IMMUNOFORTIS) intended to mimic human milk oligosaccharides</td>
<td>Same hypoallergenic formula as experimental group without the oligosaccharide supplementation</td>
<td>2 years</td>
<td>66 68 Growth (height/wt); cumulative incidences of atopic dermatitis, recurrent wheezing, and allergic urticaria; physician diagnosed infections, fever episodes witnessed by the parent.</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Starting 4 weeks before term and continuing for 3 months post partum (with breastfeeding), L rhamnosus probiotics given to mother and then to neonate</td>
<td>Placebo</td>
<td>2 years</td>
<td>30 32 Chronic relapsing atopic eczema; GI symptoms; cow’s milk allergy; SPT; serum IgE; specific IgE</td>
</tr>
</tbody>
</table>

Table 42: Food allergy prevention controlled trials: intervention characteristics and outcomes reported (Continued)
Table 42: Food allergy prevention controlled trials: intervention characteristics and outcomes reported (Continued)

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Intervention Details</th>
<th>Placebo</th>
<th>Duration</th>
<th>Atopic Sensitization of Children</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huurre, 2008&lt;sup&gt;284&lt;/sup&gt;</td>
<td>Dietary counseling, breastfeeding, L rhamnosus and B lactis from first trimester of pregnancy to the end of exclusive breastfeeding.</td>
<td>Placebo</td>
<td>1 year</td>
<td>72</td>
<td>Atopic sensitization of children measured by SPT to numerous allergens; atopic eczema; cytokine concentrations in breast milk.</td>
</tr>
<tr>
<td>Kuitunen, 2009&lt;sup&gt;286&lt;/sup&gt; and Kukkonen, 2007&lt;sup&gt;287&lt;/sup&gt;</td>
<td>Starting at week 35 gestation, mothers took 1 capsule of Lactobacillus, Bifidobacterium and propionibacterium species bid. The newborn infants received 1 opened capsule of the same mixed with 20 drops of sugar containing galacto-oligosaccharides once daily for the first 6 months of life.</td>
<td>Identical appearing capsules of cellulose</td>
<td>2 years and 5 years</td>
<td>506</td>
<td>Cumulative incidence of any allergic disease (food allergy, eczema, asthma, allergic rhinitis) and IgE associated atopic disease. Secondary outcome measure: eczema and IgE sensitization.</td>
</tr>
<tr>
<td>Abrahamsson, 2007&lt;sup&gt;288&lt;/sup&gt;</td>
<td>Mothers started taking L reuteri 4 weeks before term and continued daily after delivery. After birth, baby continued same preparation for 12 months.</td>
<td>Mothers started taking placebo 4 weeks before term and continued daily after delivery. After birth, baby continued same preparation for 12 months.</td>
<td>2 years</td>
<td>95</td>
<td>Cumulative incidence of eczema; IgE mediated eczema; SORAD scores among those with eczema; incidence of wheezing; cumulative incidence of SPT; circulating IgE to egg white; infections (otitis media); use of antibiotics; gastrointestinal symptoms; body weight</td>
</tr>
<tr>
<td>Cesarean section Delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kvenshagen, 2008&lt;sup&gt;290&lt;/sup&gt;</td>
<td>Cesarean section delivery</td>
<td>Vaginal delivery</td>
<td>2 years</td>
<td>195</td>
<td>414</td>
</tr>
</tbody>
</table>

**Table Notes:** AD atopic dermatitis; CMF=cow milk formula; DBPCFC double blind placebo-controlled food challenge; eHF-W: eHF–C Extensively hydrolyzed casein formula; Extensively hydrolyzed whey formula; sIgE antigen-specific immunoglobulin; HF Hydrolysed formula; PHF=partially hydrolysed formula;; SCORAD scoring atopic dermatitis; SPT skin prick test
ii. What methods are currently used in the management of existing food allergy?

ii. a. What are the data on the effects of allergen avoidance based on both the primary literature and the recommendations of key organizations? This question should include the effect on nutritional status.

Background

The first therapeutic approach to food allergy is often to eliminate the allergenic food from the diet. However, it may be very difficult to avoid some foods completely, and the avoidance of foods such as milk and eggs may cause nutritional problems in children.

Results

One non-randomized comparative study\textsuperscript{291} examined the effect of allergen avoidance through elimination diets on patients with food allergies (Table 44-Table 46). Agata et al\textsuperscript{291} studied the effect of an elimination diet for milk or egg allergies on atopic dermatitis. Twenty-seven patients sensitive to egg and 16 patients sensitive to milk who underwent an elimination diet for at least three months were compared with six patients sensitive to egg and five patients sensitive to milk who did not eliminate the allergic food from their diet. The results showed that in those with egg allergy, 100 percent showed improvement in their atopic dermatitis with an elimination diet (compared with 0/6 not on an elimination diet). In those with a milk allergy, 15/16 showed improvement in their atopic dermatitis with elimination diet (compared with 0/5 not on an elimination diet). They concluded that an elimination diet is a good treatment for food allergy and that specific IgE antibodies to food antigens were useful as indexes of the effect of elimination diets in patients with positive RAST.

One population-based cohort of children with cow’s milk allergy reported on the nutrient intake of cows’ milk-restricted diets\textsuperscript{213} (Table 51). The Oslo Birth cohort followed children born in Oslo until age 2. Children with diagnosed egg and milk allergy were divided into four groups: milk-free diet (totally free of any cow milk protein n=10), hypoallergenic formula diet (formula used in varying amounts n=6), milk-reduced diet that included some dairy but no cow milk (n=8), and milk diet (children allergic to egg but not to milk n=10). Parents recorded dietary intake for 4 days. Compared to the children on the milk diet, children on the milk-free diet had significantly decreased intake of energy (p<0.001), protein (p<0.001), fat (p<0.001), riboflavin (p<0.001), niacin (p<0.01), calcium (p<0.001), and potassium (p<0.01). There were no statistically significant differences between the children on the hypoallergenic formula diet compared to those on the milk diet for energy, protein, or fat but there were statistically significant decreases in riboflavin (p<0.01), calcium (p<0.001), and potassium (p<0.05). The formula-fed group had increased intake of Vitamin E (p<0.05) and iron (p<0.05). Children on the milk-reduced diet had decreased consumption only of riboflavin (p<0.001) and calcium (p<0.001) compared with children on the milk diet.
Summary
Allergen avoidance is a common treatment strategy for food allergy and may work. However, this intervention has not been adequately studied, and the quality of evidence for this key question is low, given that only one non-randomized comparative study of poor quality addresses this question. Confounding this key question is that allergen avoidance diets are commonly used as a diagnostic test in addition to a treatment strategy. If a patient is placed on an allergen avoidance diet and continues to have symptoms, it is not clear if the allergen avoidance diet is ineffective or if the patient did not in fact, have an allergy to that particular food. Complete absence of cow milk protein may result in decreased energy, protein, and fat consumption while formula and milk-restricted diets may lead to micronutrient deficiencies. The quality of evidence for this key question is low, given that only one small observational study addressed this topic.

ii. b. What are the data on the benefits and adverse effects of immunotherapy with foods (e.g., parenteral, oral, sublingual) to treat food allergy?

Background
Immunotherapy broadly encompasses those interventions that alter the immune system to treat food allergy. To clarify terminology, the term “immunotherapy” in the context of allergic conditions traditionally refers to an allergen-specific therapeutic approach by which the immune response to allergen exposure is altered using protocols designed to gradually administer over time increasing doses of native or modified forms of the causative allergen. More recently, the term “immunotherapy” has been used to describe a number of biologic agents that alter the immune response in a non-allergen specific manner (i.e. omalizumab). The discussion below focuses on allergen-specific immunotherapy for the treatment of food allergy.

Allergen-specific immunotherapy protocols vary with regard to dosing, schedule, and route of administration. Historically, oral, sublingual, and subcutaneous routes of allergen administration have most frequently been investigated. To further distinguish terminology, allergen-specific immunotherapy protocols may potentially result in “desensitization” or “tolerance” to the specific allergen. Desensitization refers to a temporary clinical state in which allergen exposure fails to cause allergic symptomatology in the allergic individual. However, this state of clinical non-reactivity must be maintained by continuous recurrent administration of the allergen. In the absence of repeat allergen dosing, the state of clinical reactivity with allergen exposure returns and the individual is at risk for recurrent allergic reactions. In contrast, immunotherapy protocols inducing specific allergen tolerance result in long-term or permanent immunological changes with the outcome of clinical nonreactivity to allergen exposure even after long periods of abstinence. Immune tolerance putatively results in measurable changes in the immunological response to allergen including decreased allergen-specific IgE and IL-4 production, and increased allergen-specific IgG and IL-10 production. Additionally, we identify studies below which distinguish between use of the native food allergen for immunotherapy (allergen-specific immunotherapy) and use of allergens that cross react with food allergens (specific-immunotherapy with cross-reactive allergens).
Allergen-specific immunotherapy

Six RCT studies used desensitization protocols with the allergic food to induce tolerance\(^{292-297}\) (Table 44-Table 46). Three observational studies with fewer than 100 patients were also included, given the paucity of data on harms for this treatment. Hoffman et al\(^{211}\) specifically reported on the safety of oral immunotherapy in 28 patients. Narisety et al\(^{212}\) reported safety results for 12 participants in the original Skripak RCT that were subsequently continued on open-label maintenance for three months after completion of the trial\(^{292}\) (Table 51). Zapatero et al reported on 18 patients undergoing oral desensitization for cow’s milk allergy.\(^{298}\)

Staden et al. assigned children with a food allergy to either milk or hen’s egg confirmed by a DBPCFC to oral immunotherapy or an elimination diet. They found that desensitization at a median of 21 months was achieved more often in the group that received oral immunotherapy (16/25) than in the group that adhered to an elimination diet (7/20) \(p=0.05\). Only 9/25 children that were tested after two months of an elimination diet demonstrated tolerance.\(^{293}\) Morisset et al.\(^{294}\) performed a randomized study to examine an oral desensitization protocol in children with IgE-mediated milk or egg allergies. Diagnosis of food allergy was established by SPT and/or specific IgE, and allergy confirmed by positive oral food challenge or complete recovery from symptoms after 3 weeks of avoiding the suspected food allergen. When the oral desensitized group was compared to the continued avoidance group for milk allergy, a significant improvement in single (S)BPCFC was found (3/27 versus 12/30; \(p<0.025\)) as well as a decrease in the size of the prick test wheal (\(p<0.002\)). Comparing the oral desensitized group to the continued avoidance group for egg allergy, a significant improvement in SBPCFC was again found (15/49 vs 17/35; \(p<0.10\)) as well as a decrease in the size of the prick test wheal (\(p<0.05\)). In addition, there was a statistically significant decrease in egg-specific IgE (\(p<0.01\)). Skripak et al\(^{292}\) studied milk oral immunotherapy in treating cow’s milk allergy in patients aged 6-21 diagnosed with SPT or specific IgE and a food challenge. Once the immunotherapy dose of 15mL of milk was reached, patients were then treated for 13 weeks. They found that the milk dose threshold was higher in the group receiving oral immunotherapy (\(p=0.002\)) and that the cow milk-specific IgG levels were reportedly higher (\(p=0.002\)) (data not shown). There was no statistically significant change in cow-milk-specific IgE. Long-term tolerance was not assessed.

Nelson et al.\(^{295}\) studied the effect of injections of subcutaneous peanut extract on patients with anaphylaxis to peanuts treated with weekly injections of peanut extract for one year. They reported a decreased peanut sensitivity at one month (\(p=0.0002\)) but no effect on SPT or peanut-specific IgE as compared to patients with peanut allergy who did not receive subcutaneous injections. Enrique et al.\(^{299}\) studied the effect of sublingual hazelnut extract on patients with a hazelnut food allergy diagnosed by positive DBPCFC. They observed that the mean hazelnut quantity that provoked symptoms increased in the group receiving hazelnut extract but not in the placebo group (\(p=0.02\)). Furthermore, there was an increase in hazelnut-specific IgG4 (\(p<0.05\)) but no difference in the hazelnut-specific IgE between the groups. Patriarca et al.\(^{296}\) evaluated oral desensitization protocols in patients with a wide variety of allergies, including milk, hen’s egg, wheat, bean, and cod diagnosed by a clinical history and allergenic workup. They found that 36/48 people assigned to the desensitization arm had a negative DBPCFC, compared with none of the control patients. Long-term tolerance was not addressed in any of these studies.

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Safety data for allergen-specific immunotherapy was reported in only four of the six studies (Table 47). The observational study by Hofmann et al\textsuperscript{211} specifically reported on the safety of peanut oral immunotherapy in 28 children with peanut allergy (Table 51). They divided the study into three separate phases (initial escalation day, buildup phase, and home dosing phase) (Table 47). They concluded that subjects were more likely to have significant allergic symptoms during the initial escalation day when they were in a closely monitored setting than during other phases of the study. Narisety et al\textsuperscript{212} reported safety data on 12 children that had completed the Skripak trial for milk oral immunotherapy and were able to tolerate >2540 mg (about 2.5 ounces) of milk. These patients were followed for an additional 3 months (Skripak trial followed for 3 months) (Table 47). Zapatero reported some safety information for 18 patients undergoing oral desensitization with cow’s milk allergy; 2/18 required epinephrine during the desensitization protocol.\textsuperscript{298}

Specific immunotherapy with cross-reactive allergens

We found four RCTs that used immunotherapy with cross-reactive allergens to treat food allergies (Table 44-Table 46).\textsuperscript{300-303} Apple allergy was examined in three studies\textsuperscript{300-302} and hazelnut allergy in one.\textsuperscript{301} One study was not directed at specific food allergies but evaluated the oral allergy syndrome in the setting of natural rubber latex allergy.\textsuperscript{303} Three studies examined the effect of tree pollen extract immunotherapy on the oral allergy syndrome.

Hansen et al. noted that clinical manifestations of allergenic cross-reactions between pollen and plant foods are frequent in birch pollen allergic patients and evaluated the effect of birch pollen extract immunotherapy in patients with apple allergy diagnosed by clinical history, SPT< specific IgE, and positive conjunctival provocation test.\textsuperscript{306} There was no statistically significant change in oral allergy syndrome response to an open apple food challenge after treatment with placebo, sublingual, or subcutaneous birch pollen extracts. There was a statistically significant decrease in apple-specific IgE in patients treated with subcutaneous birch pollen extract (from 5.9 kU/L to 1.8 kU/L, p=0.009). No statistically significant change was reported in those patients receiving sublingual birch pollen extract (pre=0.8 kU/L; post=1.4 kU/L) or placebo (pre=2.6 kU/L; post=2.1 kU/L).

Bucher et al. also examined the effect of subcutaneous immunotherapy with tree pollen extract on patients’ oral allergy syndrome to apple and hazelnuts.\textsuperscript{301} Patients with birch-pollen allergy, oral allergy syndrome, and positive SPT to apple or hazelnut were selected for study. Improvement of oral allergy syndrome was statistically significant (p<0.05) with 10/15 patients receiving subcutaneous immunotherapy showing improvement and only 2/12 control patients showing improvement. Serum-specific IgE to apple was also measured. In the immunotherapy group, the baseline value was 39.1 kU/L, which rose after a year of treatment to 42.8 kU/L. In the control group, the baseline value was 29.2, rising to 36.2 after a year of placebo. This difference was not statistically significant. This group also reported that IgG4 r Bet v1 (human IgG4 antibody that is specific for the major birch pollen antigen) was statistically significant (p<0.001) in the group treated with immunotherapy, but no values were given.

Asero at el. evaluated birch pollen-allergic patients with a clear history of apple-induced oral allergy syndrome who received injection immunotherapy with birch pollen extract.\textsuperscript{302} This
treatment was found to reduce clinical apple sensitivity (p<0.001) but not apple-specific IgE. Bernardini et al. explored the safety and efficacy of sublingual immunotherapy with a latex extract in patients with clinical history of latex food allergies. They found no significant difference in SPT for food allergies after treatment.

Safety was reported for only one of four studies that examined specific immunotherapy with cross-reactive allergens (Table 47). In this study, no signs of local or gastrointestinal symptoms were reported.

Summary

The quality of evidence for this key question—does immunotherapy improve clinical symptoms—is high, given six RCTs regarding allergen-specific immunotherapy and four RCTs regarding specific immunotherapy with cross-reactive allergens. Allergen-specific immunotherapy and specific immunotherapy with cross-reactive allergens are effective in desensitization and improve clinical symptoms of food allergy. Long-term tolerance has been inadequately studied. The safety of such treatment was reported in only four of six studies on allergen-specific immunotherapy and without doing a search specific for harms, it is difficult to draw conclusions on the safety of such an approach.

ii. c. How effective are current standards for food labeling for prevention of food allergic reactions?

In 2004, the federal government passed the Food Allergen Labeling and Consumer Protection Act, which mandated that processed foods that might contain any one of a number of common food allergens (e.g., milk, eggs, wheat, peanuts, tree nuts) were required to carry information on their labels identifying these foods. Although we identified 8 studies related to this question, no study explicitly assessed the effectiveness of food labeling, that is attempted to infer a cause-and-effect relationship between a change in frequency of severe symptoms from accidental exposure (e.g., peanut) as a consequence of implementation of food labeling. The identified studies mostly assessed knowledge and preferences for food labeling. Three studies were from the US, two studies from the United Kingdom, one study (in abstract form only) from Australia, one from Brazil and Spain, and one study compared consumer preferences across cultures. Unfortunately, even the US studies did not collect data after the most recent change in US labeling laws, so even the US studies are of limited relevance. The two most relevant studies are now described.

The first study asked 91 parents of children attending the pediatric allergy clinic at Mt. Sinai Medical Center in New York to review 23 food labels and to name the food allergens to which their child was allergic that were presented in the particular product. Forty-two percent of parents indicated their child had experienced anaphylaxis. Of 60 parents of milk allergic patients, four (seven percent) were able to correctly identify all 14 labels that indicated some form of milk was contained in the product. Six of 27 parents of soy-allergic children (22 percent) correctly identified soy protein in all seven products that contained soy, and peanut was
correctly identified by 44 of 82 (54 percent) parents in all five products containing peanut. Identification was much better for products containing wheat and egg.

The second relevant study assessed 489 respondents (84 percent response rate) from attendees at the Food Allergy and Anaphylaxis Network (FAAN) Conference, of whom 96 percent were white. The self-identified allergic foods were peanut (81 percent), tree nut (53 percent), milk (51 percent), egg (51 percent), soy (17 percent), wheat (16 percent), shellfish (17 percent), and fin fish (12 percent). Ingredient labels were “always” or “frequently” read before purchasing a product by 99 percent of consumers doing the shopping and by 94 percent of people doing the cooking for food allergic patients. Adverse reactions were attributed to misunderstanding of the food label in 16 percent of cases and to ingredients not declared on the label in 22 percent of cases.

Similar problems in identification were reported in a study of parents of children with cow milk allergy in Brazil and Spain, and difficulties interpreting labels and general dissatisfaction with current labels were noted in studies from the US, the United Kingdom, and the Netherlands and Greece. One Australian study, available only as an abstract, reported that new standards had led to food labels that were an improvement over old food labels, but that a lack of understanding still persisted. In a UK study of government advice on avoidance of peanut consumption during pregnancy and breastfeeding in women with a family history of atopy, only 65 percent of mothers successfully complied.

ii. d. What are the allergenic cross-reactivities (with other foods or non-food allergens) of foods (i.e., other legumes in peanut allergic patients, tree nuts in peanut allergic patients, etc)? What are the clinical consequences?

Only one included RCT addressed this type of cross reactivity. As described in the answer to the key question regarding the use of special diets in infants for the prevention of food allergy, the RCT by Klemola et al. evaluated the incidence of adverse reactions or allergies to soy formulas in infants with cow’s milk allergy syndrome during the first two years of life. Parents’ suspicions of adverse reactions to formula was significantly higher among children who had received soy formula but still statistically significantly greater in the soy formula group (28%, 95% CI 18-39 percent) than children who had received extensively hydrolyzed formula (11 percent, 95% CI 5-19 percent). However, the cumulative incidence of adverse reactions confirmed by DBPCFC was low for both the soy formula (8 infants, 10 percent, 95% CI 4.4-18.8 percent) and for the extensively hydrolyzed formula (two infants, 2.2 percent; 95% CI 0.3-7.8 percent; RR=4.50, p=0.03). Adverse reactions to soy were suspected in 12 of 46 infants with IgE-associated cow’s milk allergy and in 13 of 34 infants with non-IgE associated cow’s milk allergy (p=0.25). Adverse reactions to soy were confirmed by DBPCFC in five of 46 (11 percent) infants with IgE associated cow’s milk allergy and in three of 34 (9 percent) infants with non-IgE associated cow’s milk allergy (p=0.76). We conclude that there is insufficient evidence to evaluate the allergenic cross-reactivities of foods.
ii. e. What are the effects of food allergen avoidance, and other food allergy management strategies, on co-morbid conditions such as, but not limited to, atopic dermatitis, asthma, and eosinophilic gastrointestinal disorders?

Background

It is unclear which specific strategies (e.g. allergen avoidance, elimination diet, pharmacological management) are effective in the treatment and management of specific clinical conditions associated with food allergies.

Results

We identified two systematic reviews that evaluated the effect of dietary exclusion for treating atopic eczema. Two publications were on the same systematic review\(^56,\ ^{314}\) (Table 43). All reviews had a comprehensive literature search and screening process and followed the methods used by the Cochrane Collaboration. They all scored highly on the AMSTAR criteria. Kramer et al. assessed as part of their review on allergy prevention, whether maternal dietary antigen avoidance during lactation by mothers of infants with eczema could reduce eczema severity. The review found one small trial (n=17) that met inclusion criteria for this part of the review, which found no significant reduction in eczema area score (mean difference -0.8; 95% CI -4.43 - 2.83) or eczema activity score (mean difference -1.4; 95% CI -7.18 to 4.38) between infants whose mothers avoided dietary antigens and those whose mothers followed a usual diet.\(^{253}\)

Bath-Hextall et al. evaluated the effect of dietary exclusion by patients for treating established atopic eczema and reported these findings in two publications.\(^{56,\ ^{314}}\) Their search of the published literature (conducted as of March 2006) resulted in the inclusion of nine low-quality RCTs, of which they considered only two sufficiently similar to combine. Six of the RCTs examined milk and egg exclusion, one was a study of a diet including only a few foods, and two evaluated elemental diets. The authors found no evidence to support the use of these dietary exclusion strategies for treating atopic eczema in an unselected population; this finding was possibly due to patients not being allergic to the substances being eliminated or to the small study sizes and poor reporting. However, they suggested that there might be some benefit of an egg-free diet in infants with positive egg sIgE results (results from one study).

Summary

The quality of evidence for the effect of food allergen avoidance in treating atopic dermatitis is high given that we found two high-quality systematic reviews addressing this topic. Both reported no evidence supporting the use of allergen avoidance in treating atopic dermatitis. We did not find any studies specifically addressing food allergen avoidance in other co-morbid conditions.
Additional Information Relevant to Key Question H ii. Pharmacological management of food allergies

Background

Often, the first therapeutic approach to food allergy is to eliminate the food from the diet, but avoidance of foods such as milk and eggs can cause nutritional problems in children. Drug therapy is often employed as an alternate mechanism to manage food allergies, especially when diet compliance is extremely difficult. Commonly, drugs that alter the immune response to these allergens are utilized.

Results

We identified six RCTs that evaluated drugs to treat food allergy\(^{315-320}\) and one study that used probiotics to treat rectal bleeding caused by food allergy (Table 44-Table 47).\(^ {321}\)

Bindslev-Jensen et al.\(^ {315}\) examined the effect of astemizole on oral allergy syndrome induced by consumption of hazelnuts in patients with positive SPT to birch pollen. They included patients with a case history of immediate local symptoms (itching and swelling of mouth/throat) and excluded any patients with a severe reaction after intake of hazelnuts. All patients were given two open oral provocations of five hazelnuts (at least two days apart) to obtain a baseline value. Then the treatment group ingested aztemizole (10 mg each morning for 14 days) and the control group ingested placebo for 14 days, both followed by two open oral provocations for final values. Symptom severity to the oral provocation test was graded on a scale where 0=no reaction and 5=severe itching and swelling of mouth and throat. The baseline values were obtained from combining the two initial oral provocation tests and the final values were obtained from combining the two final oral provocation tests. For the treatment group, the baseline assessment was 6.33 and the final assessment was 3.67; for the placebo group, the baseline was 5.89 and the final was 5.47. Symptom severity to the oral provocation test was statistically significantly lower in the group that got aztemizole than in the placebo group (p=0.004).

Burks and Sampson\(^ {318}\) studied cromolyn in children with atopic dermatitis and documented food hypersensitivity to egg. All included patients had atopic dermatitis as defined by Hanifin and Rajka, all had positive SPT, all were on a strict egg-avoidance diet for one year, antihistamines were stopped one week before trial, and beta-agonists were stopped 12 hours before trial. Patients were treated for a week with either cromolyn or placebo and then were evaluated. Patients then had a washout period of three to five weeks and were crossed over to the other arm (cromolyn or placebo) for a week and again evaluated. Evaluations included symptoms and responses to DBPCFC. Symptom cards were assessed on a scale of 0-3 for rash distribution, pruritis, urticaria, sneezing/itching, congestion, rhinorrhea, wheezing, nausea/pain, and vomiting/diarrhea. This crossover study showed that after one week of treatment with either cromolyn or placebo, there was no statistically significant difference in the symptom score for atopic dermatitis or in the response to a DBPCFC.
Schaefer et al.\textsuperscript{319} compared oral prednisone to topical fluticasone in the treatment of eosinophilic esophagitis. Food allergy was found in only 63 percent of the patients treated with prednisone and 52.5 percent of the patients treated with fluticasone. One group received 1 mg/kg of prednisone twice daily for 12 weeks and the other group received fluticasone by MDI two puffs four times daily for 12 weeks. They found a statistically significant difference in histological response favoring the prednisone over the fluticasone group between weeks 0 and 4 \( (p=0.0440) \) and a histological improvement of distal esophageal biopsies in both groups compared to baseline \( (p<0.0001) \).

Szajewska et al.\textsuperscript{321} determined that using probiotics to treat breast-fed infants with rectal bleeding did not show a statistically significant effect on reducing the number of days of rectal bleeding.

Leung et al.\textsuperscript{316} evaluated the effect of anti-IgE therapy in patients with peanut allergy. They determined that a 450-mg dose of TNX-901, a humanized IgG1 monoclonal antibody, increased the threshold of sensitivity to peanut on oral food challenge from a level equal to one peanut to almost nine peanuts. Cavagni et al.\textsuperscript{317} evaluated the effects of adding thymomodulin to elimination diets in treating atopic dermatitis induced by food allergy. They noted a more favorable course of the skin lesions in the patients treated with thymomodulin after two weeks of food challenge. They also noted a statistically significant decrease in total and sIgE serum levels in the group receiving thymomodulin.

Businco et al.\textsuperscript{320} evaluated 31 children aged 6 months-10 years old with atopic dermatitis exacerbated by foods in a crossover study to evaluate the effects of sodium cromoglycate and an elimination diet on the severity of eczema. They concluded that eczema (measured both by the clinician and the parents) was statistically improved when the patients were receiving sodium cromoglycate.

Summary

Given the heterogeneity of the pharmacologic interventions and allergic conditions evaluated, we conclude that there is insufficient evidence to evaluate the extent to which pharmacologic therapy is useful in treating food allergies.

