

WORKING P A P E R

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

This product is part of the RAND Health working paper series. RAND working papers are intended to share researchers' latest findings and to solicit informal peer review. They have been approved for circulation by RAND Health but have not been formally edited or peer reviewed. Unless otherwise indicated, working papers can be quoted and cited without permission of the author, provided the source is clearly referred to as a working paper. RAND's publications do not necessarily reflect the opinions of its research clients and sponsors. RAND® is a registered trademark.

WR-757-1

August 2010

Prepared for the National Institute of Allergy and Infectious Diseases

Prevalence, Natural History, Diagnosis, and Treatment of Food Allergy: A Systematic Review of the Evidence

Prepared for:

National Institute on Allergy and Infectious Diseases
6610 Rockledge Drive, MSC 6612
Bethesda, MD 20892-6612

Prepared by:

RAND Corporation

1776 Main Street
Santa Monica, CA 90407

Director, Southern California EPC:

Paul Shekelle, M.D., Ph.D.

Associate Director, Southern California EPC:

Margaret Maglione, M.P.P.

Content Expert:

Marc Riedl, M.D.

Literature Reviewers:

Dena M. Bravata, M.D., M.S.
Benjamin J. Hulley, B.S.
Sydne Newberry, Ph.D.
Neil Paige, M.D.
Jennifer J. Schneider Chafen, M.D.
Vandana Sundaram, M.P.H.
Ali Towfigh, M.D.

Programmer:

Elizabeth Roth, M.A.

Staff Assistants:

Jerome Hawkins, B.S.
Breanne Johnsen, B.S.
Aneesa Motala, B.A.

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 mediated 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 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.