Additional Information Relevant to Key Question H ii. Other strategies for the management of food allergies

Results

We found five RCTs that evaluated other types of management strategies for food allergies not addressed in the other key questions (Table 44-Table 46).\textsuperscript{322-326}

Hill et al.\textsuperscript{322} evaluated the effect of a low-allergen maternal diet on colic among breastfed infants. They found a statistically significant improvement of colic in the low allergen group with adjusted RR of 37 percent (CI 18-56 percent).
Amadi et al.\textsuperscript{323} examined the role of an amino acid-based elemental feeding regimen in treating children with persistent diarrhea and malnutrition and found that the median gain in weight-for-age z score favored the amino acid-based elemental feed (p=0.002).

Cantani et al.\textsuperscript{324} studied a home-made meat-based formula for feeding atopic babies. They reported significant improvement in SCORAD scores in the group treated with the meat-based formula.

Salpietro et al.\textsuperscript{325} performed a RCT to evaluate the safety and efficacy of almond milk in infants with cow’s milk allergy. They reported reductions in a variety of symptoms (e.g., vomiting, diarrhea, wheezing, eczema) and weight gain among all infants taken off cow’s milk but no difference among those given almond milk compared to soy-based formula or hydrolyzed formula.

Viljanen et al.\textsuperscript{326} studied probiotics in the treatment of infants with atopic eczema/dermatitis and suspected of cow’s milk allergy. In addition to skin treatment and elimination of cow’s milk from the infants’ and breast-feeding mothers’ diets, 252 infants were randomized to capsules containing lactobacillus alone, a mixture of probiotics including lactobacillus, or placebo for four weeks. There was no statistically significant change in the SCORAD scores.

**Summary**

Given the heterogeneity of these studies, there is insufficient data as to whether these strategies for treating and managing food allergy are effective.

**Additional Information: Reported Variation in Management Style**

A retrospective cohort study examining the management of food related acute reactions in 21 emergency rooms in the US and Canada reported great variability in treatment across participating sites.\textsuperscript{15} Researchers reviewed a random sample of 678 food allergy patient charts. Regarding severity, only 18% arrived by ambulance, although 55% were considered "severe." Of the patients with "severe" reactions, only 24% received epinephrine. Of the total patients, 72% received antihistamines, 48% received systemic corticosteroids, 16% received epinephrine, and 33% received respiratory treatments such as inhaled albuterol. Upon discharge, 16% were prescribed self-injectable epinephrine. The authors also note that “emergency department discharge plans varied widely across participating sites.”

**Key Question H ii. f. What are the effects of co-morbid conditions on the clinical course of, and management of, food allergy?**

We did not find studies specifically focused on the effect of co-morbid conditions on the course or management of food allergy. Studies of the opposite question – the effect that food allergy management has on the co-morbid condition – are reviewed in the sections appropriate to that food or the condition.
<table>
<thead>
<tr>
<th>Author/ Year</th>
<th>Study Question</th>
<th>Databases searched/ Years</th>
<th>Intervention</th>
<th>Inclusion Exclusion</th>
<th>Total Publications Included</th>
<th>Outcomes Reported</th>
<th>AMSTAR Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer 2009\textsuperscript{253}</td>
<td>To evaluate the effect of an antigen avoidance diet during lactation for treating eczema</td>
<td>Cochrane Pregnancy and Childbirth Group Trial register; Up to March 2006</td>
<td>Mothers prescribed a diet to either exclude or reduce potentially allergenic foods: cow milk, egg, peanuts, fish, chocolate during lactation</td>
<td>RCTs or quasi-RCTs comparing diets of different levels of antigen avoidance</td>
<td>1</td>
<td>Eczema severity</td>
<td>01. Can’t Answer 02. Yes 03. Yes 04. Yes 05. Yes 06. Yes 07. Yes 08. Yes 09. Yes 10. No 11. Yes</td>
</tr>
<tr>
<td>Bath-Hextall 2009\textsuperscript{314}</td>
<td>To evaluate the effect of dietary exclusion for treating established atopic eczema</td>
<td>Cochrane Skin Group Specialized Register (to Mar 2006); Medline; EMBASE (2003-Mar 2006); LILACS (to Mar 2006); PsycINFO (1806-Mar 2006); AMED (1985-Mar 2006); ISI Web of Science (Mar 2006); CENTRAL (Mar 2006); <a href="http://www.controlledtrials.com">www.controlledtrials.com</a>; <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>; <a href="http://www.nottingham.ac.uk/ongoing">www.nottingham.ac.uk/ongoing</a> skintrials (Mar 2006)</td>
<td>Egg and milk exclusion; few foods diet; elemental diet</td>
<td>RCTs of exclusion diets; double blind placebo controlled food challenges conducted in isolation excluded</td>
<td>9</td>
<td>Short term: change in parent-rated eczema symptoms (e.g. itching); Long term: degree of control (e.g. reduction in number of flares or reduced need for other treatment); Global severity; QOL; palatability of diet; adverse events (e.g. long term consequences on growth)</td>
<td>01. Can’t Answer 02. Yes 03. Yes 04. Yes 05. Yes 06. Yes 07. Yes 08. Yes 09. Yes 10. No 11. Yes</td>
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<tr>
<td>Author/Year</td>
<td>Study Question</td>
<td>Databases searched/ Years</td>
<td>Intervention</td>
<td>Inclusion Exclusion</td>
<td>Total Publications Included</td>
<td>Outcomes Reported</td>
<td>AMSTAR Criteria</td>
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<tr>
<td>Kukuruzovic 2009</td>
<td>To evaluate medical management strategies for EE</td>
<td>Cochrane upper GI and pancreatic diseases group register (to 2006); CENTRAL (to 2006); Medline (1966 to Feb 2006); EMBASE (1980 to Feb 2006).</td>
<td>Medical (e.g. metered dose steroid, oral steroids, sodium chromoglycate, leukotriene receptor antagonists) or dietary (e.g. elemental milk formula) intervention</td>
<td>RCTs or quasi-RCTs comparing different interventions with placebo or each other</td>
<td>1 abstract from an unfinished RCT</td>
<td>Symptom improvement; potential benefits; potential harms</td>
<td>01. Can’t Answer 02. Yes 03. Yes 04. Yes 05. Yes 06. Yes 07. Yes 08. Yes 09. NA 10. No 11. Yes</td>
</tr>
</tbody>
</table>

**Table Notes:** EE eosinophilic esophagitis; GI gastrointestinal; QOL quality of life; RCT’s randomized controlled trials

AMSTAR criteria: 01. Was an a priori study design provided? 02. Was there duplicate study selection and data extraction? 03. Was a comprehensive literature search performed? 04. Was the status of publication (gray literature) used as an inclusion criterion? 05. Was a listed of studies (included/excluded) provided? 06. Were the characteristics of the included studies provided? 07. Was the scientific quality of the included studies assessed and documented? 08. Was the scientific quality of the included studies used appropriately in formulating conclusions? 09. Were the methods used to combine the findings of studies appropriate? 10. Was the likelihood of publication bias assessed? 11. Was the conflict of interest stated?
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Purpose</th>
<th>Food</th>
<th>Condition of interest</th>
<th>Study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agata, 1993291</td>
<td>Japan</td>
<td>To determine effect of elimination diets in patients with atopic dermatitis and allergies to egg or milk</td>
<td>Milk, egg</td>
<td>Atopic dermatitis</td>
<td>Poor</td>
</tr>
<tr>
<td>Staden, 2007293</td>
<td>Germany</td>
<td>To evaluate the effect of oral tolerance induction or elimination diet for managing cow milk or egg allergy in children</td>
<td>Milk, egg</td>
<td>Allergy, not specified</td>
<td>Good</td>
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<tr>
<td>Morisset, 2007294</td>
<td>France</td>
<td>To examine an oral desensitization protocol to allergenic foods in IgE-dependent milk or egg allergies in children</td>
<td>Milk, egg</td>
<td>Atopic dermatitis, urticaria, angioedema, asthma, GI symptoms</td>
<td>Fair</td>
</tr>
<tr>
<td>Skripak, 2007292</td>
<td>US</td>
<td>To evaluate milk oral immunotherapy for cow’s milk allergy</td>
<td>Milk</td>
<td>Multiple</td>
<td>Good</td>
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<tr>
<td>Nelson, 1997295</td>
<td>US</td>
<td>To determine the effect of immunotherapy in patients with anaphylaxis to peanuts</td>
<td>Peanut, tree nut</td>
<td>Anaphylaxis</td>
<td>Poor</td>
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<tr>
<td>Enrique, 2005299</td>
<td>Spain</td>
<td>To evaluate the efficacy and tolerance of sublingual immunotherapy with a hazelnut extract in patients with a hazelnut allergy</td>
<td>Hazelnut</td>
<td>Oral allergy syndrome, anaphylaxis, urticaria-angioedema</td>
<td>Good</td>
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<tr>
<td>Patriarca, 2007296</td>
<td>Italy</td>
<td>To evaluate specific oral desensitization in children with food allergies</td>
<td>Milk, whole egg, egg albumin, wheat, cod, apple, beans</td>
<td>Multiple</td>
<td>Poor</td>
</tr>
<tr>
<td>Hansen, 2004300</td>
<td>Denmark</td>
<td>To examine the effects of sublingual and subcutaneous administration of birch pollen extract in patients with apple allergy.</td>
<td>Apples</td>
<td>Oral allergy syndrome</td>
<td>Good</td>
</tr>
<tr>
<td>Bucher, 2004301</td>
<td>Switzerland</td>
<td>To evaluate the effect of subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut</td>
<td>Peanut, tree nut, apple</td>
<td>Oral allergy syndrome</td>
<td>Poor</td>
</tr>
<tr>
<td>Asero, 1998302</td>
<td>Italy</td>
<td>To evaluate the clinical and immunological effects of birch pollen specific immunotherapy on oral allergy syndrome induced by apples</td>
<td>Apples</td>
<td>Oral allergy syndrome</td>
<td>Poor</td>
</tr>
<tr>
<td>Bernadini, 2006303</td>
<td>Italy</td>
<td>To evaluate the safety and efficacy of SLIT with natural rubber latex (NRL) extract in children with NRL allergy</td>
<td>Latex, fruits</td>
<td>Oral allergy syndrome</td>
<td>Fair</td>
</tr>
</tbody>
</table>

**Table 44: Food allergy treatment/management controlled trials: study information**

**Specific immunotherapy with cross-reactive allergens**

**Pharmacological management**

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Purpose</th>
<th>Food</th>
<th>Condition of interest</th>
<th>Study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bindslev-Jensen, 1991315</td>
<td>Denmark</td>
<td>To evaluate the effect of treatment with astemizole on symptoms elicited by the ingestion of hazelnuts in birch pollen-allergic patients</td>
<td>Hazelnut</td>
<td>Oral allergy syndrome</td>
<td>Fair</td>
</tr>
<tr>
<td>Author</td>
<td>Country</td>
<td>Purpose</td>
<td>Food</td>
<td>Condition of interest</td>
<td>Study quality</td>
</tr>
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</tr>
<tr>
<td>Burks, 1988</td>
<td>US</td>
<td>To evaluate oral cromolyn in children with atopic dermatitis and documented food hypersensitivity</td>
<td>Egg</td>
<td>Atopic dermatitis</td>
<td>Fair</td>
</tr>
<tr>
<td>Schaeffer, 2008</td>
<td>US</td>
<td>To compare oral prednisone and topical fluticasone in treating EE in children**</td>
<td>Not specified</td>
<td>EE</td>
<td>Fair</td>
</tr>
<tr>
<td>Szajewska, 2007</td>
<td>Poland</td>
<td>To determine the effect of lactobacillus in infants with rectal bleeding</td>
<td>Milk</td>
<td>Cow’s milk allergy syndrome</td>
<td>Good</td>
</tr>
<tr>
<td>Leung, 2003</td>
<td>US</td>
<td>To determine the effect of anti-IgE therapy in patients with peanut allergy</td>
<td>Peanut</td>
<td>Anaphylaxis</td>
<td>Good</td>
</tr>
<tr>
<td>Cavagni, 1989</td>
<td>Italy</td>
<td>To evaluate if addition of an immunomodulating agent to an elimination diet improves food allergy in children</td>
<td>Egg, milk, pea, fish</td>
<td>Atopic dermatitis</td>
<td>Fair</td>
</tr>
<tr>
<td>Businco, 1986</td>
<td>Italy</td>
<td>To evaluate oral sodium cromoglycate in children with atopic dermatitis</td>
<td>Milk, egg, fish, wheat</td>
<td>Atopic dermatitis</td>
<td>Fair</td>
</tr>
<tr>
<td>Hill, 2005</td>
<td>Australia</td>
<td>To evaluate the effect of a hypoallergenic maternal diet on persistent crying among breastfed infants presenting with colic</td>
<td>Milk, egg, peanut, tree nut, wheat, soy, fish</td>
<td>Gastrointestinal hypersensitivity</td>
<td>Fair</td>
</tr>
<tr>
<td>Amadi, 2002</td>
<td>Zambia</td>
<td>To compare outcomes with either standard diet for diarrhea and malnutrition or an amino acid-based elemental feed</td>
<td>Milk</td>
<td>Cow’s milk allergy syndrome, Gastrointestinal hypersensitivity</td>
<td>Fair</td>
</tr>
<tr>
<td>Cantani, 2006</td>
<td>Italy</td>
<td>To evaluate the effectiveness of a home-made meat-based formula for feeding atopic babies</td>
<td>Milk</td>
<td>Atopic dermatitis</td>
<td>Poor</td>
</tr>
<tr>
<td>Salpietro, 2005</td>
<td>Italy</td>
<td>To test the safety and efficacy almond-based formula, soy formula, or hydrolyzed formula for infants with cow’s milk allergy</td>
<td>Milk</td>
<td>Cow’s milk allergy syndrome</td>
<td>Fair</td>
</tr>
<tr>
<td>Viljanen, 2005</td>
<td>Finland</td>
<td>To investigate whether probiotic bacteria have any beneficial effect on atopic eczema/dermatitis in infants with cow’s milk allergy</td>
<td>Milk</td>
<td>Atopic eczema/dermatitis syndrome</td>
<td>Good</td>
</tr>
</tbody>
</table>

Table Notes: EE= eosinophilic esophagitis; GI gastrointestinal; NRL natural rubber latex; sIgE antigen-specific immunoglobulin; SLIT sublingual immunotherapy
** Food allergy was only found only in 63% of the patients treated with prednisone and 52.5% of the patients treated with fluticasone
<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Group Selection Criteria</th>
<th>Control Selection Criteria</th>
<th>Subject Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergen avoidance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agata, 1993</td>
<td>Inclusion: clinical history of atopic dermatitis and milk/egg allergy</td>
<td>Same as intervention group</td>
<td>27 sensitive to egg, (age range: 4 months to 12 years); 16 sensitive to milk (age range 3 months to 12 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 sensitive to egg (age range: 1-10 years); 5 sensitive to milk (age range 8 months to 10 years)</td>
</tr>
<tr>
<td>Allergen-specific immunotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staden, 2007</td>
<td>Inclusion: IgE-mediated food allergy to either cow milk or hen egg as confirmed by DBPCFC Exclusions: severe atopic dermatitis with SCORAD &gt;75</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Morisset, 2007</td>
<td>Inclusion: Children with cow’s milk allergy or egg allergy as established on the basis of 1. skin prick test OR specific IgE AND 2. confirmed by either positive oral/labial food challenge OR complete recovery from symptoms after 3 weeks of food avoidance. Although, 15 cases of milk allergy were non-IgE mediated with negative skin/RAST but positive food challenge and/or recovery. These subjects were then seen 6 months to 1 year after continuous avoidance and were selected if they demonstrated non-reactivity to milk or egg (skin prick test, specific IgE, and placebo-controlled food challenge)</td>
<td>Same as intervention group</td>
<td>Milk: mean age 2.4 years (sd 1.2); Egg: mean age 3.5 years (sd 1.7)</td>
</tr>
<tr>
<td>Skripak, 2007</td>
<td>Inclusion: children aged 6-21 from pediatric allergy clinics with positive SPT to milk extract, milk IgE &gt;0.35 kU/L with a positive milk challenge result to 2.5 g or less of milk protein. Exclusion: history of anaphylaxis requiring hospitalization, history of intubation related to asthma, or a current diagnosis of severe, persistent asthma.</td>
<td>Same as intervention group</td>
<td>Males: 8/13 (62%); mean age=9.3 years (SD=3.3)</td>
</tr>
<tr>
<td>Author</td>
<td>Intervention Group Selection Criteria</td>
<td>Control Selection Criteria</td>
<td>Subject demographics</td>
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</tr>
<tr>
<td><strong>Author</strong></td>
<td><strong>Inclusion/exclusion criteria</strong></td>
<td><strong>IgE</strong></td>
<td><strong>Skin Test</strong></td>
</tr>
<tr>
<td><strong>Nelson,</strong> 1997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>295</td>
<td>Adults with a history of immediate hypersensitivity reactions to peanuts</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Enrique,</strong> 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>299</td>
<td>Potential patients were preselected on a clear history of hazelnut food allergy and positive skin prick test. Inclusion: positive DBPCFC with hazelnuts. Exclusion: pregnancy, uncontrolled asthma, systemic corticosteroids, B-blockers, antihistamines, antidepressants, systemic disease/inflammation not compatible with the treatment</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Patriarca,</strong> 2007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>296</td>
<td>Consecutive children affected by food allergy (defined by clinical history, skin prick tests, serum total and specific IgE, and DBPCFC)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Specific immunotherapy with cross-reactive allergens**

| Hansen, 2004 |
| 300           | Inclusion: Rhino-conjunctivitis during birch pollen season, combined with birch pollen specific IgE, birch pollen positive SPT, and a positive conjunctival provocation test to birch pollen using standardized extracts | Positive for birch pollen | Positive for birch pollen | No  | NR  | NR  | NR  |

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Table 45: Food allergy treatment/management controlled trials: patient characteristics (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Group Selection Criteria</th>
<th>Control Selection Criteria</th>
<th>Subject demographics</th>
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<tbody>
<tr>
<td></td>
<td>Inclusion/exclusion criteria</td>
<td>IgE</td>
<td>Skin Test</td>
</tr>
<tr>
<td>Bucher, 2004&lt;sup&gt;301&lt;/sup&gt;</td>
<td>Inclusion: oral allergy syndrome induced by apple or hazelnut with a positive SPT to birch pollen AND hazelnut or apple</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Asero, 1998&lt;sup&gt;302&lt;/sup&gt;</td>
<td>Inclusion: clear history of oral allergy syndrome</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bernadini, 2006&lt;sup&gt;303&lt;/sup&gt;</td>
<td>Inclusion: age above 4 years and below 16 with a clinical history of urticaria, rhino-conjunctivitis, and/or asthma due to natural rubber latex (NRL). Exclusion: anaphylactic shock, immunosuppressive treatment, severe immunological diseases, and dermatographism</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bindslev-Jensen, 1991&lt;sup&gt;315&lt;/sup&gt;</td>
<td>Patients with birch pollen allergy. Inclusion: case history of immediate local symptoms (itching and swelling of mouth/throat) Exclusion: anamnestic severe reaction after intake of hazelnuts</td>
<td>NR</td>
<td>All had positive skin prick test to birch pollen, but only 15 had a positive SPT to hazelnut</td>
</tr>
</tbody>
</table>

Pharmacological management

<table>
<thead>
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</tbody>
</table>
Table 45: Food allergy treatment/management controlled trials: patient characteristics (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Group Selection Criteria</th>
<th>Control Selection Criteria</th>
<th>Subject demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion/exclusion criteria</strong></td>
<td><strong>IgE</strong></td>
<td><strong>Skin Test</strong></td>
<td><strong>Clinical reaction</strong></td>
</tr>
<tr>
<td>Burks, 1988318</td>
<td>Inclusion: atopic dermatitis as defined by Hanifin and Rajka, all had positive SPT, all were on a strict egg-avoidance diet for 1 year, antihistamines were stopped 1 week before trial and beta-agonists were stopped 12 hours before trial, Exclusion: renal, hepatic, or cardiovascular disease, known tolerance to cromolyn, female patients of child-bearing potential, or a history of life-threatening anaphylactic reaction to egg</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Schaeffer, 2008319</td>
<td>Inclusion: patients between 1 and 18 years of age diagnosed with EE as defined as esophageal mucosal biopsy specimen showing ( \geq 15 ) eos/hpf, Exclusion: co-existing esophageal conditions (stricture, Barrett’s, caustic injury), H. pylori infection, IBD, inability to tolerate corticosteroids</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Szajewska, 2007321</td>
<td>Inclusion: rectal bleeding diagnosed as the presence of blood-streaked normal-to-soft stools, exclusive breast feeding, age &lt; 6 months. Exclusion: infectious origin of rectal bleeding (pathogenic bacteria/C. diff), necrotizing enterocolitis, and coagulopathies</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Leung, 2003316</td>
<td>Inclusion: Serum total IgE between 30 and 1000 IU/mL, good health, body weight within 20% of ideal,</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Author</td>
<td>Intervention Group Selection Criteria</td>
<td>Control Selection Criteria</td>
<td>Subject demographics</td>
</tr>
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</tr>
<tr>
<td></td>
<td>Inclusion/exclusion criteria</td>
<td>IgE</td>
<td>Skin Test</td>
</tr>
<tr>
<td>Cavagni, 1989&lt;sup&gt;317&lt;/sup&gt;</td>
<td>positive SPT to peanut and negative SPT to tuna oil, no prior exposure to monoclonal AB, Exclusion: pregnancy, uncontrolled asthma</td>
<td>No</td>
<td>Yes-used to determine which foods to evaluate</td>
</tr>
<tr>
<td>Businco, 1986&lt;sup&gt;320&lt;/sup&gt;</td>
<td>Children with a food allergy manifesting as atopic dermatitis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Children &lt; 12 years old with severe eczema requiring continuous therapy but no steroids and exacerbation of symptoms from food allergy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 45: Food allergy treatment/management controlled trials: patient characteristics (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Group Selection Criteria</th>
<th>Control Selection Criteria</th>
<th>Subject demographics</th>
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<tbody>
<tr>
<td></td>
<td>Inclusion/exclusion criteria</td>
<td>IgE</td>
<td>Skin Test</td>
</tr>
<tr>
<td>Hill, 2005&lt;sup&gt;322&lt;/sup&gt;</td>
<td>Inclusion: exclusively breast fed infants &lt;6 weeks of age with colic, term infants (&gt;37 weeks), normal singleton pregnancy, uneventful perinatal history, no perinatal morbidity other than distress. Exclusion: mothers on strict vegan diets</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Amadi, 2002&lt;sup&gt;323&lt;/sup&gt;</td>
<td>No specific food allergies were diagnosed, but the thought was that underlying cow’s milk allergy might be exacerbating the problem. Exclusion criteria: measles, chicken pox, neurologic disorders, and those that were exclusively breast-fed</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cantani, 2006&lt;sup&gt;324&lt;/sup&gt;</td>
<td>Inclusion: children with severe atopic dermatitis and suspected cow’s milk allergy on the basis of personal history and positive SPT to cow milk and egg</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Table 45: Food allergy treatment/management controlled trials: patient characteristics (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Group Selection Criteria</th>
<th>Control Selection Criteria</th>
<th>Subject demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inclusion/exclusion criteria</td>
<td>IgE</td>
<td>Skin Test</td>
</tr>
<tr>
<td>Salpietro, 2005</td>
<td>Infants aged 5 to 9 months with histories and symptoms suggestive of food allergy. Diagnosis of CMA was confirmed by personal and family history, physical exam, improvement on milk free diet and symptom relapse by milk challenge, SPT, and RAST. Excluded low birth weight &lt;3kg, intrauterine growth retardation, congenital anomalies, and significant perinatal medical complication. Also excluded subjects with +RAST to aeroallergens.</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Viljanen, 2005</td>
<td>Inclusion: infants under 12 months upon entering the study, symptoms suggestive of cow’s milk allergy, obligatory atopic eczema/dermatitis Exclusion: No probiotic preparations used longer than 1 week and within 6 weeks of entering the study</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Table Notes:** CMA cow’s milk allergy; DBPCFC double blind placebo-controlled food challenge; GI gastrointestinal; NRL natural rubber latex; OAS oral allergy syndrome; RAST radioallergosorbent test; SCORAD scoring atopic dermatitis; SD standard deviation; sIgE antigen-specific immunoglobulin; SPT skin prick test
### Table 46: Food allergy treatment/management controlled trials: intervention characteristics and outcomes reported

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Description</th>
<th>Timing Info</th>
<th>Sample Size</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergen avoidance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agata, 1993²⁹¹</td>
<td>Elimination diet of allergic food: egg or milk</td>
<td>No elimination diet</td>
<td>&gt;= 3 months</td>
<td>Improvement of atopic dermatitis; specific IgE antibodies; proliferative responses of PBMCs</td>
</tr>
<tr>
<td><strong>Allergen-specific immunotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staden, 2007²⁹³</td>
<td>Assigned to specific oral tolerance induction with both an induction and maintenance phase. Patients then underwent an elimination diet for 2 months prior to follow-up food challenge</td>
<td>Elimination diet median follow-up: 21 months (18-24)</td>
<td>25 20</td>
<td>Tolerance as defined by either complete or partial allergen specific IgE</td>
</tr>
<tr>
<td>Morisset, 2007²⁹⁴</td>
<td>Oral desensitization with whole pasteurized milk for those with cow’s milk allergy, in weekly increasing doses. Oral desensitization with hard-boiled eggs for those with egg allergy, in weekly increasing doses</td>
<td>Continued avoidance of either milk or egg</td>
<td>Milk: 28</td>
<td>Single blind placebo controlled food challenge; skin prick test wheals; IgE level</td>
</tr>
<tr>
<td>Skripak, 2007²⁹²</td>
<td>Immunotherapy dose schedule that was initiated in the clinic and then patient continued with maximum tolerated dose at home for 7-14 days. The patient returned to the clinic to get a dose increase. Once a dose of 500 mg (=15mL of milk) was achieved, patient continued on that dose for 13 weeks.</td>
<td>Placebo instead of immunotherapy dose</td>
<td>23 weeks</td>
<td>Milk threshold; median end-point titration SPT milk-specific IgE; milk IgG levels; reactions to doses</td>
</tr>
<tr>
<td>Nelson, 1997²⁹⁵</td>
<td>Injections of peanut extract—a maintenance level of tolerance was first achieved by a rush protocol, then maintained with weekly injections for at least a year. Maximum projected dose of 0.5 mL of 1:100 wt/vol peanut extract</td>
<td>No treatment</td>
<td>6 weeks</td>
<td>Threshold to oral peanut challenge; cutaneous reactivity to peanut challenge; peanut-specific IgE and IgG</td>
</tr>
<tr>
<td>Enrique, 2005²⁹⁹</td>
<td>Biologically standardized hazelnut extract given in increasing concentrations for 5 days.</td>
<td>Saline solution in vials with exactly the same appearance, color, and taste but without allergens</td>
<td>12 weeks</td>
<td>Quantity of hazelnut provoking objective symptoms; hazelnut specific IgE; hazelnut specific IgG4; IL-10</td>
</tr>
</tbody>
</table>
Table 46: Food allergy treatment/management controlled trials: intervention characteristics and outcomes reported (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention description</th>
<th>Timing info</th>
<th>Sample size</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Experimental</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Experimental</td>
<td>Control</td>
</tr>
<tr>
<td>Patriarca, 2007²⁹⁶</td>
<td>Desensitization per a protocol to the food(s) to which each person was allergic--increasing in dose every 3 days. If an adverse reaction was noted, H-2 blocker or cromolyn was given 20 minutes before the desensitization. Patients were then asked to eat the allergenic food at least 2x week.</td>
<td>Continued elimination diet to allergic food(s)</td>
<td>18 months</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific immunotherapy with cross-reactive allergens</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hansen, 2004³⁰⁰</td>
<td>Sublingual or subcutaneous birch pollen extract</td>
<td>2 years</td>
<td>Sublingual=12;</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>subcutaneous=16</td>
<td></td>
</tr>
<tr>
<td>Bucher, 2004³⁰¹</td>
<td>Subcutaneous immunotherapy with tree pollen extract</td>
<td>1 year</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Asero, 1998³⁰²</td>
<td>Injection of specific immunotherapy for both induction and maintenance phases; group divided to receive treatment for either 12, 24, or 36 months</td>
<td>12, 24 or 36 months</td>
<td>at 12 months n=12, at 24 months n=21, at 36 months n=13</td>
<td>Group 1: at 12 months n=7, at 24 months n=5, at 36 months, n=11. Group 2: at 12 months n=8, at 24 months n=4, at 36 months n=3</td>
</tr>
<tr>
<td>Author</td>
<td>Intervention description</td>
<td>Timing info</td>
<td>Sample size</td>
<td>Outcomes reported</td>
</tr>
<tr>
<td>--------</td>
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</tr>
<tr>
<td>Bernadini, 2006&lt;sup&gt;303&lt;/sup&gt;</td>
<td>Given a natural rubber latex extract for sublingual administration with a build up phase and maintenance phase for 12 months</td>
<td>1 year</td>
<td>12</td>
<td>Placebo: 8; control: 6</td>
</tr>
<tr>
<td></td>
<td>Placebo group: placebo; control group: nothing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmacologic management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bindslev-Jensen, 1991&lt;sup&gt;315&lt;/sup&gt;</td>
<td>Patients given two open oral provocations of five hazelnuts (at least 2 days apart). Then the treatment group ingested aztemizole 10 mg each morning for 14 days followed by 2 open oral provocations</td>
<td>Placebo</td>
<td>14 days</td>
<td>15</td>
</tr>
<tr>
<td>Author</td>
<td>Intervention description</td>
<td>Timing info</td>
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</tr>
<tr>
<td>------------------------</td>
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<td>------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Burks, 1988&lt;sup&gt;318&lt;/sup&gt;</td>
<td>Patients were treated for a week with cromolyn or placebo and then evaluated. They then had a washout period of 3-5 weeks. The patients then crossed over to the other arm for a week and were again evaluated.</td>
<td>Placebo (cross-over trial)</td>
<td>1 week</td>
<td>10 NR Symptom cards assessed on a scale of 0-3 for rash distribution, pruritis, urticaria, sneezing/itching, congestion, rhinorrhea, wheezing, nausea/pain, and vomiting/diarrhea; response to DBPCFC</td>
</tr>
<tr>
<td>Schaefer, 2008&lt;sup&gt;319&lt;/sup&gt;</td>
<td>Oral prednisone (1 mg/kg) bid</td>
<td>Fluticasone by MDI 2 puffs 4x daily</td>
<td>40</td>
<td>40 Primary endpoint: histological response by an improvement in biopsy grade after 4 weeks of corticosteroid therapy. Secondary endpoint: defined as clinical response to corticosteroids based on the presence or absence of the presenting symptom.</td>
</tr>
<tr>
<td>Szajewska, 2007&lt;sup&gt;321&lt;/sup&gt;</td>
<td>Mothers eliminated cow milk from their diet and infants received lactobacillus hhamnosus GG</td>
<td>Mothers eliminated cow milk from their diet and infants received placebo</td>
<td>Treatment period: 4 weeks</td>
<td>11</td>
</tr>
<tr>
<td>Leung, 2003&lt;sup&gt;316&lt;/sup&gt;</td>
<td>3 groups receiving different doses of TNX-901 (150 mg, 300 mg, 450 mg), a humanized IgG1 monoclonal antibody against IgE</td>
<td>Placebo</td>
<td>6-8 weeks</td>
<td>150 mg--19; 300 mg--19; 450 mg--21 Threshold of sensitivity to peanut on oral food challenge</td>
</tr>
</tbody>
</table>
### Table 46: Food allergy treatment/management controlled trials: intervention characteristics and outcomes reported (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions description</th>
<th>Timing info</th>
<th>Sample size</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavagni, 1989</td>
<td>Food to which a positive prick test was found was excluded from the diet for 90 days. During this period, treatment group received 120 mg/day of thymomodulin as syrup</td>
<td>Same as experimental group but received placebo rather than thymomodulin</td>
<td>Experimental: 10; Control: 9</td>
<td>Dermatologic condition based on &quot;The Italian Group of Pediatric Immunology&quot;; WBC; differential leukocyte count; T-cell subsets; total IgE; specific IgE; favourable change in skin lesions after 2 weeks of oral challenge in the thymomodulin group</td>
</tr>
<tr>
<td>Businco, 1986</td>
<td>Cross-over trial in which children underwent a washout elimination diet followed by on-going elimination diet with either placebo or sodium cromoglycate. Subjects then crossed into the other arm (placebo vs sodium cromoglycate)</td>
<td>Same as experimental description</td>
<td>Experimental: 31; Control: 31</td>
<td>Changes in severity of eczema</td>
</tr>
<tr>
<td>Hill, 2005</td>
<td>Maternal diet that was low allergen, excluding dairy products, soy, wheat, eggs, peanuts, tree nuts, and fish</td>
<td>Regular diet including 7 day supply of cow and soy powder, 1 serving of peanuts, 1 serving of wheat, and 1 chocolate muesli bar/day</td>
<td>Experimental: 47; Control: 43</td>
<td>Improvement of &gt;25% of cry/fuss for a duration &gt;360 min per 48 hours comparing days 1 and 2 with days 8 and 9 (after completion of the diet)</td>
</tr>
<tr>
<td>Amadi, 2002</td>
<td>Malnourished children to receive 4 weeks of standard skimmed milk/soy diet</td>
<td>Malnourished children to receive Neocate for 4 weeks</td>
<td>Experimental: 100; Control: 100</td>
<td>Weight gain; hemoglobin; serum albumin; diarrhea, activity; developmental milestones</td>
</tr>
<tr>
<td>Cantani, 2006</td>
<td>Elimination diet for 4-6 weeks, followed by 2 months of Rezza's diet</td>
<td>Continued the usual elimination diets for suspected cow’s milk</td>
<td>Experimental: 25; Control: 26</td>
<td>SCORAD; weight; open challenge test</td>
</tr>
</tbody>
</table>

**Other management strategies for food allergies**

- **Hill, 2005**
  - Maternal diet that was low allergen, excluding dairy products, soy, wheat, eggs, peanuts, tree nuts, and fish
  - Regular diet including 7-day supply of cow and soy powder, 1 serving of peanuts, 1 serving of wheat, and 1 chocolate muesli bar/day
  - Diet was followed for 7 days and then the infants underwent an 48 hours cry/fuss chart
  - Experimental: 47; Control: 43
  - Improvement of >25% of cry/fuss for a duration >360 min per 48 hours comparing days 1 and 2 with days 8 and 9 (after completion of the diet)

- **Amadi, 2002**
  - Malnourished children to receive 4 weeks of standard skimmed milk/soy diet
  - Malnourished children to receive Neocate for 4 weeks
  - Experimental: 100; Control: 100
  - Weight gain; hemoglobin; serum albumin; diarrhea, activity; developmental milestones

- **Cantani, 2006**
  - Elimination diet for 4-6 weeks, followed by 2 months of Rezza's diet
  - Continued the usual elimination diets for suspected cow's milk
  - Experimental: 25; Control: 26
  - SCORAD; weight; open challenge test
<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention description</th>
<th>Timing info</th>
<th>Sample size</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salpietro, 2005325</td>
<td>Group A received almond milk; Group B received soy based formula; Group C received protein based formula</td>
<td>6 months</td>
<td>13</td>
<td>Weight; length; head circumference; serum levels of soluble CD30 (cytokine associated with atopy)</td>
</tr>
<tr>
<td></td>
<td>&quot;Formula fed&quot; not otherwise specified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Almond milk: 26; Soy formula: 13; Protein formula: 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viljanen, 2005326</td>
<td>Elimination diet and skin treatment with 4 weeks of lactobacillus or a mixture of lactobacillus and other probiotics</td>
<td>4 weeks</td>
<td>32</td>
<td>SCORAD</td>
</tr>
<tr>
<td></td>
<td>Elimination diet and skin treatment with 4 weeks of placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactobacillus alone: 44; Mixture: 44</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table Notes:** DBPCFC double blind placebo-controlled food challenge; GG NRL natural rubber latex; IgG Immunoglobulin G; OAS oral allergy syndrome; SCORAD scoring atopic dermatitis; SD standard deviation; sIgE antigen-specific immunoglobulin; PBMCs Peripheral Blood Mononuclear Cells; SPT skin prick test; WBC white blood cells
<table>
<thead>
<tr>
<th>Symptom/Treatment</th>
<th>Study</th>
<th>Number/total doses (%)* or number/patient (%)** in immunotherapy group</th>
<th>Number/total doses (%)* or number/patient (%)** in control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Reactions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skripak, 2008²⁹²</td>
<td>1107/2437 (45.4)*</td>
<td>134/1193 (11.2)*</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Staden, 2007²⁹³</td>
<td>25/25 (100)**</td>
<td>6/20 (30.0)**</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Hofmann, 2009²¹¹</td>
<td>93% (77%-99%)***</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Hofmann, 2009²¹¹</td>
<td>46% (37%-56%)***</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Hofmann, 2009²¹¹</td>
<td>3.5% (2.3%-5.1%)***</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Local Symptoms</strong></td>
<td>Skripak, 2008²⁹²</td>
<td>870/2437 (35.7)*</td>
<td>104/1193 (8.7)*</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Narisety, 2009²¹²</td>
<td>419/2465 (17)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Enrique, 2005²⁹⁹</td>
<td>109/1466 (7.6)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Bernardini, 2006³⁰³</td>
<td>0/12 (0)**</td>
<td>0/8 (0)**</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Skripak, 2008²⁹²</td>
<td>458/2437 (18.7)*</td>
<td>16/1193 (1.3)*</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Narisety, 2009²¹²</td>
<td>90/2465 (3.7)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Staden, 2007²⁹³</td>
<td>15/25 (60.0)**</td>
<td>3/30 (10.0)**</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Enrique, 2005²⁹⁹</td>
<td>4/12 (33.3)**</td>
<td>8/65 (12.3)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Bernardini, 2006³⁰³</td>
<td>0/12 (0)**</td>
<td>0/8 (0)**</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Hofmann, 2009²¹¹</td>
<td>68% (48%-84%)***</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Hofmann, 2009²¹¹</td>
<td>5.5% (3.2%-9.2%)***</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Hofmann, 2009²¹¹</td>
<td>0.9% (0.6%-1.4%)***</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Lower respiratory</strong></td>
<td>Skripak, 2008²⁹²</td>
<td>198/2437 (8.1)*</td>
<td>28/171 (2.3)*</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Staden, 2007²⁹³</td>
<td>2/25 (9.0)**</td>
<td>0/20 (0)**</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Narisety, 2009²¹²</td>
<td>21/2465 (0.9)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Morisset, 2007²⁹⁴</td>
<td>2/76 (2.6)**</td>
<td>3/65 (4.6)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Skin (eczema and urticaria)</strong></td>
<td>Skripak, 2008²⁹²</td>
<td>22/2437 (0.9)*</td>
<td>1/1193 (0.1)*</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Narisety, 2009²¹²</td>
<td>20/2465 (0.8)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Staden, 2007²⁹³</td>
<td>24/25 (96.0)**</td>
<td>5/20 (25.0)**</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Morisset, 2007²⁹⁴</td>
<td>3/76 (3.9)**</td>
<td>6/65 (9.2)**</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Enrique, 2005²⁹⁹</td>
<td>1/12 (8.3)**</td>
<td>1/11 (9.1)**</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Hofmann, 2009²¹¹</td>
<td>61% (41%-79%)***</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Hofmann, 2009²¹¹</td>
<td>24% (17%-32%)***</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Hofmann, 2009²¹¹</td>
<td>1.1% (0.7%-1.8%)***</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Angioedema</strong></td>
<td>Staden, 2007²⁹³</td>
<td>4/25 (16.0)**</td>
<td>0/20 (0)**</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Morisset, 2007²⁹⁴</td>
<td>3/76 (3.9)**</td>
<td>4/65 (6.2)**</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Cardiovascular (not ...</strong></td>
<td>Staden, 2007²⁹³</td>
<td>0/25 (0)**</td>
<td>1/25 (4%)</td>
<td>NR</td>
</tr>
<tr>
<td>Drug Used to Treat Reaction</td>
<td>Study Year</td>
<td>Doses Used</td>
<td>Number of Doses</td>
<td>Percentage (Dose)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------</td>
<td>------------</td>
<td>-----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Multiple systems (not further defined)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skripak, 2008</td>
<td></td>
<td></td>
<td>29/2437 (1.2)*</td>
<td>0/1193 (0)*</td>
</tr>
<tr>
<td>Enrique, 2005</td>
<td></td>
<td>3/1466 (0.2)*</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Diphenhydramine used to treat reaction</strong></td>
<td></td>
<td></td>
<td>249/2437 (10.2)*</td>
<td>14/1193 (1.1)*</td>
</tr>
<tr>
<td>Nariset, 2009</td>
<td>2012</td>
<td>93/2465 (3.8)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td>Hofmann, 2009</td>
<td>2011</td>
<td>20/28 (71)**</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td>Hofmann, 2009</td>
<td>2011</td>
<td>5/301 (1.7)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td>Hofmann, 2009</td>
<td>2011</td>
<td>65/10184 (0.6)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Albuterol used to treat reaction</strong></td>
<td></td>
<td></td>
<td>21/2437 (0.9)*</td>
<td>2/1193 (0.2)*</td>
</tr>
<tr>
<td>Nariset, 2009</td>
<td>2012</td>
<td>12/2465 (0.5)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td>Hofmann, 2009</td>
<td>2011</td>
<td>3/28 (11)**</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td>Hofmann, 2009</td>
<td>2011</td>
<td>2/301 (0.7)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td>Hofmann, 2009</td>
<td>2011</td>
<td>24/10184 (0.2)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Epinephrine used to treat reaction</strong></td>
<td></td>
<td></td>
<td>4/2437 (0.2)*</td>
<td>0/1193 (0)*</td>
</tr>
<tr>
<td>Nariset, 2009</td>
<td>2012</td>
<td>4/2437 (0.2)*</td>
<td>0/1193 (0)*</td>
<td>0.1</td>
</tr>
<tr>
<td>Hofmann, 2009</td>
<td>2011</td>
<td>4/2465 (0.2)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td>Hofmann, 2009</td>
<td>2011</td>
<td>4/28 (14)**</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td>Hofmann, 2009</td>
<td>2011</td>
<td>0/301 (0)*</td>
<td>No control</td>
<td>NR</td>
</tr>
<tr>
<td>Zapatero, 2008</td>
<td>2008</td>
<td>2/18 (11)**</td>
<td>No control</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Some studies reported per dose, some reported per patient, and some had mixed depending on the symptom (per dose or per patient).
Key Question I. What methods are currently used to manage patients diagnosed with non-IgE-mediated reactions to food, and how do they differ from methods used to manage patients diagnosed with IgE-mediated food allergy?

The literature cannot readily be divided on the basis of IgE-mediated and non-IgE mediated reactions. In the relevant tables, we describe IgE-mediated reactions reported by the included prevention (Table 40) and management/treatment trials (Table 44). We also describe the use of IgE testing as inclusion criteria and the effects of interventions on both allergen specific and total IgE (e.g., see description of the RCT by Klemola et al.313 on the use of soy milk formula in children with cow’s milk allergy syndrome (Table 50).

Key Question J. What are the appropriate methods of diagnosis and treatment of acute and life-threatening, IgE-mediated food allergic reactions?

Background
Anaphylaxis is an acute multi-system and severe type-I allergic hypersensitivity reaction. After an initial exposure to a substance, the person's immune system becomes sensitized to that allergen. On a subsequent exposure, an allergic reaction occurs. This reaction is sudden, severe, and involves the whole body.

Results
No studies specifically described the diagnosis of these serious reactions to food. Also, we found no RCTs involving anaphylaxis, but we did identify three cohort studies (Table 48-Table 50).328-331

Jarvinen et al.328 distributed questionnaires to families of children with food allergies to help determine the rate, circumstances, and risk factors for repeated doses of epinephrine in the treatment of food-induced anaphylaxis (Table 48-Table 50). The population they targeted was from a hospital-based pediatric allergy clinic and a private practice-based pediatric food allergy referral clinic at Mount Sinai Hospital, New York. Of 542 distributed questionnaires, 512 (94 percent) were returned, and 413 were included (exclusions were for incomplete data, no documented food allergy, or age >18). They found that peanut, tree nut, and cow’s milk allergy were responsible for more than 75 percent of the reactions requiring epinephrine. They also found that patients requiring multiple doses of epinephrine more often had asthma (p=0.027) and that 19 percent of food-induced anaphylactic reactions were treated with more than one dose of epinephrine.

de Silva et al.329 performed a retrospective case study to describe the demographic characteristics, clinical features, causative agents, settings, and administered therapy in children presenting with anaphylaxis to an Emergency Department in Royal Children's Hospital, Melbourne (Table 48-Table 50). In 117 patients, the median age of presentation was 2.4 years, and food (85 percent) was the most common trigger and respiratory symptoms were the most common clinical presentation (97 percent). Peanut (18 percent) and cashew nut (13 percent) were
the most common causes of anaphylaxis. Adrenaline (subcutaneous, intravenous, and intramuscular) was used in 94/123 cases (76 percent) with the median time to administration of 40 minutes (range 23-78). Steroids were used in 95/123 cases (77 percent) with the median time to administration of 80 minutes (range 66-138) and antihistamines were used in 73/123 cases (59 percent) with the median time to administration of 90 minutes (range 42-132). The admission rate was 83 percent (102/12) and the median length of stay after admission was 17 hours (range 12-22).

Pouessel et al.\textsuperscript{330} performed a prospective study to assess which food allergies children who used an Anapen (an injectable epinephrine) suffered from. They sent questionnaires to families with food-allergic children (Table 48-Table 50). The questionnaires were sent to patients previously prescribed the Anapen device between June 2000 and March 2003. These children were cared for by pediatricians or allergists working in (and referring patients to) five children’s hospitals. The response rate was 73 percent. Of the 111 included children, the main food allergens were peanuts (n=89), egg (n=39), and cow’s milk (n=10).

**Summary**

There are few data on effective strategies for the prevention or management of life-threatening food allergies. In three published studies, anaphylaxis reaction to food allergy is seen most frequently in patients with a peanut allergy—however the literature is insufficient to reach conclusions regarding methods to prevent or treat this reaction.
Table 48: Cohort studies on anaphylaxis: study information

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Purpose</th>
<th>Food</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Silva, 2008³²⁹</td>
<td>Australia</td>
<td>To describe demographic characteristics, clinical features, causative agents, settings and administered therapy in children presenting with anaphylaxis.</td>
<td>Egg, cow milk, peanut, nut, fruit, vegetable, soy, rice, wheat</td>
</tr>
<tr>
<td>Pousse, 2006³³⁰</td>
<td>France</td>
<td>To determine the use of Anapen prescribed for food-allergic children; to assess parental knowledge regarding Anapen; to evaluate the arrangements for emergency kits and personalized care projects in everyday life.</td>
<td>Peanut, egg, cow milk, nut, corn mustard, fish</td>
</tr>
<tr>
<td>Jarvinen, 2008³²⁸</td>
<td>US</td>
<td>To determine the rate, circumstances, and risk factors for repeated doses of epinephrine in the treatment of food-induced anaphylaxis in children.</td>
<td>Peanut, tree nut, hen’s egg, cow milk, soybean, wheat, shellfish, fish</td>
</tr>
</tbody>
</table>

Table 49: Cohort studies on anaphylaxis: patient characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Group Selection Criteria</th>
<th>IgE</th>
<th>Skin Test</th>
<th>Clinical reaction</th>
<th>Intervention Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Silva, 2008³²⁹</td>
<td>Clinical history of anaphylaxis or generalized allergic reaction</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Median age: 2.4 years</td>
</tr>
<tr>
<td>Pousse, 2006³³⁰</td>
<td>Families of children that had previously used the ANAPEN (injection epi)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Median age: 6.5 years</td>
</tr>
<tr>
<td>Jarvinen, 2008³²⁸</td>
<td>Parents/caregivers of consecutive patients presenting for evaluation for food allergy to the pediatric allergy clinic and to private practice-based pediatric food allergy referral clinic at Mount Sinai Hospital, NY</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Male: 63%; median age: 4.5 years (0.5-17.5)</td>
</tr>
</tbody>
</table>

Table 50: Cohort studies on anaphylaxis: intervention characteristics and outcomes reported

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention description</th>
<th>Timing info</th>
<th>Sample size</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Silva, 2008³²⁹</td>
<td>Chart review to see the clinical course of patients admitted to a children's ER with anaphylaxis</td>
<td>Conducted from 1 June 1998 to 30 June 2003</td>
<td>117</td>
<td>1 death; home most common setting (48%); food (85%) most common trigger; peanut (18%) and cashew nut (13%) most common cause of anaphylaxis; median time from exposure to anaphylaxis for all agents was 10 min; median time from onset to therapy was 40 min; respiratory features principal presenting symptoms (97%); 17% had experienced anaphylaxis previously.</td>
</tr>
<tr>
<td>Pousse, 2006³³⁰</td>
<td>Questionnaire sent to families with children with history of anaphylaxis who had previously used anapen</td>
<td>June 2000-March 2003</td>
<td>111</td>
<td>Main food allergens were peanuts (n=89), egg (n=39) and cow’s milk (n=10).</td>
</tr>
<tr>
<td>Jarvinen, 2008³²⁸</td>
<td>Anonymous questionnaires were distributed to families of children with food allergies during allergy outpatient visits to a food allergy referral center.</td>
<td>Between September 2006 and February 2007.</td>
<td>413</td>
<td>Peanut, tree nut and cow’s milk allergy responsible for &gt;75% of the reactions requiring epinephrine; patients requiring multiple doses of epinephrine often had asthma (p=0.027); 19% of food-induced anaphylactic reactions were treated with &gt;1 dose of epinephrine; soybean allergy accounted for 107/413 (26%) of reactions and peanut allergy 290/413 (70%) of anaphylactic reactions.</td>
</tr>
</tbody>
</table>
Evidence for the Prevention, Treatment, or Management of Specific Food Allergies

Most of the included studies evaluated multiple foods and included patients who were allergic to several foods. The most common foods evaluated in the included trials were peanuts and tree nuts, cow’s milk, hen’s egg, and apple (Figure 11). The tables for this section only provide data not already previously presented in the other evidence tables (Table 51-Table 53).

Prevention, Treatment, Management of Cow’s Milk Allergy

Background
Cow milk protein allergy is the most common food allergy in children—some reports estimate that cow’s milk allergy or intolerance occur in two percent to seven percent of children aged 3 or younger. While many infants outgrow this allergy, people of all ages with gastrointestinal tract disease may have difficulty digesting these proteins and may absorb them as antigens.

Results
We identified 16 studies reported in 18 articles that focused on cow’s milk allergy. Those studies not previously presented in an evidence table are described in Table 51-Table 53. We note that there is considerable overlap between this section and the results presented for Key Questions H.i.c. and H.i.d (on breastfeeding and special diets in infants and children). We have organized this section according to the types of interventions but present study results according to the key outcomes reported.

Early exposure to cow’s milk
Several authors have addressed the issue of whether exposure to cow’s milk in infancy result in increased or decreased allergic disease later in life. The BOKAAL study group of Utrecht, The Netherlands randomized 1,533 newborns to either a brief exposure to cow’s milk protein or placebo in the first few days of life and compared their subsequent rates of atopic disease up to five years later. Symptom outcome: They found no difference in atopic disease or wheezing in children exposed to cow’s milk protein early in life. Lab outcome: There was no difference in specific IgE outcomes between the groups.

In contrast, Lindfors et al. randomized 207 term but low weight infants to receive cow’s milk formula in the first few days of life before initiation of full breastfeeding or breast milk only and followed them for four to six years to evaluate the rate of allergic symptoms in childhood. They reported that 9/95 (9.5%) children who had received cow’s milk and 9/88 (10.2%) children who had been exclusively breast fed had evidence of obvious allergic disease at age 4-6 years (and 16/95 (16.8%) vs 18/88 (20.5%) had suspected allergic disease). Symptom outcome: They conclude that there may be a protective effect of the introduction of cow’s milk prior to breast feeding, although the differences seen were not statistically significant.

Given the conflicting evidence and the fact that neither study controlled for exposure to cow’s milk proteins later in life or exposure to other allergens, we conclude that benefits and harms of early neonatal exposure to cow’s milk remains uncertain.
Breastfeeding vs. cow’s milk formula

Two analyses of data from the same study population randomized participants to either exclusive breastfeeding or partial or complete cow milk formula and compared their incidence of atopic dermatitis. Schoetzau et al. reported results on a sub-group of infants who were part of the GINI cohort study and found a significantly lower risk of atopic dermatitis at one year of age in infants who were exclusively breastfed compared to infants who were not (9.5% versus 14.8%, respectively, p=0.015). **Symptoms outcome:** Their logistic regression model found that the risk of AD was reduced by nearly 50% in the exclusively breastfed group, after adjusting for atopic risk factors and other confounders such as parent education, gender, pet keeping and maternal smoking (adjusted OR 0.47, 95% CI 0.3-0.74). They also conducted analysis to determine the effect of delayed introduction of solid foods between the two groups but did not find a significant effect modification of either age at first introduction (Wald-Chi square p=0.58) or diversity of foods (p=0.89). The analysis conducted in this paper differed from that by Filippiak et al. who conducted a similar analysis using the infant population from the GINI study. Schoetzau et al. compared differences based on exclusive breastfeeding or not in only intervention group infants of the GINI study whereas the Filippiak study compared breastfeeding, use of hydrolysed formulas, and delayed introduction of solid foods in intervention group infants to a separate control group of infants that did not receive these recommendations. **Symptom outcome:** They concluded that there was no evidence to support a protective effect of delayed introduction of solids for eczema.

Odelram compared whey hydrolysate and cow’s milk formula to strict breastfeeding in the prevention of atopic disease of infants. Inclusion criteria were at least two atopic family members or one atopic parent and total cord blood IgE >0.5 kU/I. Exclusion criteria were gestational age below 37 weeks, complicated delivery, neonatal illness, severe birth defects, or documented or expected noncompliance with diet prescription. **Symptom outcome:** Presence of atopic disease was 10/25 in the infants fed extensively hydrolyzed formula, 15/32 in the infants fed cow milk formula, and 3/13 in those who were breastfed. No statistical difference in the presence of atopic disease was found. **Lab outcome:** There was no significant difference in positive SPT or in sIgE at 18 months.

Cow’s milk vs. substitute milks

Several studies evaluated replacing cow’s milk with other milks. For example, Vita et al. assessed the tolerability and clinical effect of ass's milk compared with goat's milk in children with atopic dermatitis from cow’s milk allergy. **Symptom Outcome:** Ass milk significantly improved both the SCORAD index and the visual analog scale (p<0.03) where goat milk had no effect. Iacono et al. compared cow milk and soy milk in children with chronic constipation. **Symptom outcome:** Soy milk significantly increased the number of bowel movements (p<0.001). Salpietro et al. performed a RCT to evaluate the safety and efficacy of almond milk in infants with cow’s milk allergy. **Symptom outcome:** They reported reductions in a variety of symptoms (e.g., vomiting, diarrhea, wheezing, eczema) among children taken off cow’s milk but no difference in those given almond milk compared to soy-based formula or hydrolyzed formula. **Nutritional outcome:** They reported a reduction in weight gain among all infants taken off cow’s milk but no difference among those given almond milk compared to soy-based formula or hydrolyzed formula.


Reactions to various formulas

The RCT by Klemola et al.\textsuperscript{313} evaluated the incidence of adverse reactions or allergies to soy formulas in infants with cow’s milk allergy syndrome during the first two years of life. **Symptom outcome:** Parents’ suspicions of adverse reactions to formula was significantly higher among children who had received soy formula (28 percent, 95% CI 18-39 percent) than children who had received extensively hydrolyzed formula (11 percent, 95% CI 5-19 percent). The cumulative incident of adverse reactions confirmed by DBPCFC was lower for both the soy formula (8 infants: 10 percent, 95% CI 4.4-18.8 percent) and for the extensively hydrolyzed formula (2 infants: 2.2 percent; 95% CI 0.3-7.8 percent); but still statistically significantly greater in the soy formula group (relative risk =4.50, p =0.03). Adverse reactions to soy were suspected in 12 of 46 infants with IgE associated cow’s milk allergy and in 13 of 34 infants with non-IgE associated cow’s milk allergy (p=0.25). **Food challenge outcome:** Adverse reactions to soy were confirmed by DBPCFC in five of 46 (11 percent) infants with IgE associated cow’s milk allergy and in three of 34 (nine percent) infants with non-IgE associated cow’s milk allergy (p=0.76).

Niggemann et al.\textsuperscript{336} compared the tolerance and growth of infants with cow’s milk allergy who were fed a new extensively hydrolyzed formula containing lactose with those who were fed an amino acid formula. **Nutritional outcome:** They found no difference in tolerance or growth parameters. Garzi et al.\textsuperscript{337} studied extensively hydrolyzed cow milk formula in children with gastroesophageal reflux. **Symptom outcome:** Given the low number of patients with documented cow’s milk allergy, they were not able to statistically evaluate the gastric emptying time or gastroesophageal reflux symptoms. Savino et al.\textsuperscript{340} evaluated the growth of infants with atopic dermatitis and cow’s milk allergy fed a rice-hydrolysate formula compared with a soy or extensively hydrolyzed casein formula. **Nutritional outcome:** No significant differences in the z-score weight for age were found.

Jirapinyo et al\textsuperscript{333} prospectively randomized 38 infants and children (aged 2-24 months) with a diagnosis of cow’s milk allergy to 14 days of either soy formula or a formula made of chicken meat. **Symptom outcome:** They found that 12 of the 18 children who received the soy formula were intolerant to it compared to four of the 20 children who received the chicken-meat based formula (p=0.009) (although it is not clear if the assessment of “tolerance to the formula” was made by an investigator blinded to the treatment assignment).

Allergen-specific Immunotherapy

Several studies evaluated oral immunotherapy for cow’s milk. Morisset et al.\textsuperscript{294} performed a randomized study to examine an oral immunotherapy protocol in children with IgE-dependent milk or egg allergies. **Lab outcome:** When the oral desensitized group was compared to the continued avoidance group for milk allergy, a significant decrease in the size of the prick test wheal (p<0.002) was seen. **Food challenge outcome:** When the oral desensitized group was compared to the continued avoidance group for milk allergy, a significant improvement in SBPCFC was noted (3/27 vs 12/30 p<0.025). Patriarca et al.\textsuperscript{296} also evaluated oral immunotherapy protocols. **Food challenge outcome:** They found that 12/18 patients that underwent immunotherapy had a negative DBPCFC while 0/10 of the control patients had a negative DBPCFC.
Probiotics
Viljanen et al.326 studied probiotics in the treatment of infants with atopic eczema/dermatitis and suspected of cow’s milk allergy. In addition to skin treatment and elimination of cow’s milk from the infants’ and breast-feeding mothers’ diets, 252 infants were randomized to capsules containing lactobacillus alone, a mixture of probiotics including lactobacillus, or placebo for four weeks. There was no statistically significant change in the SCORAD scores.

Summary
The quality of evidence regarding the management of cow’s milk allergy is moderate given the amount of inconsistency across the studies; numerous RCTs report heterogeneous but generally favorable results for immunotherapy.

Prevention, Treatment, Management of Hen’s Egg Allergy

Background
Eggs are one of the most common allergy-causing foods. Although egg allergy can affect adults, it's more common in children. This allergy can be a challenge, as eggs and egg products are common food ingredients.

Results
We found nine RCTs and one observational study that specifically evaluated egg allergies either alone or in combination with other food allergies.

Delayed introduction of food
Halmerbauer et al.251 conducted an RCT on environmental procedures to reduce house dust-mites as well as an educational intervention to delay introduction of solid foods. They found a significantly reduced risk of parent reported food intolerance (vomiting, prolonged crying, diarrhea, or swollen lips after eating) in the intervention group. However, the study findings should be interpreted with caution with respect to the effect of delayed introduction of solids; the study was of fair quality and the multimodal nature of the intervention makes it difficult to evaluate the effect of any single component of the intervention.

Elimination diets
Agata et al.291 studied the effect of an elimination diet for egg allergies on atopic dermatitis in a non-randomized comparative study. Twenty-seven patients sensitive to egg that underwent an elimination diet for at least three months were compared with six patients sensitive to egg that did not eliminate the allergic food from their diet. The results showed that in those with egg allergy, 27/27 had improvement in their atopic dermatitis with an elimination diet (compared with 0/6 not on an elimination diet). They concluded that an elimination diet is a good treatment for food allergy and that specific IgE antibodies to food antigens were useful as indexes of the effect of elimination diets in patients with positive RAST.

Cavagni et al.317 evaluated the effects of adding thymomodulin to elimination diets in treating atopic dermatitis induced by food allergy. They noted a more favorable course of the skin
lesions in the patients treated with thymomodulin after two weeks of food challenge. They also noted a statistically significant decrease in total and specific IgE serum levels in the group receiving thymomodulin.

The fair quality RCT by Arshad et al. reported study results at eight years and found a “sustained preventive effect of egg allergen avoidance in infancy.” The non-randomized comparative study by Hermann et al. found no significant difference in either atopic dermatitis or sensitization to egg or cow milk between the intervention and control groups at 12 months.

**Pharmacology**
Burks and Sampson studied cromolyn in children with atopic dermatitis and documented food hypersensitivity. This crossover study showed that after one week of treatment with either cromolyn or placebo, there was no statistically significant difference in the symptom score for atopic dermatitis or in the response to a DBPCFC.

**Maternal diets**
Hill et al. evaluated the effect of a low-allergen maternal diet on colic among breastfed infants. They found a statistically significant improvement of colic in the low allergen group with adjusted RR of 37 percent (CI 18-56 percent).

**Allergen-specific immunotherapy**
Morisset et al. performed a randomized study to examine an oral desensitization protocol in children with IgE-dependent egg allergies. When the oral desensitized group was compared to the continued avoidance group for egg allergy, a significant improvement in SBPCFC (15/49 vs 17/35; p<0.1), and a statistically significant decrease in egg-sIgE, as well as a decrease in the size of the SPT wheal (p<0.005) were noted. Similarly, Patriarca et al. evaluated oral desensitization protocols and found that 12/17 patients who underwent desensitization had a negative DBPCFC (compared with 0/10 of the control patients).

Staden et al. assigned children with a food allergy to either milk or hen’s egg to oral immunotherapy or an elimination diet. They found that tolerance was achieved more often in the group that received oral tolerance induction (16/25) than in the group that adhered to an elimination diet (7/20) p=0.05.

**Summary**
A variety of strategies have been used to prevent and treat egg allergies in children. Although the heterogeneity of the studies on this topic preclude definitive conclusion, delayed introduction of foods, hypoallergenic maternal diets, and elimination diets are worthy of additional study as promising methods for the reduction of egg allergies in children.

**Prevention, Treatment, Management of Peanut and Hazelnut Allergy**

**Background**
Nut allergies are common and often appear in the first years of life. An allergic reaction to peanuts can range from a minor irritation to a life-threatening reaction called anaphylaxis. Even
people who have had only had a mild reaction in the past are thought to be at risk of a more serious future reaction.

**Results**

We identified two controlled trials\(^{295,316}\) and three cohort studies\(^{214,342}\) that examined the treatment and management of peanut allergy.\(^{328}\) Leung et al.\(^{316}\) evaluated the effect of anti-IgE therapy in patients with peanut allergy. They found that a 450 mg dose of TNX-901, a humanized IgG1 monoclonal antibody, increased the threshold of sensitivity to peanut on oral food challenge from a level equal to one peanut to almost nine peanuts.

Nelson et al.\(^{295}\) studied the effect of injections of subcutaneous peanut extract on patients with peanut allergy (Table 44-Table 46). They enrolled 12 patients, six of whom agreed to be treated with injections of peanut extract and six of whom served as a control. They reported a decreased peanut sensitivity at one month (p=0.0002) but no effect on SPT or peanut-sIgE as compared to patients with peanut allergy who did not receive subcutaneous injections.

Ewan and Clark\(^{214}\) followed 567 patients with peanut allergy, unselected consecutive referrals to a regional specialist allergy clinic (Table 51-Table 53). After giving them verbal and written advice on nut avoidance as well as on self-recognition of reactions, they found that 88 (15 percent) of 567 patients had a follow-up reaction of reduced severity and only three (0.5 percent) of 567 patients, had a severe follow-up reaction, compared with 12 percent initially. They concluded that self-treatment combined with advice for nut avoidance was effective.

Jarvinen et al.\(^{328}\) distributed questionnaires to families of children with food allergies to help determine the rate, circumstances, and risk factors for repeated doses of epinephrine in the treatment of food-induced anaphylaxis (Table 48-Table 50). The population they targeted was from a hospital-based pediatric allergy clinic and a private practice-based pediatric food allergy referral clinic at Mount Sinai Hospital, New York. Of 542 distributed questionnaires, 512 (94 percent) were returned, and 413 were included in the study (exclusions were for incomplete data, no documented food allergy, or age >18). They found that peanut allergy accounted for 290/413 (70 percent) of anaphylactic food reactions.

Jones et al.\(^{342}\) evaluated the clinical efficacy and immunological changes associated with oral immunotherapy in patients with peanut allergy. They found that of 29 subjects who completed the protocol, 27 ingested 3.9 g peanut protein during food challenge. Further, most symptoms noted during immunotherapy resolved spontaneously or with antihistamines.

Because nut allergies can be so severe and because we found little evidence from RCTs or large cohort studies about these allergies, we sought additional studies on this topic. We found one small cohort study on hazelnuts. Hansen et al.\(^{343}\) report a case series of 17 patients with food challenge-confirmed allergy to hazelnuts. Roasting the hazelnuts at 140 degrees centigrade for 40 minutes resulted in only five of these 17 patients having a reaction on DBPCFC. Despite this significant reduction, about 30 percent of patients remained sensitive even to roasted hazelnuts, so the authors concluded that roasting hazelnuts cannot be considered "safe" for hazelnut-allergic patients.
Summary
The quality of evidence is moderate in support of immunotherapy in the treatment and management of peanut allergy, and advice on nut avoidance accompanied by instructions for self-administered medication should be utilized.

Prevention, Treatment, Management of Fin Fish Allergy

Background
Pollock, salmon, cod, tuna, snapper, and tilapia are among the fish that commonly trigger fish allergies. Fin fish allergies are similar to shellfish allergies in that they are more likely than many food allergies to start during adulthood and less likely than other allergies to be outgrown. While it is easier to avoid fish than it is to avoid many other allergens, fish allergies are often quite severe in their symptoms.

Results
We found four RCTs studies of the prevention and treatment of fish allergies—all were of elimination diets (Table 44-Table 46).

The fair quality RCT by Arshad et al. reported study results at eight years and found a “sustained preventive effect of allergen avoidance in infancy.”

Cavagni et al evaluated the effects of adding thymomodulin to elimination diets in treating atopic dermatitis induced by food allergy. They noted a more favorable course of the skin lesions in the patients treated with thymomodulin after two weeks of food challenge. They also noted a statistically significant decrease in total and sIgE serum levels in the group receiving thymomodulin.

Hill et al evaluated the effect of a low-allergen maternal diet on colic among breastfed infants. They found a statistically significant improvement of colic in the low allergen group with adjusted RR of 37 percent (CI 18-56 percent).

Patriarca et al evaluated oral desensitization protocols and found that 9/9 patients completing the oral desensitization had a negative DBPCFC (compared with 0/10 control patients).

Summary
No studies were found that evaluated fish allergy alone; instead, studies included a small sample of patients with fish allergy among a larger sample of patients with other allergies. While definitive conclusions are hard to reach, allergen avoidance holds promise in the prevention, treatment and management of fish allergy.
Prevention, Treatment, Management of Apple Allergy

Background
The prevalence of apple allergy is most frequently associated with birch pollinosis in Northern Europe and North America. It is estimated that 40 to 90 percent of birch pollen allergic patients are sensitized to apples. Apple is one of the major foods involved in Oral Allergy Syndrome, which presents IgE-mediated symptoms that occur mainly at the mucosa of lips, tongue and throat after ingestion of apples and other fruits. Oral allergy syndrome is not a major clinical problem.

Results
We found four RCTs\textsuperscript{296, 300-302} that specifically evaluated apple allergies either alone or in combination with other food allergies.

Hansen et al.\textsuperscript{300} noted that clinical manifestations of allergenic cross-reactions between pollen and plant foods are frequent in birch pollen allergic patients and evaluated the effect of birch pollen extract immunotherapy in patients with apple allergy. There was no statistically significant change in oral allergy syndrome responses to an open apple food challenge after treatment with placebo, sublingual, or subcutaneous birch pollen extracts. However, there was a statistically significant decrease in apple sIgE in patients treated with subcutaneous birch pollen extract from 5.9 kU/L to 1.8 kU/L (p=0.009). No statistically significant change was reported in those patients receiving sublingual birch pollen extract or placebo.

Bucher et al.\textsuperscript{301} also examined the effect of subcutaneous immunotherapy with tree pollen extract on patients’ oral allergy syndrome to apple and hazelnuts. Improvement of oral allergy syndrome was statistically significant (p<0.05) with 10/15 patients receiving subcutaneous immunotherapy showing improvement (compared with only 2/12 control patients). sIgE to apple was also measured and the difference was found to be non-significant. However, it was reported that IgG4 r Bet v1 was significantly different (p<0.001) in the group treated with immunotherapy, but no values were given in the publication.

Asero et al.\textsuperscript{302} evaluated birch pollen-sensitive patients with apple-induced oral allergy syndrome who received injection immunotherapy with birch pollen extract. This treatment was found to reduce clinical apple sensitivity (p<0.001) but not apple sIgE.

Patriarca et al.\textsuperscript{296} evaluated oral desensitization protocols and found that 1/1 patients completing the oral desensitization had a negative DBPCFC (compared with 0/10 control patients).

Summary
The quality of evidence for apple allergy is moderate and indicates that immunotherapy with tree pollen appears to be effective in treating the apple-induced oral allergy syndrome. Oral
desensitization may also help in the management of apple allergy, although further exploration of this treatment modality is warranted.

Prevention, Treatment, Management of Soybean Allergy

Background
Soybean allergy is of concern because soy protein is prevalent in the diets of millions of people worldwide.

Results
We identified one cohort study that examined soybean allergies.328 Jarvinen et al.328 distributed questionnaires to families of children with food allergies to help determine the rate, circumstances, and risk factors for repeated doses of epinephrine in the treatment of food-induced anaphylaxis. They found that soybean allergy accounted for 107/413 (26 percent) of anaphylactic food reactions.

Summary
There are insufficient data to reach conclusions for the management of soybean allergies.
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Purpose</th>
<th>Study design</th>
<th>Condition of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peanut/Hazelnut Allergy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewan, 2001&lt;sup&gt;214&lt;/sup&gt;</td>
<td>UK</td>
<td>To determine effect of a management plan for peanut and nut allergy</td>
<td>Cohort</td>
<td>Multiple</td>
</tr>
<tr>
<td>Jones, 2009&lt;sup&gt;232&lt;/sup&gt;</td>
<td>United States</td>
<td>To investigate the clinical efficacy and immunologic changes associated with oral immunotherapy in patients with peanut allergy.</td>
<td>Cohort</td>
<td>Multiple</td>
</tr>
<tr>
<td>Hansen, 2003&lt;sup&gt;243&lt;/sup&gt;</td>
<td>Switzerland/Denmark</td>
<td>To evaluate the reduction in allergenicity by roasting hazelnuts</td>
<td>Cohort</td>
<td>Multiple</td>
</tr>
<tr>
<td>Hofmann et al., 2009&lt;sup&gt;211&lt;/sup&gt;</td>
<td>US</td>
<td>To examine safety during the initial escalation day, buildup phase, and home dosing phase in subjects enrolled in a peanut oral immunotherapy study</td>
<td>Cohort</td>
<td>Multiple</td>
</tr>
<tr>
<td><strong>Cow’s milk allergy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jong, 2002&lt;sup&gt;332&lt;/sup&gt;</td>
<td>Netherlands</td>
<td>To determine effect of brief exposure to cow’s milk in the neonatal period on later development of atopic disease.</td>
<td>RCT</td>
<td>Allergy, not specified</td>
</tr>
<tr>
<td>Lindfors, 1992&lt;sup&gt;339&lt;/sup&gt;</td>
<td></td>
<td>To evaluate the longer term (age 4-6yrs) incidence of allergic symptoms in children given cow's milk neonatally</td>
<td>RCT</td>
<td>Not specified</td>
</tr>
<tr>
<td>Iacono, 1998&lt;sup&gt;335&lt;/sup&gt;</td>
<td>Italy</td>
<td>To compare cow’s milk and soy milk in children with chronic constipation</td>
<td>RCT</td>
<td>Chronic constipation</td>
</tr>
<tr>
<td>Klemola, 2002&lt;sup&gt;313&lt;/sup&gt;</td>
<td>Finland</td>
<td>To evaluate incidence of allergy or other adverse reactions to soy formula and to hydrolyzed formula in patients with cow’s milk allergy</td>
<td>RCT</td>
<td>Cow’s milk allergy syndrome</td>
</tr>
<tr>
<td>Niggemann, 2008&lt;sup&gt;336&lt;/sup&gt;</td>
<td>Germany</td>
<td>To compare tolerance and growth of infants with CMPA who were fed a new extensively hydrolyzed formula containing lactose with those who were fed an amino acid formula</td>
<td>RCT</td>
<td>Cow’s milk allergy syndrome, Rhinitis, rhino-conjunctivitis, conjunctivitis</td>
</tr>
<tr>
<td>Jirapinyo, 2007&lt;sup&gt;333&lt;/sup&gt;</td>
<td>Thailand</td>
<td>To compare the ability of children with cow’s milk allergy to tolerate chicken-based formula and soy formula</td>
<td>RCT</td>
<td>Cutaneous, respiratory, gastrointestinal symptoms (not otherwise specified)</td>
</tr>
<tr>
<td>Garzi, 2002&lt;sup&gt;337&lt;/sup&gt;</td>
<td>Italy</td>
<td>To examine effects of a hydrolyzed cow milk formula on GERD and gastric emptying time</td>
<td>CT</td>
<td>Cow’s milk allergy syndrome</td>
</tr>
<tr>
<td>Vita, 2007&lt;sup&gt;338&lt;/sup&gt;</td>
<td>Italy</td>
<td>To assess tolerability and clinical effect of ass's milk compared with goat's milk to manage atopic dermatitis and cow's milk allergy in children</td>
<td>RCT</td>
<td>Cow’s milk allergy syndrome; atopic dermatitis</td>
</tr>
<tr>
<td>Savino, 2005&lt;sup&gt;340&lt;/sup&gt;</td>
<td>Italy</td>
<td>To evaluate growth of infants with AD and CMA fed a rice-hydrolysate formula compared with a soy or extensively hydrolysed casein formula</td>
<td>CT</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>Narisetty, 2009&lt;sup&gt;372&lt;/sup&gt;</td>
<td>US</td>
<td>To assess the efficacy and safety of open-label maintenance after milk oral immunotherapy in children with cow’s milk allergy</td>
<td>Cohort</td>
<td>Multiple</td>
</tr>
<tr>
<td>Henriksen, 2000&lt;sup&gt;215&lt;/sup&gt;</td>
<td>Norway</td>
<td>To examine nutrient intake in children with cow’s milk allergy on diets with variable amounts of cow milk protein.</td>
<td>Cohort</td>
<td>Cow’s milk allergy</td>
</tr>
<tr>
<td>Zapatero, 2008&lt;sup&gt;298&lt;/sup&gt;</td>
<td>Spain</td>
<td>To assess cow’s milk desensitization protocol</td>
<td>Cohort</td>
<td>Cow’s milk allergy</td>
</tr>
</tbody>
</table>

**Table Notes:** AD atopic dermatitis; CMA = cow’s milk allergy; CMF = cow milk formula; CMPA = cow’s milk protein allergy; CT = controlled trial (not randomized); EHF = extensively hydrolysed formula; GERD = Gastroesophageal reflux disease

**Only 3/10 infants with GERD were diagnosed with cow’s milk allergy.**
Table 52: Treatment/management - specific food allergy studies: patient characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Group Selection Criteria</th>
<th>IgE</th>
<th>Skin Test</th>
<th>Clinical rxn</th>
<th>Control Selection Criteria</th>
<th>Subject Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peanut Allergy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewan, 2001214</td>
<td>Inclusion: patients with peanut and nut allergy</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Median age: 7.5 years</td>
</tr>
<tr>
<td>Jones, 2009342</td>
<td>Inclusion: Age 1-16 years with a clinical history of reaction to peanut within 60 minutes of ingestion, a positive peanut skin prick test and a peanut CAP. Exclusion: history of severe, life-threatening anaphylaxis (with hypotension) to peanut, severe or poorly controlled asthma, or a medical condition preventing undergoing a food challenge</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Median age: 57.5 months, 64% male</td>
</tr>
<tr>
<td>Hansen, 2003343</td>
<td>Inclusion: Food allergy to hazelnuts Exclusion: Anaphylaxis due to hazelnuts</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>Median age: 24.5 years, 65% female</td>
</tr>
<tr>
<td>Hofmann et al., 2009211</td>
<td>Inclusion: Age 1-16 years with peanut allergy. Exclusion: Severe anaphylaxis, inability to cooperate with challenge procedures or follow-up</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Mean age 4.8 years (1.1-9.4)</td>
</tr>
<tr>
<td><strong>Cow’s milk allergy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jong, 2002332</td>
<td>Inclusion: pregnant women recruited from midwives practices who intended to breastfeed for at least 6 weeks who spoke Dutch, birth weight &gt;2749g, gestational age over 36wks, newborn not treated with oxygen for longer than 30 minutes after birth, newborn not needing ICU services/parenteral feeding/or IV antibiotics; newborn did not have any disorder that required substitution or supplementation.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Same as intervention group</td>
<td>high family risk of atopy: 58%</td>
</tr>
<tr>
<td>Lindfors, 1992339</td>
<td>Term but low birth weight infants (-1 to -2 SD)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Same as intervention group</td>
<td>age 4.8 years</td>
</tr>
</tbody>
</table>

[^214]: Reference number
[^211]: Reference number
[^332]: Reference number
[^339]: Reference number
[^342]: Reference number
[^343]: Reference number
[^339]: Reference number
[^342]: Reference number
[^332]: Reference number
### Table 52: Treatment/management - specific food allergy studies: patient characteristics (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Group Selection Criteria</th>
<th>IgE</th>
<th>Skin Test</th>
<th>Clinical rxn</th>
<th>Control Selection Criteria</th>
<th>Subject Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savino, 2005</td>
<td>Inclusion: born at term with a birthweight between 2500 and 4000 grams, Apgar &gt;7 at 5 minutes, no clinical evidence of acute or chronic diseases that affect growth, atopic dermatitis, absence of GI symptoms of food allergy, cow’s milk allergy</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Same as intervention group but without cow’s milk allergy</td>
<td>age: 3.27 months +/- 0.32</td>
</tr>
<tr>
<td>Iacono, 1998</td>
<td>Inclusion: chronic constipation (1 bowel movement every 3-15 days). Exclusion: anatomical reasons for constipation (i.e. Hirschsprung, spinal disease), constipation due to another disorder (i.e. hypothyroidism/ psychomotor-retardation), prior surgery, use of medications that cause constipation (i.e. chlorpromazine), and referral for reasons other than constipation</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Same as intervention group: cross-over study</td>
<td>29 males; 36 females; mean age 34.6 months (range 11-71 months)</td>
</tr>
<tr>
<td>Klemola, 2002</td>
<td>Infants with IgE or non-IgE cow’s milk allergy as diagnosed by double blind placebo controlled food challenge or a history of anaphylaxis with cow’s milk and presence of IgE specific antibodies</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Same as intervention group</td>
<td>Age: 7.1 years; Immediate/ delayed CMA: 41/39; atopic eczema: 52%; GI symptoms: 19%; IgE antibodies+ to CM: 37%; SPT+ with CM: 38%</td>
</tr>
<tr>
<td>Niggemann, 2008</td>
<td>Inclusion: healthy infants who had previously been diagnosed with CMPA; birth at term (37-42 weeks), birth weight between 2500 and 4000 grams, maximum intake of breast milk 2x/day Exclusion: malformations, congenital cardiovascular, kidney, liver, CNS, or metabolic diseases, serious GI tract disease, or lactose intolerance</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Same as intervention group</td>
<td>13 males; 19 females; age: 250 days (75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 males; 18 females; age: 236 days (91)</td>
</tr>
<tr>
<td>Author</td>
<td>Intervention Group Selection Criteria</td>
<td>Control Selection Criteria</td>
<td>Subject Demographics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Inclusion/exclusion criteria</td>
<td>IgE</td>
<td>Skin Test</td>
<td>Clinical rxn</td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>Jirapinyo, 2007333</td>
<td>Inclusion: infants aged 2-24 months with diagnosis of cow’s milk allergy based on disappearance of symptoms with elimination of cow’s milk and reappearance on reintroduction of it. Excluded: infants with systemic diseases or severe malnutrition</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Same as intervention group</td>
<td>Parental allergy: 12/18; 17% with respiratory sx; 44% with cutaneous sx; 39% with GI sx; 22% with eosinophilia; 22% with specific IgE elevation</td>
</tr>
<tr>
<td>Garzi, 2002337</td>
<td>Inclusion: exclusively fed with cow milk derived formula and had clinical symptoms of GERD with symptom score &gt;7</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Exclusively fed with cow milk derived formula without GERD and not taking any medications</td>
<td>average age: 4.9 months (range 2-6)</td>
</tr>
<tr>
<td>Vita, 2007338</td>
<td>Inclusion: age between 6 months and 3 years, clinical history or cow’s milk allergy, positive prick test to cow milk, positive DBPCFC to cow milk, active atopic dermatitis with SCORAD Index &gt;20 Exclusion: Previously been fed with either ass milk or goat milk</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Same as intervention group</td>
<td>First received ass milk: 8 males; 6 females; mean age: 2.7 years (0.8-3.8), First received goat milk: 6 males; 8 females; mean age: 2.5 (0.6-3.7)</td>
</tr>
<tr>
<td>Narisety et al., 2009312</td>
<td>Participants that could tolerate &gt;2540 mg in their post-milk oral immunotherapy challenge upon conclusion of the Skripak RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Age range 6-16 years</td>
</tr>
<tr>
<td>Henriksen et al., 2000313</td>
<td>Children with parentally perceived reactions to milk or egg at the age of 2 years</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Mean age: 2.5 years</td>
</tr>
<tr>
<td>Zapatero, 2008298</td>
<td>Children aged 4 or older with confirmed allergy to cow’s milk</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Mean age: 5.05 years</td>
</tr>
</tbody>
</table>

Table Notes: CM cow’s milk; CMA cow’s milk allergy; CMF cow milk formula; CMPA cow milk protein allergy; CNS central nervous system; GERD GI gastrointestinal; DBPCFC double blind placebo controlled food challenge; EHF extensively hydrolysed formula; GERD Gastroesophageal reflux disease ICU intensive care unit; RCT randomized controlled trial; SCORAD scoring atopic dermatitis; SD standard deviation; sIgE antigen-specific immunoglobulin; SPT skin prick test;
<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Description</th>
<th>Timing Info</th>
<th>Sample Size</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peanut allergy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewan, 2001</td>
<td>Advice on avoidance and medications to use in case of an accidental ingestion of peanuts; medications also provided.</td>
<td>Not applicable</td>
<td>1 year</td>
<td>567 NA Follow-up reaction</td>
</tr>
<tr>
<td>Jones, 2009</td>
<td>Oral immunotherapy protocol including initial day escalation, buildup, and maintenance phases, and then oral food challenge</td>
<td>Not applicable</td>
<td>18 months</td>
<td>29 NA Skin prick tests, peanut-specific IgE and IgG, IL-10, IL-5, interferon-gamma, TNF-alpha</td>
</tr>
<tr>
<td>Hansen, 2003</td>
<td>Patients ingested raw and roasted hazelnuts</td>
<td>Not applicable</td>
<td>Immediate after intervention</td>
<td>17 NA DBPCFC, Clinical symptoms of OAS, SPT, Heart rate, specific IgE</td>
</tr>
<tr>
<td>Hofmann et al., 2009</td>
<td>Oral immunotherapy protocol with the goal to achieve ingestion of a daily maintenance dose of 300 mg of peanut protein</td>
<td>Not applicable</td>
<td>24 months</td>
<td>28 NA Symptoms (upper respiratory tract, skin, abdominal, chest) or treatment (diphenhydramine, albuterol, or epinephrine) after treatment with oral immunotherapy</td>
</tr>
<tr>
<td><strong>Cow’s milk allergy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jong, 2002</td>
<td>Supplementation with whey protein dominant cows' milk formula given at least 3 times during first 3 days after randomization. Then, women breast feed for 6 months thereafter. No instructions given with respect to avoidance of cow's milk proteins after this first 3 day period.</td>
<td>Placebo formula free of cows' milk protein given during first 3 days after randomization.</td>
<td>5 years</td>
<td>758 775 Presence of atopic eczema, rhinoconjunctivitis, wheezing, and other clinical signs of allergy; specific IgE by RAST against cows' milk, hen's egg, house dust mite, cat dander and dog dander, grass pollen, tree pollen, and moulds.</td>
</tr>
<tr>
<td>Author</td>
<td>Intervention Description</td>
<td>Timing Info</td>
<td>Sample Size</td>
<td>Outcomes reported</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Lindfors, 1992</strong></td>
<td>Cow milk formula from the first day of life until normal breastfeeding started</td>
<td>Breast milk only</td>
<td>4-6 years</td>
<td>109 98 Clinical allergy as defined by pediatrician examination; SPT IgE for antibodies against airway allergens and a custom pediatric food allergen mix for egg, milk, wheat, peanut and soy bean.</td>
</tr>
<tr>
<td><strong>Iacono, 1998</strong></td>
<td>Patients given soy milk or cow milk for 2 weeks and then had chronic constipation assessed. This was followed by a 1 week washout period and then 2 weeks with the opposite food, either cow or soy</td>
<td>Cow milk</td>
<td>2 weeks</td>
<td>65 Not reported Median number of bowel movements before and after treatment</td>
</tr>
<tr>
<td><strong>Klemola, 2002</strong></td>
<td>Soy formula</td>
<td>Extensively hydrolyzed formula</td>
<td>2 year</td>
<td>80 90 Parents suspicion of adverse reactions to formula</td>
</tr>
<tr>
<td><strong>Niggemann, 2008</strong></td>
<td>New extensively hydrolyzed formula</td>
<td>Amino acid formula</td>
<td>Infants evaluated at 30, 60, 90, and 180 days</td>
<td>34 32 Z-scores for length, head circumference, and weight; SCORAD scores; IgE titers</td>
</tr>
<tr>
<td><strong>Jirapinyo, 2007</strong></td>
<td>Formula made from chicken meat</td>
<td>Soy formula</td>
<td>14 days</td>
<td>20 18 Intolerance to formula, any cutaneous, respiratory, or GI symptoms (not otherwise specified)</td>
</tr>
<tr>
<td><strong>Garzi, 2002</strong></td>
<td>Infants with GERD fed an extensively hydrolyzed hypoallergenic formula</td>
<td>Continued to feed on cow milk formula</td>
<td>1 week after formula</td>
<td>10** 10 Gastric emptying time; symptom scale of GERD</td>
</tr>
<tr>
<td><strong>Vita, 2007</strong></td>
<td>Crossover trial; subjects received either goat milk or ass milk for 6 months, were evaluated and then received the other type of milk for 3 months. Treatment group was first assigned ass milk.</td>
<td>Cross-over trial</td>
<td>Evaluated 6 months after first treatment and then again 3 months after next treatment</td>
<td>14 14 SCORAD to assess atopic dermatitis; VAS</td>
</tr>
</tbody>
</table>
### Table 53: Treatment/management - specific food allergy studies: intervention characteristics and outcomes reported (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Description</th>
<th>Timing Info</th>
<th>Sample Size</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savino, 2005&lt;sup&gt;290&lt;/sup&gt;</td>
<td>Either rice based hydrolysate formula (RHF), soy-based formula (SF), or extensively hydrolyzed casein formula (eHCF)</td>
<td>Free diet; Every 3 months in the 1st year of life and then at 6 month intervals in 2nd year of life</td>
<td>RHF--15; SF--17; eHCF--26</td>
<td>30; Z-score of weight</td>
</tr>
<tr>
<td>Narisety et al., 2009&lt;sup&gt;212&lt;/sup&gt;</td>
<td>Gradual home dose escalations of milk of no more than 50% increments every 2 weeks</td>
<td>Not applicable; Median=17 weeks (range 13-75 weeks)</td>
<td>15 NA</td>
<td>Adverse reactions, milk threshold, SPT, IgE, IgG</td>
</tr>
<tr>
<td>Henriksen et al., 2000&lt;sup&gt;213&lt;/sup&gt;</td>
<td>Divided into 4 groups: milk-free, formula, milk-reduced, and milk</td>
<td>Not applicable; 4 day</td>
<td>34 NA</td>
<td>Dietary recall recorded by parents</td>
</tr>
<tr>
<td>Zapatero, 2008&lt;sup&gt;298&lt;/sup&gt;</td>
<td>Desensitization protocol to cow’s milk</td>
<td>Not applicable; Median=14 weeks (range 9-32 weeks)</td>
<td>18 NA</td>
<td>Tolerance to cow’s milk</td>
</tr>
</tbody>
</table>

** Only 3/10 infants with GERD were diagnosed with cow’s milk allergy.

**Table Notes:** EHF=extensively hydrolyzed formula; CMF=cow milk formula; NA=not applicable; GERD=gastroesophageal reflux disease; GI gastrointestinal; HCF hydrolysed casein formula; IgG immunoglobulin G; RAST=radioallergosorbent test; RHF rice-based hydrolysate formula; SCORAD=scoring atopic dermatitis; SF soy-based formula; sIgE antigen-specific immunoglobulin; SPT skin prick test
Figure 11: Treatment/management - summary of Evidence by Food Type

<table>
<thead>
<tr>
<th>Prevention Strategies</th>
<th>Peanut/Hazelnut</th>
<th>Cow's Milk</th>
<th>Hen's Egg</th>
<th>Fish</th>
<th>Apple</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delayed introduction of foods</strong></td>
<td></td>
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<tr>
<td><strong>Maternal diets</strong></td>
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<tr>
<td><strong>Breast feeding</strong></td>
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</tr>
<tr>
<td><strong>Special diets for infants and young children</strong></td>
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<tr>
<td><strong>Probiotics</strong></td>
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<tr>
<td><strong>Elimination diet</strong></td>
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<tr>
<td><strong>Immunotherapy</strong></td>
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</tr>
<tr>
<td><strong>Allergen avoidance</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Pharmacology</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Probiotics</strong></td>
<td></td>
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</tr>
</tbody>
</table>

- ● Statistically significant improvement
- ○ No statistically significant improvement
- Ψ Some statistically significant improvement in some outcomes but not in all outcomes measured.

C=Cohort study. Other studies are controlled trials.
Evidence for the Prevention, Treatment, or Management of Specific Clinical Conditions Associated with Food Allergies

Most of the included studies evaluated multiple clinical conditions associated with food allergies. The most common food allergy-related conditions studied were asthma, oral allergy syndrome, AD, EE, and dermatitis herpetiformis (Figure 11). The tables for this section only provide data not already previously presented in the other evidence tables.

Prevention, Treatment, Management of Asthma

Background
Crosssectional studies of adults with asthma report that in excess of 20 percent have allergic/asthmatic symptoms to at least one food. Moreover, these patients are more likely than the non-food allergic asthma patients to have increased health care utilization (e.g., hospitalizations and emergency department visits for asthma).

Results
Eight studies evaluated strategies for the prevention, treatment, and/or management of asthma in the setting of food allergy.

Mass et al performed a review of mono or multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma. The literature search and screening process was comprehensive and followed the methods used by the Cochrane Collaboration. The search was conducted in December, 2008 and included 9 randomized controlled trials of allergen exposure reduction for the primary prevention of asthma in children with follow up to a minimum of two years of age in 3,271 children. The review scored highly on the AMSTAR criteria for evaluating systematic reviews (9 criteria met). They reported that the reduction of exposure to multiple allergens (inhalant and food), resulted in fewer cases of physician diagnosed asthma for children < 5 years of age; OR 0.72; 95% CI 0.54-0.96 and fewer cases of asthma as defined by respiratory symptoms and lung function for children > 5 years of age OR 0.52; 95% CI 0.32-0.85. However, there was no statistical difference in cases of physician diagnosed asthma from the reduction of exposure to monofaceted allergens (inhalant or food); OR 1.12; 95% CI 0.76-1.64 for < 5 years of age and OR 0.83; 95% CI 0.59-1.16 for > 5 years of age.

Von Berg performed a study to investigate the long-term allergy-preventive effect of three hydrolyzed infant formulas compared with cow’s milk formula. Between 1995 and 1998, 2,252 newborns with atopic heredity were randomly assigned at birth to receive one of four blinded formulas: partially or extensively hydrolyzed whey formula, extensively hydrolyzed casein formula, or CMF as milk substitute for the first four months when breast feeding was insufficient. At three years of follow-up, there was no statistically significant effect on the incidence of asthma. In an intention to treat analysis of 2,252 children at six years of follow-up, it was found that only the extensively-hydrolyzed whey formula had an increased RR of asthma of 2.16 (95%CI, 1.02, 4.58). This was not found in the per protocol analysis.

In a meta-analysis, by Osborn and Sinn, three studies exploring the effect of soy formula vs. cow milk formula in the prevention of asthma were synthesized (Miskelly 1988, Johnstone 1966,
and Kjellman 1979). A weighted least squares regression for soymilk found a non-significant RR of 0.71 (95%CI, 0.26, 1.92). Burr et al\textsuperscript{226} studied 453 children with a family history of allergic disease. Withholding cow milk and replacing it with soymilk during the first three months of life did not significantly decrease the incidence of wheezing at a follow-up of seven years of age. Children who had ever been breastfed had a lower incidence of wheeze than children who had not (59 percent vs. 74 percent).

Kajosaari\textsuperscript{252} performed a five-year prospective study to determine the benefits of exclusive breastfeeding for six months combined with delayed introduction of solid foods in children at high risk for atopic disease. In an examination at 5 years of age, 8 percent of infants who were exclusively breastfed until 6 months of age had asthma while 15 percent of those who started solid foods at three months of age had asthma, a non-significant difference.

Abrahamsson et al\textsuperscript{288} studied the prevention of eczema and sensitization using oral supplementation of probiotics in infants with a family history of allergic disease. After treatment, the cumulative incidence of asthma was not significantly different between the placebo group (10 percent) and the group receiving probiotics (7 percent).

Sigurs et al\textsuperscript{255} studied the effect of maternal avoidance of egg, cow milk, and fish during the first three months of lactation on allergic manifestations in children at 4 years of age. There was no effect on the cumulative incidence of asthma in children with mothers on a restricted diet (11 percent) and those with mothers on a non-restricted diet (12 percent).

**Summary**

The quality of evidence for interventions aimed at preventing, treating, or managing asthma is highly heterogeneous in that there is not a preponderance of literature for any particular type of intervention. Avoidance of food allergens in combination with avoidance of inhalant allergens does appear to prevent asthma, but solely avoiding food allergens does not.

**Prevention, Treatment, Management of Oral Allergy Syndrome**

**Background**

In adults, up to 60 percent of all food allergic reactions are due to cross-reactions between foods and inhaled allergens. OAS is a type of food allergy typified by a cluster of allergic reactions in the mouth in response to eating certain fruits and nuts that typically develops in adults who suffer from hay fever. OAS sufferers may have any of a number of allergic reactions that usually occur very rapidly, within minutes of eating a trigger food. The most common reaction is an itching or burning sensation in the lips and mouth.
Results

Four RCT studies evaluated the prevention, treatment, or management of OAS. Three of these studies examined immunotherapy as a treatment for the oral allergy syndrome, and one studied the effect of drug therapy with an H2-blocker. In addition, one study was an open observational study that examined the effect of pollen-specific sublingual immunotherapy on OAS triggered by several foods.

Hansen et al. noted that clinical manifestations of allergenic cross-reactions between pollen and plant foods are frequent in birch pollen allergic patients and evaluated the effect of birch pollen extract immunotherapy in patients with apple allergy. **Symptom Outcome:** There was no statistically significant change in oral allergy syndrome to an open apple food challenge after treatment with placebo, or sublingual or subcutaneous birch pollen extracts. **Lab Outcome:** There was a statistically significant decrease in apple sIgE in patients treated with subcutaneous birch pollen extract from 5.9 kU/L to 1.8 kU/L ($p=0.009$). No statistically significant change was reported in those patients receiving sublingual birch pollen extract or placebo.

Bucher et al. also examined the effect of subcutaneous immunotherapy with tree pollen extract on patients’ OAS-related responses to apple and hazelnuts. **Symptom Outcome:** Improvement of OAS was statistically significant ($p<0.05$) with 10/15 patients receiving subcutaneous immunotherapy showing improvement (compared with only 2/12 controls). **Lab Outcome:** changes in sIgE to apple were also measured and found to be non-significant. However, it was reported that changes in IgG4 r Bet v1 were statistically significant $p<0.001$ in the group treated with immunotherapy, but no values were given.

Asero at el. evaluated birch pollen-sensitive patients with apple-induced OAS who received injection immunotherapy with birch pollen extract. **Symptom Outcome:** This treatment was found to reduce clinical apple sensitivity ($p<0.001$). **Lab Outcome:** No reduction in apple sIgE was noted.

Bindslev et al. examined the effect of astemizole (an H2-blocker) on oral allergy syndrome induced by consumption of hazelnuts in patients with positive SPT to birch pollen. **Symptom Outcome:** Symptom severity to the oral provocation test was significantly lower in the group that got aztemizole than the placebo group ($p=0.004$).

The open observational study by Bergmann et al. studied pollen-specific sublingual immunotherapy in treating the OAS. **Symptom Outcome:** The investigators rated OAS severity at baseline as at least moderate in 94.9 percent of patients compared with 36.9 percent after 12 months of treatment with pollen-specific sublingual immunotherapy. After 12 months, OAS was rated as much- or very much improved in 72.9 percent of patients.

Summary

The quality of evidence here is high. Immunotherapy is effective in improving some outcomes for patients with OAS. IgG4 levels appear to increase with treatment while allergen-sIgE levels may or may not decrease with immunotherapy.
Prevention, Treatment, Management of Atopic Dermatitis

Background

Atopic dermatitis, a type of eczema, is an inflammatory, chronically relapsing, non-contagious, and pruritic skin disease often triggered by irritants such as food and environmental allergens.

Results

Two reviews and six RCTs evaluated atopic dermatitis prevention, management, or treatment. We identified two reviews that evaluated the effect of dietary exclusion for treating atopic eczema and one controlled trial not included in the review. Probiotics for the treatment of atopic eczema/dermatitis was reported in one study. One study reported the effect of sodium cromoglycate and an elimination diet on the severity of eczema. We also identified one study that reported the effect of adding thymomodulin to an elimination diet in the treatment of food allergen-induced atopic dermatitis. Two studies evaluated formulas in infants with atopic dermatitis. One evaluated a home-made meat based formula for feeding atopic babies and the other compared a rice-hydrolysate formula with soy or extensively hydrolyzed casein formula. The effect of cromolyn in children with atopic dermatitis and food sensitivity was also explored.

Both reviews had a comprehensive literature search and screening process and followed the methods used by the Cochrane Collaboration. They both scored highly on the AMSTAR criteria. As part of their review on allergy prevention, Kramer et al. whether maternal dietary antigen avoidance during lactation by mothers of infants with eczema could reduce eczema severity. The review found one small trial (n=17) that met their inclusion criteria for this part of the review, which found no significant reduction in eczema area score (mean difference -0.8; 95% CI -4.43 to 2.83) or eczema activity score (mean difference -1.4; 95% CI -7.18 to 4.38) between infants whose mothers avoided dietary antigens and those whose mothers followed a usual diet.

Bath-Hextall et al. evaluated the effect of patient dietary exclusion for treating established atopic eczema. Their search of the published literature (conducted as of March 2006) resulted in the inclusion of nine low-quality RCTs of which they considered only two sufficiently similar to combine. Six of the RCTs examined milk and egg exclusion, one was a study of a diet limited to only a few foods, and two evaluated elemental diets. The authors found no evidence to support the use of these dietary exclusion strategies for treating atopic eczema in an unselected population, possibly due to patients not being allergic to the substances being eliminated or because of small study sizes and poor reporting. However, the authors suggested that there might be some benefit of an egg-free diet in infants with positive egg sIgE results (results from one study).

Agata et al. studied the effect of an elimination diet for milk or egg allergies on atopic dermatitis in a non-randomized comparative study. Twenty-seven patients sensitive to egg and 16 patients sensitive to milk underwent an elimination diet for at least three months. They were
compared with six patients sensitive to egg and five patients sensitive to milk who did not eliminate the allergen from their diets. The results showed that in those with egg allergy, 27/27 showed improvement in their atopic dermatitis with an elimination diet (compared with 0/6 not on an elimination diet). In those with a milk allergy, 15/16 showed improvement in their atopic dermatitis with elimination diet (compared with 0/5 not on an elimination diet). They concluded that an elimination diet is a good treatment for food allergy and that sIgE antibodies to food antigens were useful as indexes of the effect of elimination diets in patients with positive RAST.

Cavagni et al.\textsuperscript{317} evaluated the effects of adding thymomodulin to elimination diets in treating atopic dermatitis induced by food allergy. They noted a more favorable course of the skin lesions in the patients treated with thymomodulin after two weeks of food challenge. They also noted a statistically significant decrease in total and sIgE serum levels in the group receiving thymomodulin.

Cantani\textsuperscript{324} studied the effect of a home-made meat-based formula for feeding atopic babies. They reported significant improvement in SCORAD scores in the group treated with the meat-based formula.

Savino et al.\textsuperscript{340} evaluated the growth of infants with atopic dermatitis and cow’s milk allergy fed a rice-hydrolysate formula compared with a soy or extensively hydrolyzed casein formula. No significant differences in the z-score weight for age were found.

Burks and Sampson\textsuperscript{318} studied cromolyn in children with atopic dermatitis and documented food hypersensitivity. This crossover study showed that after one week of treatment with either cromolyn or placebo, there was no statistically significant difference in the symptom score for atopic dermatitis.

Vita et al.\textsuperscript{338} assessed the tolerability and clinical effect of ass's milk compared with goat's milk in children with atopic dermatitis from cow’s milk allergy. Ass milk significantly improved both the SCORAD index and the visual analog scale (p<0.03) whereas goat milk had no effect.

Businco et al.\textsuperscript{320} evaluated 31 children aged 6 months-10 years old with atopic dermatitis exacerbated by foods in a crossover study to evaluate the effects of sodium cromoglycate and an elimination diet on the severity of eczema. They concluded that eczema (measured both by the clinician and the parents was statistically improved when the patients were receiving sodium cromoglycate.

**Maternal/neonatal interventions**

One RCT\textsuperscript{262} and two non-randomized comparative studies\textsuperscript{261, 341} evaluated the effect of restricted maternal diet during pregnancy or lactation, supplementation with either soy or hydrolyzed formulas and delayed introduction of solids to infants, on the incidence of atopic disease in children.
Two of the studies\textsuperscript{261, 262} found a protective effect of the intervention on atopic disease, while the third\textsuperscript{341} found no significant difference in either atopic dermatitis or sensitization to egg or cow milk between the intervention and control groups at 12 months. The fair quality RCT by Arshad et al.\textsuperscript{262} reported study results at eight years and found a “sustained preventive effect of allergen avoidance in infancy” (Table 38-Table 41).

Filipiak et al. reported their results based on an expanded analysis of the GINI (German Infant Nutritional Intervention Program) cohort study. They examined the effect of a multimodal intervention (exclusive breastfeeding or supplementation with one of four hydrolyzed formulas and delayed introduction of solid foods) on the occurrence of eczema during the first four years of life.\textsuperscript{260} They compared infants at high risk of developing atopic disease whose mothers were given recommendations to delay solid food introduction to infants without a family history of allergy or those infants whose parents refused to participate in the intervention. They found significantly higher rates of doctor-diagnosed eczema in the intervention group (29 percent) compared to the control group (20 percent) (p<0.001), but found no association between eczema and feeding practices (time of introduction or diversity of foods introduced); this study was rated as poor quality.

Summary

The quality of evidence here is moderate. Maternal avoidance diets appear to have no effect on infant atopic dermatitis while elimination diets of persons suffering from atopic dermatitis and food allergy may improve atopic dermatitis.

Prevention, Treatment, Management of Eosinophilic Esophagitis

Background. Eosinophilic esophagitis (EE) is characterized by infiltration of the esophagus with eosinophils without infiltration in other parts of the gastrointestinal tract. The symptoms of EE are similar to gastroesophageal reflux disease (GERD) but patients with EE are unresponsive to standard GERD treatment and have normal pH probe results.

Results. We identified one systematic review,\textsuperscript{327} two RCTs,\textsuperscript{319, 345} and two cohort studies\textsuperscript{204, 346} that evaluated dietary or medical interventions for treating EE.

Kukuruzov et al.\textsuperscript{327} conducted a comprehensive literature search and screening process and followed the methods used by the Cochrane Collaboration; the review scored highly on the AMSTAR criteria. Their search found an abstract of preliminary results from one unfinished RCT comparing topical (swallowed metered dose) fluticasone with oral prednisone in children. In the 50 children enrolled to date the results indicated no difference between the two treatments. The authors also identified another ongoing RCT comparing swallowed fluticasone with placebo among 3- to 21-year-olds; no results are available on this RCT as yet.

Schaefer et al.\textsuperscript{319} compared oral prednisone to topical fluticasone in the treatment of EE. They found a statistically significant difference in histologic response favoring the prednisone over the fluticasone group between weeks 0 and 4 (p=0.0440).
Konikoff et al.\textsuperscript{345} randomly assigned 36 patients to receive 880\textmu g of swallowing of inhaled fluticasone or placebo. They found that disease remission, defined as a peak eosinophil count $\leq$ 1 eosinophils per high-powered field (eo/HPF), favored the fluticasone group with a $p=0.47$.

Spergel et al.\textsuperscript{204} performed a cohort study to evaluate the effect of an elimination diet in treating EE. They found a decrease in the number of eo/HPF in 112/146 patients.

Liacouras et al.\textsuperscript{346} reported a retrospective study of 381 children with EE. They found that clinical symptoms improved in 27 of 29 patients treated with oral methylprednisolone for four weeks and the number of eo/HPF decreased from 33.5 (9.5) to 0.9 (0.6). In patients treated with inhaled fluticasone, 14/17 showed clinical improvement and the eo/HPF decreased from 27.7 (5.0) to 11.2 (2.7). All of these findings reversed within 4-6 months upon removal of the medication. In 14 patients treated with cromolyn there was no improvement in clinical symptoms or reduction in eosinophils. Elimination diet was found to be helpful in reducing clinical symptoms in 75/132 patients, and 160/164 patients who underwent complete dietary elimination with an amino-acid based formula showed clinical improvement.

**Summary**

The quality of evidence here is moderate and supports the use of oral corticosteroids and elimination diets to treat eosinophilic esophagitis.
Table 54: Specific clinical conditions associated with food allergies: design and patient characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Purpose</th>
<th>Study design</th>
<th>Food of interest</th>
<th>Intervention Group Selection Criteria</th>
<th>Intervention Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral allergy syndrome (OAS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bergmann, 2008344</td>
<td>Germany</td>
<td>To examine the effect of pollen-specific sublingual immunotherapy on OAS</td>
<td>Prospective</td>
<td>apple, hazelnut, carrot</td>
<td>Patients had pollen-induced allergic rhinoconjunctivitis and concomitant OAS and did not have known contraindications to specific immunotherapy.</td>
<td>No No Yes</td>
</tr>
<tr>
<td><strong>Eosinophilic esophagitis (EE)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spergel, 2005204</td>
<td>US</td>
<td>To determine if an elimination diet is useful in treating EE</td>
<td>Prospective</td>
<td>milk, egg, soy, peanut, chicken, wheat, peas, beef, corn, potatoes, rice</td>
<td>Diagnosis of EE with one or more of the following: vomiting, regurgitation, abdominal pain, or dysphagia unresponsive to 2 months of PPI and EGD bx with &gt; 15 eosinophils per hpf</td>
<td>No Yes Yes</td>
</tr>
<tr>
<td>Liacouras, 2005346</td>
<td>US</td>
<td>To describe EE in children</td>
<td>Retrospective</td>
<td>milk, egg, wheat, soy, corn, beef, chicken, potatoes, oats, peanuts, turkey, barley, rice, pork, green beans, apples, pineapple</td>
<td>All patients diagnosed with eosinophilic esophagitis from Jan 1 1994-Jan 1 2004 at the Children's hospital in Philadelphia</td>
<td>No Yes Yes</td>
</tr>
<tr>
<td><strong>Dermatitis herpetiformis (DH)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gariouch, 1994437</td>
<td>UK</td>
<td>To describe 25 years of experience in patients on a gluten-free diet to treat DH</td>
<td>Cohort</td>
<td>Gluten</td>
<td>Patients seen in dermatology clinic with dermatitis herpetiformis.</td>
<td>No No Yes</td>
</tr>
</tbody>
</table>

Table Notes: DH dermatitis herpetiformis; EGD Esophagastroduodenoscopy; EE eosinophilic esophagitis; OAS oral allergy syndrome; PPI protein pump inhibitors
### Table 55: Specific clinical conditions associated with food allergies: intervention characteristics and outcomes reported

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention Description</th>
<th>Timing Info</th>
<th>Sample Size</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral allergy syndrome (OAS)</strong></td>
<td>An open observational study examined the effect of pollen specific sublingual immunotherapy on OAS triggered by several foods</td>
<td>NA</td>
<td>12 months</td>
<td>102</td>
</tr>
<tr>
<td>Bergmann, 2008&lt;sup&gt;344&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eosinophilic esophagitis (EE)</strong></td>
<td>People were asked to follow an elimination diet for 6 weeks and then underwent a repeat EGD to determine if their EE had improved or worsened</td>
<td>Not applicable</td>
<td>6 weeks</td>
<td>146</td>
</tr>
<tr>
<td>Spergel, 2005&lt;sup&gt;204&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liacouras, 2005&lt;sup&gt;346&lt;/sup&gt;</td>
<td>Multiple: medications; elimination diet</td>
<td>Not applicable</td>
<td>6 months</td>
<td>381</td>
</tr>
<tr>
<td><strong>Dermatitis herpetiformis (DH)</strong></td>
<td>Gluten-free diet</td>
<td>Not applicable</td>
<td>1967-1992</td>
<td>212</td>
</tr>
<tr>
<td>Gariouch, 1994&lt;sup&gt;197&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table Notes:** DH dermatitis herpetiformis; EGD Esophagogastroduodenoscopy; EE eosinophilic esophagitis; OAS oral allergy syndrome; PPI protein pump inhibitors
### Figure 12: Summary of Evidence by Specific Clinical Condition

<table>
<thead>
<tr>
<th>Prevention Strategies</th>
<th>Specific Clinical Condition</th>
<th>Asthma</th>
<th>Oral Allergy Syndrome</th>
<th>Atopic Dermatitis</th>
<th>Eosinophilic Esophagitis</th>
<th>Dermatitis Herpetiformis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed introduction of foods</td>
<td>○255</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal diets</td>
<td>○262</td>
<td>●C261</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevented Introductions of Foods</td>
<td>○255</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast feeding</td>
<td>○252</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special diets for infants and young children</td>
<td>○R269</td>
<td>○270</td>
<td>○226</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○288</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Probiotics</td>
<td>○288</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergen Avoidance</td>
<td>○289</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elimination diet</td>
<td>○R14</td>
<td>○R253</td>
<td>○291</td>
<td>○317</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>○300</td>
<td>○301</td>
<td>○302</td>
<td>○299</td>
<td>○303</td>
<td>○C344</td>
</tr>
<tr>
<td>Desensitization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergen avoidance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacology</td>
<td>○315</td>
<td>○318</td>
<td>○320</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

243
<table>
<thead>
<tr>
<th>Probiotics</th>
<th>$\bigcirc$</th>
<th>$\bigotimes$</th>
</tr>
</thead>
</table>

- Statistically significant improvement
- Some statistically significant improvement in some outcomes but not in all outcomes measured.
- No statistically significant improvement

*C=Cohort study; R=Systematic review; Other studies are controlled trials. *This review included only one RCT that evaluated elimination diet.
Conclusions

A principal conclusion of this review is that the quality of evidence is poor for most aspects of food allergy. After screening more than 11,000 titles from which we identified and read in more detail nearly 1,000 published papers, we found very few areas where we could draw anything more than tentative conclusions. Central to the problem of synthesizing the literature on food allergy is the lack of an agreed-upon criteria for diagnosis. This lack of a standardized, operational criteria means that results of incidence, prevalence, and natural history cannot be compared across studies, that there is no single “gold standard” to use for assessing the sensitivity, specificity, and other properties of diagnostic tests, and that studies of treatments may not be comparable due to differing methods used to identify patients with food allergy for inclusion in the study. The lack of standardized criteria for what constitutes a diagnosis of food allergy is a major limitation to further understanding of this.

With that limitation in mind, there are a few consistent findings that we can point to. First, while the prevalence of food allergies varies from study to study and depends greatly on the criteria used for diagnosis, in general it is not much more than 10%, and may be much lower. For specific foods, allergy to cow’s milk is generally greater than allergies to other foods, at least in children, but the prevalence of cow’s milk allergy declines in adults, while the prevalence of allergies to other foods generally remains more constant. Allergies to other foods are common in patients with one identified food allergy, and other conditions such as asthma and atopic dermatitis are extremely common in individuals identified as food-allergic. Cow’s milk allergy clearly lessens in prevalence over time. While there are documented cases of some patients “outgrowing” their allergy, in general this does not happen for nuts, peanuts, and shellfish; although reactions to any particular exposure can be variable. The natural history of other food allergies has not been studied in US populations.

Second, with regard to diagnosis, the double-blind placebo-controlled food challenge remains the gold standard, although concerns exist regarding its practicality, validity, and safety. As a result, simpler, less intensive tests are often used. The skin prick test is one such method. Studies assessing its utility are plagued by lack of standardization of how to administer the test and what constitutes a positive test. Compared to a food challenge, sensitivities of 60%-95% and specificities of 40%-95% are commonly reported, and depend on food type and wheal size, among other things. Blood tests for antigen-specific IgE are also commonly used, and also suffer from differing thresholds being used to classify a test as “positive”, along with differences in the type of test and type of food. Compared to a food challenge, sensitivities of 44%-57% are reported, with specificities of 95% to 100%. Atopy patch testing is commonly used to assess delayed immunologic response, but also suffers from lack of standardization. A number of other tests have been proposed as useful for diagnosing food allergies, but few have been subjected to rigorous assessment. Combinations of tests may offer some benefits, but the incremental value, and optimal sequencing, of series of tests remains uncertain. Our meta-analysis of those conditions (cow’s milk, egg, wheat) and those tests (SPT, sIgE, APT) where data
were efficient to support construction of Receiver Operator Characteristic curves did not find evidence that any one test was more accurate than any other tests either, within foods or across foods.

Third, with regard to treatment, special diets in infancy seem to help reduce the occurrence of childhood atopic diseases in high-risk babies, some forms of immunotherapy with or without desensitization improve some symptoms of food allergy, and allergen avoidance is a commonly recommended management strategy for specific food allergies but has been relatively little studied, in part perhaps because of uncertainty regarding how to assess a “failed” trial of allergen avoidance (was the diet a failure or is the patient not allergic to the food that was avoided?)

Fourth, the most common treatment for food allergies—allergen avoidance—was evaluated in only one small non-randomized comparative study which suggested that it may be an effective means of reducing allergy symptoms. A key gap in the food allergy literature is a detailed evaluation of how to assess a “failed” trial of allergen avoidance. Some forms of allergen specific immunotherapy improve some symptoms of food allergy. The potential for anaphylaxis and other significant side effects, coupled with the fact that only four of the six studies of this treatment strategy specifically reported side effects, suggests that future studies of immunotherapy should systematically assess and report on common and serious side effects.

The importance of guidelines for the diagnosis and management of food allergy are made clear by two studies we identified as part of this literature review. In the first, caregivers of children attending the University of Maryland Allergy practice were invited to complete a survey that included the Food Allergy Impact Scale. Of 101 caregivers approached, 87 (86 percent) agreed to participate. More than 60 percent of respondents stated that the presence of food allergy affected meal preparation, more than half stated that it affected family social activities, and one quarter stated they never allowed a child to go to camp or a sleepover because of food allergy. With these kinds of effects on their lives of children and their families, the need for accurate diagnosis is clear.

The second article reported on the treatment of food allergy patients at 21 emergency departments in 5 US states and 4 Canadian provinces. In this study, 678 records were reviewed from among 5296 charts identified as having a physician-diagnosed food-related acute allergic reaction. In 51 percent of cases the reaction was considered severe. Thirty three percent of patients had a documented respiratory rate. Four patients (0.5 percent) had a peak flow recorded. About three quarters of patients received an antihistamine, and almost half received systemic steroids, while only 16 percent received epinephrine. These data indicate that current care is probably not adequate for acute allergic reactions. Similar data are not available describing the details of chronic management, but it can be expected to also vary. Effective practice guidelines will be a first step at improving care for food allergies.
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Appendix A: Search Strategies

FOOD ALLERGIES – SEARCH METHODOLOGIES

SEARCH #1a (Diagnosis/Testing):

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2008 (December)

LIMITERS:
Human

SEARCH STRATEGY:
food hypersensitivity/diagnosis
OR
food hypersensitivity AND (Diagnostic Techniques and Procedures[majr] OR Diagnostic Equipment[majr])
OR
food hypersensitivity AND (test[tiab] OR testing[tiab] OR tests[tiab])
OR
(food*[tiab] AND allerg*[tiab]) AND (diagnosis OR diagnose OR diagnosing OR diagnostic* OR test[tiab] OR testing[tiab] OR tests[tiab])
NOT
case report*

NUMBER OF ITEMS RETRIEVED: 4654

SEARCH #1b (Diagnosis/Testing - Revision)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March 3)

LIMITERS:
Human

SEARCH STRATEGY:
food hypersensitivity* OR food allerg*
AND
predictive value of tests OR skin tests OR patch tests OR immunologic tests OR radioallergosorbent tests OR in vitro tests OR immunoassay OR basophil histamine release assay OR food challenge* OR diagnosis[ti] OR diagnoses[ti] OR diagnostic[ti] OR diagnosing

NUMBER OF ITEMS RETRIEVED: 3131
SEARCH #1c (Diagnosis/Testing)

DATABASE:
Cochrane Database of Systematic Reviews

SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, abstract, full text, keywords, caption text]
AND
(diagnosis or diagnoses or diagnose or diagnostic* or diagnosing or test or tests or testing).mp.

NUMBER OF ITEMS RETRIEVED: 82

SEARCH #1d (Treatment)

DATABASE:
Cochrane Database of Systematic Reviews

SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, abstract, full text, keywords, caption text]
AND
(treatment or treat or treating or treated or therapy or therapies or therapeutic or manage or management or managing).mp
NOT
Results of Search 1c

NUMBER OF ITEMS RETRIEVED: 7

SEARCH #1e (Diagnosis/Testing)

DATABASE:
Cochrane Database of Abstracts of Reviews of Effects (DARE)

SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, abstract, full text, keywords, caption text]
AND
(diagnosis or diagnoses or diagnose or diagnostic* or diagnosing or test or tests or testing).mp.

NUMBER OF ITEMS RETRIEVED: 2

SEARCH #1f (Treatment)

DATABASE:
Cochrane Database of Abstracts of Reviews of Effects (DARE)

SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, abstract, full text, keywords, caption text]
AND
(treatment or treat or treating or treated or therapy or therapies or therapeutic or manage or management or managing).mp
NOT
Results of Search 1e

NUMBER OF ITEMS RETRIEVED: 4

SEARCH #1g (Diagnosis/Testing)

DATABASE:
Cochrane Central Register of Controlled Trials

SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
AND
(diagnosis or diagnoses or diagnose or diagnostic* or diagnosing or test or tests or testing).mp.

NUMBER OF ITEMS RETRIEVED: 372 (Sample of 200 reviewed)

SEARCH #1h (Treatment)

DATABASE:
Cochrane Central Register of Controlled Trials

SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
AND
(treatment or treat or treating or treated or therapy or therapies or therapeutic or manage or management or managing).mp
NOT
Results of Search 1g

NUMBER OF ITEMS RETRIEVED: 101

SEARCH #2 (Acute Allergic Reaction - Treatment)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (January)

LIMITERS:
Human

SEARCH STRATEGY:
acute AND (allergy OR allergies OR allergic) AND (react OR reaction*)
AND
treat OR treated OR treatment* OR therapy OR therapies
NOT
drug allerg* OR drug reaction* OR drug hypersensitiv* OR reaction to drug*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 1030

SEARCH #3 (Anaphylaxis)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND allergy OR allergies OR allergic OR hypersensitiv*)
AND
anaphylaxis OR anaphylactic
AND
treat OR treated OR treatment* OR therapy OR therapies
NOT
drug allerg* OR drug reaction* OR drug hypersensitiv* OR reaction to drug*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 558

SEARCH #4a (Specific Conditions - Angioedema)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
angioedema*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 238
SEARCH #4b (Specific Conditions - Asthma)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
asthma*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 2291

SEARCH #4c (Specific Conditions – Celiac Disease) Omitted at request of the NIAID

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
celiac disease OR celiac[tiab]
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 211

SEARCH #4d (Specific Conditions – Colitis)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)

SEARCH STRATEGY:
food hypersensitivit* OR food allerg*
AND
colitis

NUMBER OF ITEMS RETRIEVED: 106

SEARCH #4e (Specific Conditions – Cow Milk-Induced Colitis or Blood in Stool)

DATABASE & TIME PERIOD COVERED:
SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR 
hypersensitiv*))
AND
cow* AND milk
AND
colitis OR (blood AND stool*) OR proctocolitis OR (rectal AND bleed*)
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 83

-------------------------------------------------------------------------

SEARCH #4f (Specific Conditions – Dermatitis, Atopic & Contact)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR 
hypersensitiv*))
AND
dermatitis
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 1919

-------------------------------------------------------------------------

SEARCH #4g (Specific Conditions – Dermatitis Herpetiformis) Omitted at request of the 
NIAID

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR 
hypersensitiv*))
AND
dermatitis herpetiformis
NOT
case report* OR case reports[pt]
NOT
animal NOT human
NOT
Results of Search 4f
NUMBER OF ITEMS RETRIEVED: 507

SEARCH #4h (Specific Conditions – Eosinophilic Esophagitis)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
eosinophilic esophagitis
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 326

SEARCH #4i (Specific Conditions – Eosinophilic Gastroenteritis)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
eosinophilic gastroenteritis
NOT
case report* OR case reports[pt]
NOT
animal NOT human
NOT
Results of Search 4h

NUMBER OF ITEMS RETRIEVED: 200

SEARCH #4j (Specific Conditions – Exercise-Induced)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)

SEARCH STRATEGY:
food hypersensitivit* OR food allerg*
AND
exercise OR exercise-induced OR physical activity
NUMBER OF ITEMS RETRIEVED: 196

SEARCH #4k (Specific Conditions – Flushing)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)

SEARCH STRATEGY:
food hypersensitivit* OR food allerg*
AND
flushing

NUMBER OF ITEMS RETRIEVED: 27

SEARCH #4l (Specific Conditions – Food-Induced Proctocolitis Syndrome)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
(food induced OR food-induced) AND proctocolitis AND syndrome*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 2

SEARCH #4m (Specific Conditions – Food Protein-Induced Enterocolitis Syndrome)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
food AND (protein OR proteins) AND enterocolitis AND syndrome*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 28

SEARCH #4n (Specific Conditions – Gastrointestinal Hypersensitivity)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)
SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypo-sensitiv*))
AND
gastrointestinal hypersensitiv* OR vomiting OR colic OR diarrhea
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 475

SEARCH #4o (Specific Conditions – Heiner’s Syndrome)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypo-sensitiv*))
AND
heiner* OR pulmonary hemisiderosis
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 6

SEARCH #4p (Specific Conditions – Inflammatory Bowel Disease)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypo-sensitiv*))
AND
inflammatory bowel diseases[mh] OR inflammatory bowel disease*[tiab]
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 170

SEARCH #4q (Specific Conditions – Laryngeal Edema)

DATABASE & TIME PERIOD COVERED:
SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
laryngeal edema
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 27

SEARCH #4r (Specific Conditions – Milk Protein Allergy of Infancy)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
milk AND (protein OR proteins) AND infan*
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 1059

SEARCH #4s (Specific Conditions – Oral Allergy Syndrome)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)

SEARCH STRATEGY:
food hypersensitivit* OR food allerg*
AND
oral allergy syndrome*

NUMBER OF ITEMS RETRIEVED: 219

SEARCH #4t (Specific Conditions – Rhinitis)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)

SEARCH STRATEGY:
food hypersensitivit* OR food allerg*
AND
rhinitis

NUMBER OF ITEMS RETRIEVED: 641

SEARCH #4u (Specific Conditions – Rhinoconjunctivitis)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)

SEARCH STRATEGY:
food hypersensitivit* OR food allerg*
AND
rhinoconjunctivitis OR conjunctivitis

NUMBER OF ITEMS RETRIEVED: 186

SEARCH #4v (Specific Conditions – Urticaria)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (March)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
urticaria OR hives
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 687

SEARCH #5 (Epinephrine)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009 (February)

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
epinephrine
NOT
case report* OR case reports[pt]
NOT
animal NOT human
NUMBER OF ITEMS RETRIEVED: 244

SEARCH #6

DATABASE & TIME PERIOD COVERED:
World Allergy Organization Journal – 1988-2009 (February)

SEARCH STRATEGY:
food

NUMBER OF ITEMS RETRIEVED: 163

SEARCH #7 (Cow’s Milk Allergy - Revision)

DATABASE & TIME PERIOD COVERED:
PUBMED – 1988-2009/7/20

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
cow* AND milk
NOT
case report* OR case reports[pt]
NOT
animal NOT human

NUMBER OF ITEMS RETRIEVED: 1264

SEARCH #8a (Food Allergy/Food Hypersensitivity - Revision)

DATABASE & TIME PERIOD COVERED:
PUBMED – 2008/11-2009/8/24

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
NOT
animal* NOT (human OR humans)

NUMBER OF ITEMS RETRIEVED: 777

SEARCH #8b (Food Allergy/Food Hypersensitivity - Revision)

DATABASE & TIME PERIOD COVERED:
PubMed 1988-2009/9/2
SEARCH STRATEGY:
food hypersensitivity[mh]
NOT
food hypersensitivit*
NOT
animal* NOT (human OR humans)

NUMBER OF ITEMS RETRIEVED: 1427
NUMBER OF ITEMS AFTER REMOVING DUPLICATES FROM PREVIOUS SEARCHES: 409

SEARCH #8c (Food Allergy/Food Hypersensitivity - Revision)
DATABASE & TIME PERIOD COVERED:
Cochrane Database of Systematic Reviews – 2008-2009
SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp.
NUMBER OF ITEMS RETRIEVED: 54

SEARCH #8d (Food Allergy/Food Hypersensitivity - Revision)
DATABASE & TIME PERIOD COVERED:
Cochrane Controlled Trials Register (CCTR) – 2008-2009
SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp.
NUMBER OF ITEMS RETRIEVED: 23

SEARCH #8e (Food Allergy/Food Hypersensitivity - Revision)
DATABASE & TIME PERIOD COVERED:
Cochrane Database of Abstracts of Reviews of Effects (DARE) – All years
SEARCH STRATEGY:
(food hypersensitivity or (food* and (allergy or allergies or allergic or allergen*))).mp.
NUMBER OF ITEMS RETRIEVED: 11

SEARCH #9 (Author L. Schwartz articles on Tryptase)
DATABASE & TIME PERIOD COVERED:
PubMed – All years
SEARCH STRATEGY:
schwartz l*  
AND  
tryptase* OR trypsin* OR beta-tryptase*  

NUMBER OF ITEMS RETRIEVED: 164  

SEARCH #10a (Atopic Dermatitis and Food Avoidance)  
DATABASE & TIME PERIOD COVERED:  
PubMed 1988-2009/9/2  

SEARCH STRATEGY:  
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))  
AND  
atopic dermatitis  
AND  
avoid* OR exclusion OR exclude*  
AND  
(randomized controlled trial* OR rct* OR random allocation OR randomi*[tiab])  
OR Limits: Randomized Controlled Trial  

NUMBER OF ITEMS RETRIEVED: 32  

SEARCH #10b (Atopic Dermatitis and Food Avoidance)  
DATABASE & TIME PERIOD COVERED:  
Cochrane Database of Systematic Reviews, DARE, Controlled Trials Register – All years  

SEARCH STRATEGY:  
atopic dermatitis and (food or foods)).mp.  
AND  
(avoid* or exclusion* or exclude*).mp.  

NUMBER OF ITEMS RETRIEVED: 38  

SEARCH #11a (Anaphylaxis – Systematic Reviews)  
DATABASE & TIME PERIOD COVERED:  

SEARCH STRATEGY:  
anaphyla*  
AND  
systematic[sb]
NUMBER OF ITEMS RETRIEVED: 183

SEARCH #11b (Anaphylaxis – Systematic Reviews)

DATABASE & TIME PERIOD COVERED:
Cochrane Database of Systematic Reviews – 1988-2009

SEARCH STRATEGY:
(anaphylaxis or anaphylactic).af.

NUMBER OF ITEMS RETRIEVED: 48
NUMBER OF ITEMS RELEVANT TO TOPIC: 4

SEARCH #11c (Anaphylaxis – Systematic Reviews)

DATABASE & TIME PERIOD COVERED:
Cochrane DARE – 1988-2009

SEARCH STRATEGY:
(anaphylaxis or anaphylactic).af.

NUMBER OF ITEMS RETRIEVED: 14
NUMBER OF ITEMS RELEVANT TO TOPIC: 2

SEARCH #12a (Influenza Vaccine and Egg Allergy)

DATABASE & TIME PERIOD COVERED:

SEARCH STRATEGY:
food hypersensitivity OR ((food OR foods) AND (allergy OR allergies OR allergic OR hypersensitiv*))
AND
influenza vaccine OR ((vaccine* OR vaccination) AND (flu OR influenza))
AND
egg OR eggs
NOT
animal* NOT (human OR humans)

NUMBER OF ITEMS RETRIEVED: 31

SEARCH #12b (Influenza Vaccine and Egg Allergy)

DATABASE & TIME PERIOD COVERED:
Cochrane Database of Systematic Reviews – All years

SEARCH STRATEGY:
(egg or eggs).af.
AND
(allerg* or hypersensitiv*).af.
AND
(vaccin* or immuniz* or immunis*).af.
AND
(flu or influenza).af.

NUMBER OF ITEMS RETRIEVED: 3

SEARCH #12c (Influenza Vaccine and Egg Allergy)

DATABASE & TIME PERIOD COVERED:
Cochrane Controlled Trials Register – All years

SEARCH STRATEGY:
(egg or eggs).af.
AND
(allerg* or hypersensitiv*).af.
AND
(vaccin* or immuniz* or immunis*).af.
AND
(flu or influenza).af.

NUMBER OF ITEMS RETRIEVED: 3
Appendix B: Screening Form

4/10/2009

Food Allergies Screener

1. Article type
   - Original data
   - Systematic review
   - Background/contextual
   - Non-systematic review, Commentary, Other

2. Purpose of the study
   - Incidence/prevalence/natural history
   - Diagnosis
   - Treatment/management/prevention
   - Not a food allergy study
   - Other (specify: ____________) STOP

3. Food of concern
   - Multiple foods (>2) or NOS
   - Milk
   - Egg
   - Peanut/tree nut
   - Fish/shellfish
   - Soy
   - Wheat
   - Other (specify: ____________)
   - Other (specify: ____________)
   - Other (specify: ____________)

4. Sample size
   - ____________
   - Unclear Enter '88,888,888'
   - Not specified Enter '99,999,999'

5. Condition
   - Food allergy, multiple condition (>2) or NOS
   - Allergy, NOS
   - Classic food-related anaphylaxis
   - Food-associated, exercise-induced syndromes
   - Celiac disease
   - Colitis
   - Eosinophilic Esophagitis/Gastroenteritis
   - Cow milk allergy syndrome:
     - Induced colitis (and blood in the stools)
     - Food-induced enterocolitis syndrome
     - Food-induced proctocolitis syndrome
     - Milk protein allergy of infancy
   - Gastrointestinal hypersensitivity
     - (e.g. vomiting, colic, diarrhea)
   - Laryngeal edema
     - Contact dermatitis
     - Dermatitis herpetiformis
     - Raynaud, atopic dermatitis
     - Generalized flushing
     - Oral Allergy Syndrome
     - Rhinitis, rhinoconjunctivitis, conjunctivitis
     - Urticaria
     - Angioedema
     - Asthma
     - Heiner's Syndrome (pulmonary hemosiderosis)
     - Other (specify: ____________)
     - Other (specify: ____________)
     - Other (specify: ____________)

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Food Allergies Screener

Incidence/prevalence/natural history studies

6. From where were the patients identified?
   - Single clinic or hospital: 1
   - Regional: 2
   - National: 3
   - International: 4
   - Other (specify): 5

7. How were patients selected?
   - Population-based/systematic: 1
   - Convenience/nonrepresentative sample: 2
   - Combination: 3
   - Unclear/unknown: 4
   - Other (specify): 5

8. Country
   - US: □
   - Canada, UK, Ireland, Australia, New Zealand: □
   - Scandinavia, Europe: □
   - Japan, China, Taiwan, Korea, Singapore: □
   - Mediterranean: □
   - Other (specify):  □

9. How was food allergy assessed?
   - Self-report/parent report:  □
   - Administrative data/medical records:  □
   - Testing:
     - Skin:  □
     - Blood (e.g., RAST):  □
     - Oral/labial food challenge:  □
     - Elimination diet:  □
     - Other (specify):  □

Diagnosis studies

10. How were patients identified?
    - Primary care: 1
    - Specialist: 2
    - Mixed: 3
    - Unclear/unknown: 4
    - Other (specify): 5

11. Diagnostic test(s)
    - Patient history, physical exam:  □
    - Immediate skin testing:
      - Total serum IgE:  □
      - Allergen-specific serum IgE:  □
      - Other tests:  □
      - In vitro:
        - Basophil activation:  □
        - Basophil activation:  □
      - Atopy patch testing:  □
      - Elimination diet:  □
      - Oral/labial food challenge:  □
      - Other (specify):  □

12. Reference test(s)
    - Patient history, physical exam:  □
    - Immediate skin testing:
      - Total serum IgE:  □
      - Allergen-specific serum IgE:  □
      - Basophil activation:  □
      - Other tests:  □
      - In vitro:
        - Basophil activation:  □
        - Basophil activation:  □
      - Atopy patch testing:  □
      - Elimination diet:  □
      - Oral/labial food challenge:  □
      - Other (specify):  □

13. Were data reported on sensitivity or specificity or positive/negative predictive value or false positive/false negative rate?
    - Yes: 1
    - No: 2
    - Unclear/unknown: 3

Treatment/management/prevention studies

14. Study Design
    - Controlled trial: 1
    - Cohort/case series: 2
    - Case control: 3
    - Case study: 4
    - Decision analysis: 5
    - Mixed: 6
    - Unclear/None of the above: 9

15. Target of the intervention
    - Patient: □
    - Maternal/prenatal: □
    - Unclear: □
    - Other (specify): □

16. Interventions:
    - 1 2 3 4 5
      - Placebo/usual care: 1 2 3 4 5
      - Elimination diet: □ □ □ □ □
      - Desensitization: □ □ □ □ □
      - Pharmacological: □ □ □ □ □
      - Modified food product: □ □ □ □ □
      - Other: □ □ □ □ □
      - Other: □ □ □ □ □
      - Other: □ □ □ □ □
Appendix C: Study Design Definitions

**Review/meta-analysis**

**Review:** A review article that summarizes a number of different studies and may draw conclusions about a particular intervention. The methods used to identify, select and appraise the studies are not systematic or necessarily reproducible. (Any review article that is not clearly a systematic review or a meta-analysis is a "review.") The summary in a review is generally narrative.

**Systematic review:** A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods are NOT used to analyze and summarize the results of the included studies.

**Meta-analysis:** A systematic review that uses statistical methods to integrate the results of the individual studies. A meta-analysis contains at least one pooled analysis.

**Controlled trials**

**Randomized clinical trial:** includes a trial in which the participants (or other units) were definitely assigned prospectively to one or two (or more) alternative forms of health care [interventions] using a process of random allocation.$^1$

**Trial with open-label extension:** Randomized clinical trial or controlled clinical trial with an open-label extension.

**Controlled clinical trial:** includes a trial in which participants (or other units) were: a) definitely assigned prospectively to one or two (or more) alternative forms of health care [interventions] using a quasi-random allocation method or; b) possibly assigned prospectively to one or two (or more) alternative forms of health care using a process of random or quasi-random allocation.

**Cohort / case series**

**Cohort:** two or more groups assembled on a specific characteristic or characteristics are subjected to an exposure, and followed.

In a *retrospective cohort* study, all the events - exposure, latent period, and subsequent development of disease, have already occurred in the past. The investigators collect the data now and establish the risk of developing a disease if exposed to a particular risk factor. In contrast, a *prospective cohort* study is conducted by starting with two groups at the current point, and following up in future for occurrence of disease, if any. Prospective cohorts should be summarized with the relative risk; retrospective cohorts should be summarized with the odds ratio.
**Case series**: a group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients, including demographic information and information on diagnosis, treatment, response to treatment, and follow-up after treatment.

**Case-control**

A retrospective design in which cases are matched to controls and then exposure is compared.

**Case study**

A case study is a medical case report describing the course of an illness or a response to treatment in a single patient. Published case reports can be the first indication of a new benefit of a treatment in an unexpected population group or a may act as the first warning of a new unexpected adverse event.

**Mixed**

Any combination of the above.

**Unsure / None of the above**

Includes any study design not listed above, such as editorials, letters, general clinical review articles, etc.

---

\(^1\)Adapted from Cochrane Effective Practice and Organization of Care Review Group, The Data Collection Checklist, Inclusion Criteria.
Appendix D: Criteria for Assessing the Quality of Studies of Diagnostic Accuracy

**Lijmer Criteria for Scoring Study Quality**

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<thead>
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<th>Study Characteristic</th>
<th>Score</th>
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<tr>
<td>Spectrum</td>
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<td>Clinical population</td>
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<td>Case-control</td>
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<td>Verification</td>
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<td>Different reference tests</td>
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<td>Interpretation of test results</td>
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<td>Insufficient</td>
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</tbody>
</table>

QUADAS Tool for Assessing Study Quality (Each item is assessed as yes (1), no (2), or unclear (3) For the present study, domains 12 and 13 were not assessed

1. Was the spectrum of patients representative of the patients who will receive the test in practice? (CIRCLE ONE)
   Yes ................................................................. 1
   No ................................................................. 2
   Unclear ............................................................ 3
   *How to score: Score ‘yes’ if based on information reported from study’s authors, you believe the spectrum of patients included in the study is representative of those in whom the test will be used in practice. Judgment should be based on both method of recruitment and the characteristics of those recruited. Score ‘no’ if you think the study used does not fit into what was specified as acceptable. Score ‘no’ if studies recruit a group of healthy controls and a group known to have the target disorder.

2. Were selection criteria clearly described? (CIRCLE ONE)
   Yes ................................................................. 1
   No ................................................................. 2
   Unclear ............................................................ 3
   *How to score: Score ‘yes’ if you think all relevant information regarding how participants were selected for inclusion has been provided. Score ‘no’ if study selection criteria are not clearly reported.

3. Is the reference standard likely to correctly classify the target condition? (CIRCLE ONE)
   Yes ................................................................. 1
   No ................................................................. 2
   Unclear ............................................................ 3
   *How to score: Score ‘yes’ if you believe the reference standard is likely to correctly classify the target condition or is the best method available. Score ‘no’ if you do not think the reference standard was likely to have correctly classified the target condition.

4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? (CIRCLE ONE)
   Yes ................................................................. 1
   No ................................................................. 2
   Unclear ............................................................ 3
   *How to score: For conditions that progress rapidly, should be scored ‘yes’ if delay between performance of index and reference test if very short. If condition is chronic, longer delay periods may be appropriate. You will have to determine what is ‘short enough.’ Score ‘no’ if you think performance of index test and reference standard was sufficiently long that disease status may have changed between the performance of the two tests.

5. Did the whole sample or a random selection of the sample, receive verification using a reference standard? (CIRCLE ONE)
   Yes ................................................................. 1
   No ................................................................. 2
   Unclear ............................................................ 3
   *How to score: Score ‘yes’ if it is clear that all patients or a random selection of patient who received index test went on to receive verification of disease status using reference standard. Score ‘no’ if some patients did not receive verification of disease status and selection of patient to receive reference standard was not random.

6. Did patients receive the same reference standard regardless of the index test result? (CIRCLE ONE)
   Yes ................................................................. 1
   No ................................................................. 2
   Unclear ............................................................ 3
   *How to score: Score ‘yes’ if it is clear that patients received verification of their true disease status using the same reference standard. Score ‘no’ if some patients received verification using a different reference standard.
### RAND EPC - QUADAS questionnaire

7. Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?

<table>
<thead>
<tr>
<th></th>
<th>(Circle One)</th>
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<tr>
<td>No</td>
<td>2</td>
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<tr>
<td>Unclear</td>
<td>3</td>
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</tbody>
</table>

*How to score: Score ‘yes’ if it is clear from the study that the index test did not form part of the reference standard. Score ‘no’ if it appears that the index test formed part of the reference standard.

8. Was the execution of the index test described in sufficient detail to permit replication of the test?

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
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<tr>
<td>No</td>
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<tr>
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</table>

*How to score: See following question.

9. Was the execution of the reference standard described in sufficient detail to permit its replication?

<table>
<thead>
<tr>
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<th>(Circle One)</th>
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</thead>
<tbody>
<tr>
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<td>1</td>
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<tr>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Unclear</td>
<td>3</td>
</tr>
</tbody>
</table>

*How to score: Score ‘yes’ if study reports sufficient details or citations to permit replication of the index test and reference standard. Score ‘no’ in other cases.

10. Were the index test results interpreted without knowledge of the results of the reference standard?

<table>
<thead>
<tr>
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</tr>
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<td>2</td>
</tr>
<tr>
<td>Unclear</td>
<td>3</td>
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</table>

*How to score: See following question.

11. Were the reference standard results interpreted without knowledge of the results of the index test?

<table>
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<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Unclear</td>
<td>3</td>
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</tbody>
</table>

*How to score: Score ‘yes’ if study clearly states that the test results (index or reference standard) were interpreted blind to the results of the other test. Score ‘no’ if it does not appear that test results were interpreted blind to results of the other test.

12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?

<table>
<thead>
<tr>
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<th>(Circle One)</th>
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<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Unclear</td>
<td>3</td>
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</tbody>
</table>

*How to score: Score ‘yes’ if clinical data would normally be available when the test is interpreted in practice and similar data were available when interpreting the index test in the study and when clinical data were not available in practice and those data were not available when the index test results were interpreted. Score ‘no’ if this is not the case.

13. Were uninterpretable/indeterminate/test results reported?

<table>
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<tr>
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<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Unclear</td>
<td>3</td>
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</tbody>
</table>

*How to score: Score ‘yes’ if it is clear that all test results, including uninterpretable/indeterminate/intermediate results are reported. Score ‘no’ if you think that such results occurred but have not been reported.

14. Were withdrawals from the study explained?

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</tr>
<tr>
<td>Unclear</td>
<td>3</td>
</tr>
</tbody>
</table>

*How to score: Score ‘yes’ if it is clear what happened to all patients who entered the study, for example if a flow diagram of study participants is reported. Score ‘no’ if it appears that some of the participants who entered the study did not complete the study (i.e., did not receive both the index test and reference standard and these patients were not accounted for).

<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Item #</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE/ABSTRACT/KEYWORDS</td>
<td>1</td>
<td>Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>2</td>
<td>State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.</td>
</tr>
<tr>
<td>METHODS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>3</td>
<td>The study population: The inclusion and exclusion criteria, setting and locations where data were collected.</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?</td>
</tr>
<tr>
<td>Test methods</td>
<td>7</td>
<td>The reference standard and its rationale.</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>The number, training and expertise of the persons executing and reading the index tests and the reference standard.</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12</td>
<td>Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Methods for calculating test reproducibility, if done.</td>
</tr>
<tr>
<td>RESULTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>14</td>
<td>When study was performed, including beginning and end dates of recruitment.</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).</td>
</tr>
<tr>
<td>Test results</td>
<td>17</td>
<td>Time-interval between the index tests and the reference standard, and any treatment administered in between.</td>
</tr>
<tr>
<td>18</td>
<td>Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Any adverse events from performing the index tests or the reference standard.</td>
<td></td>
</tr>
<tr>
<td>Estimates</td>
<td>21</td>
<td>Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).</td>
</tr>
<tr>
<td>Estimates</td>
<td>22</td>
<td>How indeterminate results, missing data and outliers of the index tests were handled.</td>
</tr>
<tr>
<td>Estimates</td>
<td>23</td>
<td>Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.</td>
</tr>
<tr>
<td>Estimates</td>
<td>24</td>
<td>Estimates of test reproducibility, if done.</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>25</td>
<td>Discuss the clinical applicability of the study findings.</td>
</tr>
</tbody>
</table>

Appendix E. Excluded Studies: Incidence/Prevalence, Natural History

**Population-based/systematic sample**


Scandinavia/Europe


44. De Swert LF, Cadot P, Ceuppens JL. Allergy to cooked white potatoes in infants


68. Gustafsson D, Sjoberg O, Foucard T. Sensitization to food and airborne allergens


318


121. Oldak E. The incidence and clinical manifestation of food allergy in unselected Polish infants: follow-up from birth to one year of age. 1997;42(1):196-204.


168. Stewart AG, Ewan PW. The incidence, aetiology and management of anaphylaxis presenting to an accident and emergency department. QJM. 1996;89(11):859-64.


176. Virtanen SMK, M. Pekkanen, J. Kenward, M. G. Uusitalo, U. Pietinen, P.


Japan/China/Taiwan/Korea/Singapore


**Mediterranean**


328


Argentina

Bangladesh

Brazil


Chile


Hongkong

India


**International**

**Iran**

**Israel**


**Malaysia**

**Mexico**

**Netherlands**

**Phillipines**
Russia

South Africa


Thailand


Unclear


**Vietnam**


## Appendix F: Food allergy treatment/management controlled trials: study quality characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomized</th>
<th>Randomization approp.</th>
<th>Treatment allocation concealed</th>
<th>Double blind</th>
<th>Blinding approp.</th>
<th>Outcome assessor blinded</th>
<th>Care provider blinded</th>
<th>Patients blinded</th>
<th>Co-interventions</th>
<th>Drop-out &lt;50%</th>
<th>ITT</th>
<th>Overall quality</th>
</tr>
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<td>NA</td>
<td>NA</td>
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<td>NA</td>
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<td>NS</td>
<td>NA</td>
<td>Yes</td>
<td>Poor</td>
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<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Note: NS=Not stated; NA=not applicable; ITT=intention to treat analysis
### Appendix G: Abbreviations used in this report

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
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<tbody>
<tr>
<td>AAAAI</td>
<td>American Academy of Allergy Asthma and Immunology</td>
</tr>
<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
</tr>
<tr>
<td>ACAAI</td>
<td>American College of Allergy, Asthma &amp; Immunology</td>
</tr>
<tr>
<td>AD</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>AGA</td>
<td>Alpha gliadin antibody</td>
</tr>
<tr>
<td>ALA</td>
<td>Alpha lactalbumin</td>
</tr>
<tr>
<td>AMSTAR</td>
<td>Assessment of multiple systematic reviews</td>
</tr>
<tr>
<td>APT</td>
<td>Atopy patch test</td>
</tr>
<tr>
<td>BLG</td>
<td>beta-lactoglobulin</td>
</tr>
<tr>
<td>CD</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>CLA receptor</td>
<td>Cutaneous lymphocyte-associated antigens receptor</td>
</tr>
<tr>
<td>CLEIA</td>
<td>Chemiluminescent enzyme immunoassay</td>
</tr>
<tr>
<td>CM</td>
<td>Cow’s milk</td>
</tr>
<tr>
<td>CMA</td>
<td>Cow’s milk allergy</td>
</tr>
<tr>
<td>CMPA</td>
<td>Cow’s milk protein allergy</td>
</tr>
<tr>
<td>CME</td>
<td>Continuing medical education</td>
</tr>
<tr>
<td>CMF</td>
<td>Cow milk formula</td>
</tr>
<tr>
<td>CMPPI</td>
<td>Cow’s milk protein intolerance</td>
</tr>
<tr>
<td>CMPIE</td>
<td>Cow’s milk protein induced enteropathy</td>
</tr>
<tr>
<td>ConA</td>
<td>Concanavalin A</td>
</tr>
<tr>
<td>COU</td>
<td>Chronic ordinary urticaria</td>
</tr>
<tr>
<td>DARE</td>
<td>Cochrane Database of Abstracts of Reviews of Effects</td>
</tr>
<tr>
<td>DBPCFC</td>
<td>Double blind placebo controlled food challenge</td>
</tr>
<tr>
<td>DH</td>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>ECAAI</td>
<td>European Academy of Allergy and Clinical Immunology)</td>
</tr>
<tr>
<td>EE/EG</td>
<td>Eosinophilic esophagitis/gastroenteritis</td>
</tr>
<tr>
<td>EGID</td>
<td>Eosinophil-associated gastrointestinal disorders</td>
</tr>
<tr>
<td>eHF</td>
<td>Extensively hydrolyzed formulas</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>EmA</td>
<td>Endomysial antibody</td>
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<td>Eos/HPF</td>
<td>Eosinophils per high-powered field</td>
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<td>EPC</td>
<td>Evidence-based Practice Center</td>
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<tr>
<td>FAAN</td>
<td>Food Allergy and Anaphylaxis Network</td>
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<tr>
<td>FC</td>
<td>Food challenge</td>
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<tr>
<td>FDEIA</td>
<td>Food-associated, exercise-induced syndromes</td>
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<td>FEIA</td>
<td>Fluorescent enzyme immunoassay</td>
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<td>FHx</td>
<td>Family History</td>
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<tr>
<td>GA</td>
<td>Gastrointestinal age</td>
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<tr>
<td>GFD</td>
<td>Gluten free diet</td>
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<tr>
<td>GERD</td>
<td>Gastroesophageal reflux disease</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<td>GINI</td>
<td>German infant nutritional intervention</td>
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<td>HE</td>
<td>Hen’s egg</td>
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<tr>
<td>HCF</td>
<td>Hydrolysed casein formula</td>
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<tr>
<td>Abbreviation</td>
<td>Term</td>
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<tr>
<td>HF</td>
<td>Hydrolyzed formula</td>
</tr>
<tr>
<td>HLA</td>
<td>Human Leukocyte antigen</td>
</tr>
<tr>
<td>IgA/E/G</td>
<td>Immunoglobin class A/E/G</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>L/M</td>
<td>Lactulose/Mannitol</td>
</tr>
<tr>
<td>LP</td>
<td>Lymphocyte proliferation</td>
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<tr>
<td>ME</td>
<td>Milk-induced enterocolitis syndrome</td>
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<tr>
<td>NASPGHN</td>
<td>North American Society for Pediatric Gastroenterology, Hepatology and Nutrition</td>
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<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
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<tr>
<td>NIAID</td>
<td>National Institutes of Allergy and Infectious Disease</td>
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<td>NIH</td>
<td>National Institute of Health</td>
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<tr>
<td>NRL</td>
<td>Natural rubber latex</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
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<td>OAS</td>
<td>Oral allergy syndrome</td>
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<td>OFC</td>
<td>Open food challenge</td>
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<td>OVA</td>
<td>Ovalbumin</td>
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<tr>
<td>OVM</td>
<td>Ovomucoid</td>
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<tr>
<td>OVT</td>
<td>Ovotransferrin</td>
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<td>PAR</td>
<td>Perennial allergic rhinoconjunctivitis</td>
</tr>
<tr>
<td>PBMC</td>
<td>Peripheral blood mononuclear cells</td>
</tr>
<tr>
<td>PHA</td>
<td>Phytohemagglutinin</td>
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<tr>
<td>pHF</td>
<td>Partially hydrolyzed formulas</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
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<tr>
<td>QUADAS</td>
<td>Quality Assessment of Studies of Diagnostic Accuracy</td>
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<td>RAST</td>
<td>Radioallergosorbid test</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>RHF</td>
<td>Rice-based hydrolysate formula</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver-operating characteristics</td>
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<tr>
<td>ROU</td>
<td>Recurrent oral ulceration</td>
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<tr>
<td>SAR</td>
<td>Seasonal allergic rhinoconjunctivitis</td>
</tr>
<tr>
<td>SCORAD</td>
<td>Scoring atopic dermatitis</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>Se</td>
<td>Sensitivity</td>
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<tr>
<td>SES</td>
<td>Socioeconomic Status</td>
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<td>SF</td>
<td>Soy-based Formula</td>
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<td>sIgE</td>
<td>Antigen-specific Immunoglobulin</td>
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<tr>
<td>SLIT</td>
<td>Sublingual immunotherapy</td>
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<tr>
<td>Sp</td>
<td>Specificity</td>
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<td>SPT</td>
<td>Skin prick test</td>
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<tr>
<td>STARD</td>
<td>Standards for the Reporting of Diagnostic Accuracy</td>
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<tr>
<td>TEP</td>
<td>Technical Expert Panel</td>
</tr>
<tr>
<td>Th2</td>
<td>T-helper type 2 cell</td>
</tr>
<tr>
<td>TN</td>
<td>Tree nut</td>
</tr>
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<td>Abbreviation</td>
<td>Term</td>
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<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
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<tr>
<td>tTG</td>
<td>Tissue transglutaminase</td>
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## Appendix H: Evidence Tables-Diagnosis Studies

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<tr>
<th>Author, Yr</th>
<th>Food(s)</th>
<th>Condition</th>
<th>Population</th>
<th>Reference test</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
<th>Comments, Conclusions, (values for QUADAS domains)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernardi, 2008&lt;sup&gt;195&lt;/sup&gt;</td>
<td>19 different foods</td>
<td>Multiple gastrointestinal symptoms and headache</td>
<td>68 consecutive patients seen at a university hospital allergy clinic for symptoms, after ruling out lactose intolerance, celiac disease, pathological GI disease, and psychological disorders</td>
<td>History suggestive of food intolerance and elimination diet</td>
<td>Serum IgG4 Cow’s milk: CM $\geq$2.8 U/L&lt;br&gt;Se Sp PP NP&lt;br&gt;0.83 0.92 0.35 0.99 Hen’s Egg: $\geq$2.0 U/L&lt;br&gt;Se Sp PP NP&lt;br&gt;0.73 0.83 0.25 0.99&lt;br&gt;*Estimated Prevalence 5%</td>
<td>Negative predictive value for sIgG4 may allow it to be used to rule out food allergy (1,1,3,1,1,1,1,1,3,1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bischoff, 1996&lt;sup&gt;156&lt;/sup&gt;</td>
<td>Unclear</td>
<td>Gastrointestinal disease</td>
<td>375 randomly selected patients in GI clinic (Germany) with Crohn’s, ulcerative colitis, or other GI conditions who fit clinical criteria of intestinal food allergy (3 of the following 6 (clinical history): Hx of food-related GI symptoms, increased total sIgE, food sIgE, eosinophilia, improvement w/ cromoglycate, clinical atopy; and 1 of the following 2: +response to provocation or + response to elimination)</td>
<td>Clinical history and + elimination response</td>
<td>Endoscopic allergen provocation: 13 patients underwent a total of 34 tests. Sensitivity: 59% Specificity: 97%</td>
<td>Conclusion not related to Dx test but to possibility that food allergy may be cause of some % of GI disease (2,2,3,1,2,1,3,1,3,3)</td>
<td></td>
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</tr>
<tr>
<td>Calvani 2007&lt;sup&gt;174&lt;/sup&gt;</td>
<td>Milk</td>
<td>CMA</td>
<td>104 children consecutively</td>
<td>Food challenge (70 open and 34</td>
<td>SPT with: - lactalbumin</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Author, Yr</td>
<td>Food(s)</td>
<td>Condition</td>
<td>Population</td>
<td>Reference test</td>
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</tr>
<tr>
<td>Canani, 2007</td>
<td>CM, HE, wheat</td>
<td>Suspected food-related GI symptoms</td>
<td>All children 3-48 months referred to Pediatric gastroenterology center in Naples for suspected FA-related symptoms</td>
<td>OFC with fresh CM, HE, and wheat powder based on reactions to SPT, APT, and sIgE: 89 challenges performed in 60 patients CM: 31/55 positive (10 early reax, 21 late reax) HE: 19/28 positive (5 early reax, 14 late reax)</td>
<td>SPT with fresh foods Positive reaction ≥3mm with no reaction to control Cow’s milk:</td>
<td>sIgE Cow’s milk:</td>
<td>APT with fresh vs. commercial food extracts APT with fresh food Cow’s milk:</td>
<td>APT commercial assay (freeze-dried) Cow’s milk:</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>DBPCFC) 28/104 tests were positive</td>
<td>Se Sp PP NP V V</td>
<td>0.45 0.70 0.67 0.51 Hen’s Egg:</td>
<td>0.32 0.67 0.67</td>
<td>Occlusion time 48 hours; Results read at 72 hours; Positive test defined as a minimum of erythema and slight infiltration</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>- casein - beta-lactoglobulin - fresh milk with positive tests defined as mean wheal diameters 3mm ≥ the negative control.</td>
<td>Hen’s Egg:</td>
<td>0.58 0.67 0.79 0.43 Hen’s Egg:</td>
<td>0.84 1.00 1.00 0.75 APT using fresh food or SPT Cow’s milk:</td>
<td>Fresh foods provided more sensitive APT than extracts; “combination” of test results (APT + SPT and/or sIgE) also increased sensitivity (1,1,1,1,1,1,1,1,1,1,1,2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Se Sp PP NP V V</td>
<td>0.87 0.65 0.77 0.79 Hen’s Egg:</td>
<td>0.95 0.67 0.86 0.86 APT using fresh food or SPT or sIgE Cow’s milk:</td>
<td>0.90 0.52 0.72 0.80 Hen’s Egg:</td>
</tr>
<tr>
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<td></td>
<td>Hen’s Egg:</td>
<td>0.84 0.65 0.77 0.79 Hen’s Egg:</td>
<td>0.95 0.67 0.86 0.86 APT using fresh food or SPT or sIgE Cow’s milk:</td>
<td>0.90 0.52 0.72 0.80 Hen’s Egg:</td>
</tr>
<tr>
<td>Author, Yr</td>
<td>Food(s)</td>
<td>Condition</td>
<td>Population</td>
<td>Reference Test</td>
<td>Test 1</td>
<td>Test 2</td>
<td>Test 3</td>
<td>Comments, Conclusions, (values for QUADAS domains)*</td>
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</tr>
<tr>
<td>Celik-Bilgili, 2005</td>
<td>CM, egg, wheat, soy</td>
<td>AD(88%)</td>
<td>501 children (1 mo-16.1 yr)</td>
<td>Food challenge: DBPCFC if &gt; 1 yr</td>
<td>sIgE CAP system</td>
<td>0.95</td>
<td>0.44</td>
<td>0.78</td>
</tr>
<tr>
<td>Clark, 2007</td>
<td>Egg</td>
<td>Egg allergy</td>
<td>24 children in the UK (2.6-14 yoa) with suspected egg allergy (parent report or Objective symptoms of DBPCFC)</td>
<td>Facial thermography in DBPCFC: Sensitivity: 0.92</td>
<td>(3,3,1,1,1,2,1,3,1,3)</td>
<td></td>
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</tr>
<tr>
<td>Author, Yr</td>
<td>Food(s)</td>
<td>Condition</td>
<td>Population</td>
<td>Reference test</td>
<td>Test 1</td>
<td>Test 2</td>
<td>Test 3</td>
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<tr>
<td>Cobbaert, 2005&lt;sup&gt;191&lt;/sup&gt;</td>
<td>Egg white, milk, codfish, wheat, peanut, soy</td>
<td>positive SPT) challenged with cooked (CE) or uncooked egg (UE)</td>
<td>118 pts &gt;=15 yrs</td>
<td>Clinical HX+SPT?</td>
<td>slgE using DPC Immulite® 2000</td>
<td>Immulite 2000 AlaTOP</td>
<td>Pharmacia??</td>
<td>Referred to as 3&lt;sup&gt;rd&lt;/sup&gt; generation slgE test systems (1,3,1,1,1,3,1,1,1,1,3)</td>
</tr>
<tr>
<td>Cudowska, 2005&lt;sup&gt;199&lt;/sup&gt;</td>
<td>Milk</td>
<td>AEDS</td>
<td>34 children (5 mos-16 yrs) A: 20&lt; 3yrs B: 14≥3 yrs</td>
<td>Food challenge: A: 65%+ B: 35.7%+</td>
<td>APT (delayed) A. Sensitivity 0.80 Specificity 0.79 PPV 0.73 NPV 0.22 +LR 2.67 -LR 0.29 B. Sensitivity 0.80 Specificity 0.89 PPV 0.80 NPV 0.11 +LR 7.2 -LR 0.23</td>
<td>SPT+slgE (immediate) A. Sensitivity 1 Specificity 0.94 PPV 0.75 NPV 0</td>
<td>SPT+slgE+APT A. Sensitivity 0.92 Specificity 0.71 PPV 0.85 NPV 0.17 +LR 3.23 -LR 0.11 B. Sensitivity 0.80 Specificity 0.89 PPV 0.80 NPV 0.11 +LR 7.2 -LR 0.23</td>
<td>APT superior to SPT+slGE for diagnosing delayed CMA. APT + SPT enhances identification of CMA. Age doesn’t seem to affect APT outcome. (1,1,1,1,1,1,1,1,1,3)</td>
</tr>
<tr>
<td>De Boissieu, 2003&lt;sup&gt;194&lt;/sup&gt;</td>
<td>Milk</td>
<td>CMA</td>
<td>35 patients, 2-57 months, referred for diagnosis of non-specific persistent digestive symptoms.</td>
<td>Food challenge (open with f/u DBPCFC if open challenge equivocal) 24 allergic, 11 not allergic</td>
<td>APT positive in 19/24 with CMA, positive in 1/11 w/o CMA</td>
<td>slgE positive in 3/24 with CMA (0.6 KUI/L, 0.36 KUI/L, and 0.49 KUI/L), positive in 0/11 w/o CMA</td>
<td>History: (number positive in CMA and non CMA groups) GERD 15/24, 4/11; colic 11/24, 4/11; diarrhea 13/24, 6/11; constipation</td>
<td>Also reports no positive slgE tests in 6 CMA and 6 nonCMA patients. (2,2,1,3,1,1,1,1,1,3,1)</td>
</tr>
<tr>
<td>Author, Yr</td>
<td>Food(s)</td>
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<tr>
<td>Dieguez, 2008&lt;sup&gt;177&lt;/sup&gt;</td>
<td>Egg</td>
<td>Egg allergy</td>
<td>104 milk allergic children with no prior egg exposure.</td>
<td>Food challenge</td>
<td>SPT Egg white Cutoff 3mm Sensitivity0.95 Specificity0.40 PPV0.59 NPV0.89 +LR1.58 -LR0.14</td>
<td>SPT Egg white Cutoff 6mm Sensitivity0.95 Specificity0.81 PPV0.73 NPV0.81 +LR2.95 -LR0.59</td>
<td>SPT OVM Cutoff 3mm Sensitivity0.67 Specificity0.95 PPV0.71 NPV0.71 +LR4.53 -LR0.39</td>
<td>SPT OVM Cutoff 6mm Sensitivity0.58 Specificity0.97 PPV0.95 NPV0.69 +LR20.42 -LR0.43 (1,1,1,1,1,1,1,1,1,1,3,1)</td>
</tr>
<tr>
<td>Fiocchi, 2004&lt;sup&gt;188&lt;/sup&gt;</td>
<td>Milk, alpha-lactalbumin, casein, egg white, egg yolk, peanut, wheat, codfish, soy, tomato</td>
<td>Wheezing, excema</td>
<td>147 children (0.1-4 yoa)</td>
<td>Food challenge, SPT, History 61 received Dx of IgE-mediated allergy 78 received Dx of non-IgE mediated 8 were considered inconclusive (Exact criteria somewhat unclear)</td>
<td>sIgE Phadiatop Infant Results not reported by food Sensitivity: 0.92 Specificity: 0.82 PPV: 80 NPV: 93</td>
<td>Pharmacia CAP Results not reported</td>
<td>Phadioatop Infant found to be useful for diagnosing IgE-mediated food allergy in children. (1,3,3,1,3,3,1,3,2,3,3,3)</td>
<td></td>
</tr>
<tr>
<td>Garcia-Ara, 2001&lt;sup&gt;167&lt;/sup&gt;</td>
<td>Milk</td>
<td>CMA</td>
<td>170 infants (aged 1-12 months) consecutively seen at a Madrid children’s hospital allergy</td>
<td>Open controlled challenge tests performed in 161 infants; remaining 9 had history of severe</td>
<td>SPT Skin prick test with alpha-lactalbumin (ALA), beta-lactoglobulin</td>
<td>sIgE CAP FEIA using milk, ALA, BLG, and casein;</td>
<td>(1,1,1,2,2,1,1,1,2,3)</td>
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<tr>
<td>Author, Yr</td>
<td>Food(s)</td>
<td>Condition</td>
<td>Population</td>
<td>Reference test</td>
<td>Test 1</td>
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<tr>
<td>Hill, 1988</td>
<td>Milk</td>
<td>CMA</td>
<td>135 children referred to specialist with CMA (5 mos-13 yrs)</td>
<td>allergic reaction to cow’s milk protein and evidence of milk sIgE</td>
<td>(BLG), whole milk, and casein; positive test defined as a net wheel diameter 3mm&gt;negative control (see Table 19)</td>
<td>positive test defined as sIgE≥0.35 (see Table 24)</td>
<td></td>
<td>Children divided into &lt;5 and 5 and over. Predictive value of RAST alone not reported (1,1,1,1,1,1,1,1,1,3)</td>
</tr>
<tr>
<td>Hwang, 2008</td>
<td>Milk</td>
<td>Cow milk protein-induced enterocolitis</td>
<td>16 Korean patients (14-44 days) admitted to hospital with suspected CMPIE: (vomiting, diarrhea, failure to thrive, lethargy). Infants switched to protein hydrolysate formula and/or breast milk, other factors ruled out (e.g., infection), and weight stabilized prior to challenge</td>
<td>&gt;1 of vomiting, lethargy, diarrhea, GJA for leuks, peripheral blood leukocyte count and ANC, CRP, stool smear test for occult blood or leuks following food challenge test</td>
<td>Gastric Juice Analysis (leukocyte ct.) 15/16 positive Cf. 14/16 positive for vomiting</td>
<td>14/16 vomiting+ 5/16+ Peripheral absolute neutrophil count 12/16+ Fecal white blood cells 0/16+ C-reactive protein (&gt;1mg/dL)</td>
<td>GJA was positive in 15 of 16 patients with CMPIE (though the definitive diagnosis appeared to have used GJA). (3,1,1,1,1,2,1,1,3,3,1)</td>
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<tr>
<td>Iacono, 2006</td>
<td>Milk</td>
<td>CMPI</td>
<td>796 children (aged 1 month to 10 years) consecutively referred to the gastroenterology clinic at an Italian hospital with suspected CMPI</td>
<td>Elimination and DBPCFC</td>
<td>Umbilical erythema: Of 384 diagnosed with CMPI, 36 children had umbilical erythema: sensitivity=0.09. There were no cases of children with umbilical erythema and</td>
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<td>(1,1,1,1,1,1,1,3,1,1,3)</td>
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<td>Isolauri, 1996</td>
<td>Milk</td>
<td>CMA</td>
<td>183 patients (2-36 months) referred to specialist for evaluation of AD</td>
<td>Food challenge (open and DBPCFC)</td>
<td>SPT sensitivity 0.48, specificity 0.86</td>
<td>APT: sensitivity 0.61, specificity 0.81</td>
<td>SPT+APT: parallel: sensitivity 0.86, specificity 0.72 serial: specificity 0.24 sensitivity 0.94</td>
<td>(3,1,1,1,1,1,1,1,1,1,3,1)</td>
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<td>Jarvinen, 2003</td>
<td>Cereals Milk</td>
<td>AD (SCORAD)</td>
<td>90 children (2.5-36 months) w/CMA (both IgE- and non-IgE-mediated) controlled via elimination but w/ residual symptoms that did not respond to elimination of eggs, nuts, fruits, chocolate, fish</td>
<td>Elimination and Open Challenge w/oats, wheat, rye, barley: +challenge 73% (17% immediate, 83% delayed) (Elimination led to improvement in AD) (Blinding?)</td>
<td>SPT cereal (wheat) Sensitivity: 0.23(0.17) Specificity: 1.0 (1.0) PPV: 1.0 (1.0) NPV: 0.32 (0.36)</td>
<td>APT cereal (wheat) Sensitivity: 0.67 (0.7) Specificity: 0.79 (0.71) PPV: 0.9 (0.84) NPV: 0.46 (0.53)</td>
<td>SPT+APT Sensitivity: 0.73 (0.77) Specificity: 0.83 (0.17) PPV: 0.92 (0.85) NPV: 0.53 (0.59)</td>
<td>APT as sensitive as SPT for immed hypersensitivity but far more efficient for detecting delayed. APT aids in Dx cereal allergy, esp. w/SPT, but challenge still needed to confirm Dx (3,1,1,1,1,1,1,1,1,3,3)</td>
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<tr>
<td>Keskin, 2005</td>
<td>Milk</td>
<td>CMA</td>
<td>37 children referred to specialist for suspected CMA.</td>
<td>DBPCFC</td>
<td>SPT</td>
<td>Cutoff point≥3mm</td>
<td>Sensitivity 0.91</td>
<td>Specificity 0.50</td>
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<td>Lee, 2009</td>
<td>Egg, milk, peanut, shrimp</td>
<td>Unspecified</td>
<td>283 Korean patients with suspected allergy from 1-75 years old</td>
<td>SPT</td>
<td>slgE</td>
<td>Immulite 2000</td>
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<tr>
<td>Lilja, 1995</td>
<td>CM, egg, fish, hazelnut, soy, peanut, wheat</td>
<td>Atopy (AD or asthma)</td>
<td>193 children w/ FHx of atopy (4.7-5.9 yrs) followed from birth</td>
<td>Summarized SPT and clinical hx at 5 yoa: 20 children w/+SPT to food (94% specificity cf. clinical signs/symptoms); 36 children w/+SPT to food or aeroallergen; 68 children w/+clinical signs/symptoms</td>
<td>Phadiatop paediatric (PP) (food+inhalant allergens): 44 children (23%) w/+test Sensitivity, specificity, and efficacy lower than for P where efficacy=#true positives + #true negatives)/total n</td>
<td>Phadiatop (P) (inhalant allergens only) cf. +SPT: Sensitivity:0.86 Specificity:0.94 Efficacy:92%</td>
<td>P+Mixed Food RAST (PMF) cf. +SPT: Sensitivity:0.89 Specificity:0.83 Efficacy:0.84</td>
<td>In preschool children, identification of source of atopic allergy depends highly on test chosen. P appears preferable to PP or PMF, esp. where birch pollen is common allergen (3,3,3,1,1,1,1,1,1,1,1,1,3)</td>
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<tr>
<td>Maloney, 2008</td>
<td>Peanut, tree nuts, seeds</td>
<td>Suspected allergy to peanuts, tree nuts, seeds: AD, asthma</td>
<td>All individuals referred to pediatric allergy clinic in Boulder CO for suspected allergy to peanut, tree nut, seeds; 324 patients (2.4 months – 40.2 years)</td>
<td>Clinical history, questionnaire, and/or SPT or slgE 72% had convincing history of peanut allergy</td>
<td>ImunoCAP slgE Peanut Cutoff: ≥13 kU/L</td>
<td>0.60 0.96 0.99 0.35</td>
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<tr>
<td>Mehl, 2006</td>
<td>Milk, egg, wheat, soy</td>
<td>various</td>
<td>437 children referred to specialist (Germany) for diagnosis of suspected food allergy (3 mos-14 yrs.)</td>
<td>Food challenge</td>
<td>SPT CM: Sensitivity 0.85 Specificity 0.70 PPV 0.73 NPV 0.83 Efficiency 0.78</td>
<td>Egg: Sensitivity 0.93 Specificity 0.54 PPV 0.79 NPV 0.81 Efficiency: 0.79</td>
<td>Wheat: Sensitivity 0.75 Specificity 0.64 PPV 0.49 NPV 0.85 Efficiency 0.68</td>
<td>Soy: Sensitivity 0.29 Specificity 0.85 PPV: 0.33 NPV: 0.82 Efficiency: 0.73</td>
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| Monti | Egg | AD | 107 children (1-19) | Oral challenge | SPT w/albumin Specific | | | | | | | | | | 347
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<tr>
<td>Ninimaki, 1995182</td>
<td>Spices, fruits, vegetables</td>
<td>AD, respiratory symptoms</td>
<td>49 patients (1-51 yrs) with strongly + (≥5mm wheal) SPT results to ≥1 native spice</td>
<td>Repeat SPT w/native spices and extracts: 46/49 +SPT</td>
<td>Total IgE: No correlation w/ SPT</td>
<td>Antigen- Specific IgE: Correlated with +SPT to correspondi ng spice extracts</td>
<td>Clinical signs/symptoms of ingesting or handling spices: No correlation w/ SPT or specific IgE; only a minority seem to produce clinical symptoms</td>
<td>(3,2,3,1,1,1,1,1,1,3,3)</td>
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<tr>
<td>Osterballe, 2004169</td>
<td>CM and HE</td>
<td>Report of food hypersensitivity by questionnaire</td>
<td>495 children 3 years of age with and without AD (Danish birth cohort)</td>
<td>OFC to assess both early and late reactions: 3/8 positive for CM 8/14 positive for HE</td>
<td>SPT Cutoff: ≥3mm Cow’s milk: 2/8 positive</td>
<td>APT Scoring after 72 hours; positive test ranged from erythema and slight infiltration to papules and vesicles Cow’s milk: 0/8 positive</td>
<td>slgE (Magic Lite) Cutoff: 1.43 sU/ml Cow’s milk: 3/8 positive</td>
<td>Basophil Histamine Release (n=305) Cutoff: ≥10ng/ml Cow’s milk: 3/8 positive</td>
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<tr>
<td>Prahl, 1988166</td>
<td>Milk</td>
<td>CMA</td>
<td>26 children (aged 1-63 months) consecutively</td>
<td>Open food challenge Skin prick test with raw cow’s milk, positive test</td>
<td>sIgE (RAST) Basophil histamine release test</td>
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<td>(1,3,1,1,1,1,1,1,3,3,3)</td>
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<td>Rance, 2002&lt;sup&gt;165&lt;/sup&gt;</td>
<td>Peanut</td>
<td>363 children referred for suspected peanut allergy</td>
<td>DBPCFC: 177 + 186 --</td>
<td>SPT: NPV for raw extract =1 SPT&gt;3mm: specificity 74% SPT≥16mm: PPV=1</td>
<td>slgE (CAP) Median kU/L + reax: 10 (0-100) - reax: 0 (0-56) kU/L≥57: PPV=1</td>
<td>slgE+SPT Predictive values of nearly 1 for the following cutoffs: + Dx: SPT≥16 and slgE≥57 -Dx: SP&lt;3 and slgE&lt;57</td>
<td>Performance characteristics of raw extracts were superior to commercial. DBPCFC can be avoided if SPT&lt;3 and slgE&lt;57 (neg Dx) or if SPT≥3 and slgE≥57 (pos Dx) (3,3,1,1,1,1,1,1,1,1)</td>
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<tr>
<td>Rancé, 2004&lt;sup&gt;170&lt;/sup&gt;</td>
<td>Cow’s milk, fresh egg, peanut, wheat powder, soymilk mustard powder</td>
<td>AD</td>
<td>48 children, 3-29 months, consecutively recruited to a French pediatric hospital allergy clinic</td>
<td>OFC (based on results of APT, SPT, or slgE) or slgE</td>
<td>APT Occlusion times: 1st row: 24 hr; 2&lt;sup&gt;nd&lt;/sup&gt; row: 48 hr.</td>
<td>SPT Fresh foods Cutoff: ≥3mm greater than negative control and at least 50% greater than positive control Cow’s milk:</td>
<td>Sensitivity, PPV, and NPV were all better for the 48-hour occlusion time (1,1,1,1,1,1,1,1,1,1,1,1)</td>
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### Food(s) Condition
- **Cow’s milk, fresh egg, peanut, wheat powder, soymilk mustard powder**
- **Peanut**
- **Cow’s milk**
- **Fresh foods**
- **Cow’s milk, wheat powder, soymilk mustard powder**

### Reference test
- **DBPCFC:**
  - 177 + 186 --
- **SPT:**
  - NPV for raw extract =1
  - SPT>3mm: specificity 74%
  - SPT≥16mm: PPV=1

### Test 1
- **slgE (CAP):**
  - Median kU/L + reax: 10 (0-100)
  - - reax: 0 (0-56)
  - kU/L≥57: PPV=1

### Test 2
- **slgE+SPT:**
  - Predictive values of nearly 1 for the following cutoffs:
    - + Dx: SPT≥16 and slgE≥57
    - -Dx: SP<3 and slgE<57

### Comments, Conclusions, (values for QUADAS domains)*
- Performance characteristics of raw extracts were superior to commercial. DBPCFC can be avoided if SPT<3 and slgE<57 (neg Dx) or if SPT≥3 and slgE≥57 (pos Dx) (3,3,1,1,1,1,1,1,1,1,1)
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<tr>
<td>Ricci, 2003</td>
<td>Cow’s milk (CM) and hen’s egg (HE)</td>
<td>Multiple allergic symptoms</td>
<td>151 children consecutively referred to a university hospital pediatric allergy clinic in Bologna</td>
<td>FC (blinding not specified) 27 positive for CM 40 positive for HE</td>
<td>Se Sp PP NP</td>
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<td>SPT</td>
<td>Cutoff: wheal diameter ≥ 3 mm</td>
<td>Cow’s milk: 17/22 positive</td>
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<td>0.77 0.88 0.63 0.94</td>
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<td>Hen’s Egg: 31/34 positive</td>
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<td>sIgE Pharmacia UniCAP cutoff &gt; 0.35 kU/L</td>
<td>Cow’s milk:</td>
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<td>sIgE ADVIA Centaur cutoff &gt; 0.35 kU/L</td>
<td>Cow’s milk:</td>
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<td>0.88 0.52 0.46 0.90</td>
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<td>UniCAP system is slightly more sensitive than Centaur (and more sensitive than SPT) for both allergens (1,1,1,1,1,1,1,3,1,2)</td>
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<tr>
<td>Rodriguez, 2000</td>
<td>Melon (and avocado, banana, kiwi, chestnut)</td>
<td>Oral allergy syndrome, anaphylaxis</td>
<td>53 consecutive adult patients (15-69 years) referred to a university hospital allergy clinic in Madrid complaining of reaction to melon</td>
<td>OFC followed by DBPCFC unless history of anaphylactic reaction to food (2 pts) 59 OFC and 25 DBPCFC performed in remaining 51 pts: 25 OFC positive 17/25 DBPCFC positive So 19/53 positive</td>
<td>SPT Cutoff: wheal diameter ≥ 3 mm using fresh foods</td>
<td>slgE Pharmacia ImmunoCAP cutoff &gt; 0.35 kU/L</td>
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<td>SPT and slgE not considered useful for diagnosis of melon allergy (1,1,3,1,1,3,1,3,1,1,3,1)</td>
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<td>Roehr, 2001</td>
<td>Milk, egg, wheat, soy</td>
<td>Food allergy in children with AD</td>
<td>98 children (2 months-11 years) consecutively admitted to a Berlin university hospital pneumonology ward with atopic dermatitis</td>
<td>71 DBPCFC with cow milk based on history 45/71 diagnosed with milk allergy</td>
<td>SPT Skin prick test with fresh milk; positive test defined as a net wheel diameter ≥ 3 mm with no reaction to negative control; 43/98 positive reactions (see Tables 19-23)</td>
<td>APT One drop of fresh cow’s milk placed on filter paper and applied to patients’ backs using 12 mm aluminum cups; occlusion time, 48 hours, read 20 minutes after removal of the cup, and then again at 72 hours; erythema with infiltration constituted positive</td>
<td>slgE Pharmacia CAP</td>
<td>Additional comparisons included the following: combinations of SPT+APT, slgE+APT, SPT+slgE, and SPT+APT+slgE Early vs. late reaction slgE, SPT, APT, slgE+APT (see Tables 33-36) (1,3,1,1,1,1,1,3,1,3,2)</td>
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<td>Rottem, 2008&lt;sup&gt;187&lt;/sup&gt;</td>
<td>Cow’s milk</td>
<td>Cow’s milk allergy</td>
<td>All individuals seen between 1994 and 2006 for suspected milk allergy (1800 infants and children 0-18 years of age)</td>
<td>Food challenge or suggestive history and sIgE</td>
<td>Immulite sIgE to whole milk and component Cutoff ≥1 kU/L</td>
<td>Immulite sIgE: Cutoff ≥3 kU/L at ≤1 year of age as prediction of persistent milk allergy at age 3:</td>
<td>CM sIgE ≥3 kU/L at ≤1 year of age was considered predictive of persistent CM allergy at 3 years of age (1,1,1,2,1,1,1,2,1,2,2)</td>
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<td>Saarinen, 2001&lt;sup&gt;172&lt;/sup&gt;</td>
<td>Milk</td>
<td>CMA</td>
<td>239 infants (6-7 months) from a prospective Finnish birth cohort study on the effect of infant formulae on development of cow’s milk allergy with symptoms that disappeared on withdrawal of milk</td>
<td>239 open challenges</td>
<td>SPT</td>
<td>APT</td>
<td><strong>sIgE</strong></td>
<td>Additional test: Serum Eosinophil Cationic Protein 15.0, 20.0, and 24.7 micrograms(µg)/L. Cutoff ≥15.9 µg/L: sensitivity: 0.27 specificity: 0.74; PPV 0.67; NPV 0.34; Cutoff value 24.7 µg/L: Sensitivity: 0.13 Specificity: 0.98; PPV 0.93; NPV 0.37) (1,1,1,1,1,1,1,1,1,1,2,1)</td>
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<td>Sampson, 2001&lt;sup&gt;186&lt;/sup&gt;</td>
<td>Egg, milk, peanut, soy, wheat, fish</td>
<td>Misc. atopy</td>
<td>100 consecutive children (0.4-14.3 yrs)</td>
<td>Hx or DBPCFC:</td>
<td>90% predictive decision points for food-sIgE levels</td>
<td>Food-specific IgE useful for Dx allergy to egg, milk, peanut, fish; better for egg and milk (1,1,1,1,3,1,1,1,2,3)</td>
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<tr>
<td>Author, Yr</td>
<td>Food(s)</td>
<td>Condition</td>
<td>Population</td>
<td>Reference test</td>
<td>Test 1</td>
<td>Test 2</td>
<td>Test 3</td>
<td>Comments, Conclusions, (values for QUADAS domains)*</td>
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<td>Tainio, 1990&lt;sup&gt;183&lt;/sup&gt;</td>
<td>Milk</td>
<td>CMA (cutaneous, respiratory, and/or GI symptoms)</td>
<td>34 patients w/ suspected CMA (3-51 mos) (19 confirmed with challenge: 14 immediate and 5 delayed)</td>
<td>Elimination and challenge</td>
<td>1. Total IgE: Sensitivity: 11/19 Specificity: 11/15 2. CM-specific IgE (RAST) Sensitivity: 0.63 Specificity: 0.8</td>
<td>3. Serum IgG 4. Serum IgM 5-6. Complement fractions 3 and 4 7. CM-specific IgG 8. CM-specific IgM 9. CM-specific IgA 10-12. Lymphocyte stimulation with PHA, ConA, BLG</td>
<td>Combinations of tests: CM-specific IgE + BLG-mediated lymphocyte proliferation (LP): Sensitivity: 0.88 Specificity: 0.67</td>
<td>No one test alone had the sensitivity or specificity to predict challenge outcomes. The combination of CM-specific IgE and BLG-mediated LP was the best (1,3,1,1,1,1,1,3,3,3)</td>
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<td>Wainstein, 2007&lt;sup&gt;178&lt;/sup&gt;</td>
<td>Peanut</td>
<td>Peanut allergy</td>
<td>84 children consecutively recruited in a Sydney pediatric hospital allergy clinic with positive SPT (defined as a wheal 3x3mm&gt; control)</td>
<td>DBPCFC or documented recent reaction to peanut</td>
<td>1 gram commercial peanut extract; geometric mean of wheal calculated</td>
<td>SPT Cutoff: ≥8mm Sensitivity: 0.75, Specificity: 0.67, PPV: 0.78 NPV: 0.63</td>
<td>Immediate Skin Application Food Test 1 gram commercial peanut butter on a cardboard square applied directly to the skin; response read after 15 minutes. Positive score consisted of the appearance of any wheal in the area Cutoff: 10.0kU/L Sensitivity: 0.54, Specificity: 1.00, PPV: 1.00 NPV: 0.58</td>
<td>Combination of three tests also assessed; neither the individual tests nor the combination had sensitivity or specificity adequate to replace FC (1,1,1,1,2,1,1,1,1,3,3,3)</td>
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<tr>
<td>Author, Yr</td>
<td>Food(s)</td>
<td>Condition</td>
<td>Population</td>
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<td>Test 1</td>
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<td>Wananukul, 2005181</td>
<td>CM, HE, wheat, shrimp</td>
<td>Urticaria</td>
<td>100 consecutive patients with urticaria who presented at a university hospital pediatric dermatology clinic in Bangkok over 2 years</td>
<td>DBPCFC or OFC in 22 patients, recent history of anaphylactic reaction to foods in 5 patients</td>
<td>SPT Cutoff: not reported All foods together</td>
<td>Se 0.83 Sp 0.38 PP 0.28 NP 0.89</td>
<td>(1,1,1,3,2,1,1,3,1,1,2,1)</td>
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<td>Wang, 2008192</td>
<td>Milk, Egg, Peanut</td>
<td>Not specified</td>
<td>50 consecutive patients at an allergy clinic, 3-18 years</td>
<td>ImmunoCAP (sIgE): concordance with ImmunoCAP; milk 46%, egg 42%, peanut 56%</td>
<td>Turbo-MP (sIgE): concordance with ImmunoCAP: milk 52%, egg 64%, peanut 60%</td>
<td>Immulite 2000 (sIgE): concordance with ImmunoCAP: milk 52%, egg 64%, peanut 60%</td>
<td>(1,3,3,1,1,1,3,1,1,3,1,3)</td>
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**Table Notes:** AD Atopic dermatitis; AGA anti-gliadin antibodies; ALA α-lactalbumin; APT atopic patch test; BLG beta lactoglobulin; CD Celiac Disease; cf compared with; CM cow’s milk; CMA cow’s milk allergy; ConA Concanavalin A; DBPCFC double blind placebo-controlled food challenge; DH dermatitis herpetiformis; EMA Endomyosial antibodies; FC food challenge; FEIA fluorescent enzyme immunoassay FHx family history; GFD gluten-free diet; HE hen’s egg; HLA Human Leukocyte antigen; L/M Lactulose/Mannitol; NPV Negative predictive value; OFC open food challenge; OVM ovomucoid; PHA Phytohemagglutinin; PPV positive predictive value; RAST radioallergosorbent test; Se sensitivity; sIgE antigen-specific immunoglobulin E; Sp Specificity; SPT skin prick test; tTg tissue transglutaminase; *QUADAS domains are shown in Appendix D; for the present study, domains 12 and 13 were not assessed; the grades are yes(1), no (2), and unclear (3).
Appendix I. Excluded Studies at screener level

Not a Food Allergy study


8.


64. Shaheen SON, K. Newson, R. B. Emmett, P. M. Sherriff, A. Henderson, A. J. Dietary


81. Wickman M. Experience with quantitative IgE antibody analysis in relation to allergic disease within the BAMSE birth cohort--towards an improved diagnostic process. 2004;59 Suppl 78:30-1.


29. de Boissieu D. [Do breast-feeding and "diet" milks have any preventive or curative effect in the management of atopic dermatitis in children?]. Ann Dermatol Venereol. 2005;132 Spec No 1:1S104-11.

30. de Seta L, Siani P, Cirillo G, Di Gruttola M, Cimaduomo L, Coletta S. [The prevention of


44. Hanifin JM, Cooper KD, Ho VC, Kang S, Krafchik BR, Margolis DJ, et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology.


53. Host A, Halken S. Hypoallergenic formulas--when, to whom and how long: after more than 15 years we know the right indication! Allergy. 2004;59 Suppl 78:45-52.


88. Sampson HA. The role of food allergy and mediator release in atopic dermatitis. J


Not Incidence/Prevalence/Natural History, Diagnosis, Treatment/Management/Prevention, or Background


27. Tripodi SB, A. D. Alessandri, C. Panetta, V. Restani, P. Matricardi, P. M. Predicting the


Duplicate Data


*Has duplicate data of the following article:*

Appendix J. Excluded Studies: Diagnosis

No sensitivity/specificity information


63. Oranje AP, Aarsen RS, Mulder PG, van Toorenenbergen AW, Liefaard G, Dieges PH.


Poorly defined population
Diagnosis


25. De Swert LF, Cadot P, Ceuppens JL. Diagnosis and natural course of allergy to cooked


75. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the


No Gold Standard


Retrospective Data Collection
Diagnosis


Wrong Test-Diagnosis


The above citation was a study of the use of colonoscopy with lymphoid nodular biopsy for diagnosis. This test was not within the scope of our report; therefore the study was excluded.
Celiac Disease


Appendix K. Excluded Studies: Treatment/Management/Prevention

Neither a Randomized Controlled Trial (RCT) nor Observational


12. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and


Observational and sample < 100
-Treatment/Management/Prevention


27. Hofmann AMS, A. M. Jones, S. M. Palmer, K. P. Lokhnygina, Y. Steele, P. H. Kamilaris, J. Burks, A. W. Safety of a peanut oral immunotherapy protocol in children with


40. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral


Observational and prevention article
Treatment/Management/Prevention


Appendix L. Assessed for their definition of food allergy


