Diagnosing and Managing Common Food Allergies
A Systematic Review

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FOOD ALLERGIES HAVE SIGNIFICANT deleterious effects on family economics, social interactions, school and work attendance, and health-related quality of life.[1,2] However, currently licensed treatments target only the symptoms of reactions and anaphylaxis, not the allergies themselves.

Food allergies are heterogeneous in terms of both their underlying pathophysiology (eg, mediated via both IgE and non-IgE immunologic pathways) and their clinical manifestations (ranging from mild rashes to life-threatening anaphylaxis). The literature on food allergies lacks a clear consensus regarding the most effective diagnostic and management approaches to even the most common conditions.

Under contract from the National Institute of Allergy and Infectious Diseases (NIAID) and in support of ongoing work to produce clinical practice

See also Patient Page.

Context There is heightened interest in food allergies but no clear consensus exists regarding the prevalence or most effective diagnostic and management approaches to food allergies.

Objective To perform a systematic review of the available evidence on the prevalence, diagnosis, management, and prevention of food allergies.

Data Sources Electronic searches of PubMed, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials. Searches were limited to English-language articles indexed between January 1988 and September 2009.

Study Selection Diagnostic tests were included if they had a prospective, defined study population, used food challenge as a criterion standard, and reported sufficient data to calculate sensitivity and specificity. Systematic reviews and randomized controlled trials (RCTs) for management and prevention outcomes were also used. For foods where anaphylaxis is common, cohort studies with a sample size of more than 100 participants were included.

Data Extraction Two investigators independently reviewed all titles and abstracts to identify potentially relevant articles and resolved discrepancies by repeated review and discussion. Quality of systematic reviews and meta-analyses was assessed using the AMSTAR criteria, the quality of diagnostic studies using the QUADAS criteria most relevant to food allergy, and the quality of RCTs using the Jadad criteria.

Data Synthesis A total of 12 378 citations were identified and 72 citations were included. Food allergy affects more than 1% to 2% but less than 10% of the population. It is unclear if the prevalence of food allergies is increasing. Summary receiver operating characteristic curves comparing skin prick tests (area under the curve [AUC], 0.87; 95% confidence interval [CI], 0.81-0.93) and serum food-specific IgE (AUC, 0.84; 95% CI, 0.78-0.91) to food challenge showed no statistical superiority for either test. Elimination diets are the mainstay of therapy but have been rarely studied. Immunotherapy is promising but data are insufficient to recommend use. In high-risk infants, hydrolyzed formulas may prevent cow's milk allergy but standardized definitions of high risk and hydrolyzed formula do not exist.

Conclusion The evidence for the prevalence and management of food allergy is greatly limited by a lack of uniformity for criteria for making a diagnosis.

JAMA. 2010;303(18):1848-1856   www.jama.com

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guidelines, we reviewed the available evidence on the prevalence, diagnosis, management, and prevention of food allergies.[3] This review presents our findings for the most common allergenic foods: cow's milk, hen's egg, peanut, tree nut, fish, and shellfish, which account for more than 50% of all allergies to food.[4]

METHODS
Literature Search and Study Selection

We searched 4 electronic databases: PubMed, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials (eAppendix, available at http://www.jama.com). We restricted searches to English-language articles between January 1988 and September 2009; however, we included older articles identified via reference mining or expert input. *Food allergy* is not a Medical Subject Headings (MeSH) term; therefore, the search terms included the MeSH term *food hypersensitivity,* text words such as *food allerg**, and terms for foods and conditions such as *cow milk*, *peanut*, *asthma*, *oral allergy syndrome,* and *anaphylaxis.*

Our initial inclusion criteria were broad and included prior systematic reviews, meta-analyses, or both, and studies presenting original data related to the prevalence, diagnosis, management, or prevention of food allergy. After assessing the relative quantities of studies on these topics, we restricted studies of prevalence to those with population-based samples (and systematic reviews of such studies); studies of diagnostic tests to those that presented sufficient data to calculate both sensitivity and specificity, had a prospective, defined study population, and used food challenge as a criterion standard; and studies of management and prevention to those that were either controlled trials (both randomized and nonrandomized) or systematic reviews. For food allergies where anaphylaxis is disproportionately common (eg, shellfish, fish, or peanut), we included cohort studies with a sample size of more than 100 participants. Complete inclusion and exclusion criteria are available in our evidence report.[3]

Data Abstraction

Two investigators (S.J.N. and P.G.S.) independently reviewed all titles and abstracts to identify potentially relevant articles. We independently abstracted articles that met inclusion criteria and resolved discrepancies by repeated review and discussion. The principal investigator (P.G.S.) served as the arbiter for conflict resolution. If 2 or more studies presented the same data from a single patient population, we included these data only once in our analysis.

Quality Assessment

We assessed the quality of systematic reviews and meta-analyses using the AMSTAR criteria, the quality of diagnostic studies using the QUADAS criteria most relevant to food allergy, and the quality of randomized controlled trials (RCTs) using the Jadad criteria.[5-8] For studies on prevalence, we evaluated quality based on the criterion standard used for diagnosis, evaluation of a population-based sample, and participation rate. For management studies, we initially considered all observational studies to be of poor quality but then upgraded the rating to good if the study had a high level of follow-up ($\geq$90%), large sample size (>500 patients), and made attempts to reduce bias either through study design or statistical analysis.

Data Synthesis

For prevalence studies, we reported the literature estimates. The heterogeneity of management and prevention studies prevented data pooling; therefore, we summarized those data narratively.

For diagnostic studies, we examined the distribution of sensitivity and specificity pairs by food allergy, test type, and food allergy × test type. We calculated summary receiver operator characteristic (ROC) curves by transforming sensitivity and specificity pairs (weighted by sample size) using logistic transforms and regressing logit sensitivities on logit specificities.[9] Summary ROC curves were calculated by back transforming predicted values from these regression models. We calculated the 95% confidence interval (CI) for the summary ROC curves by reestimating the curves on bootstrap samples. The bootstrap was also used to test differences in areas under the curves 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. These analyses were performed with Stata version 10.0 (StataCorp LP, College Station, Texas).

RESULTS

Our searches identified 12 378 titles, of which 1216 articles underwent full text review and 182 studies met inclusion criteria for allergies to any food (eFigure 1). Our review is restricted to the 72 studies that reported data on food allergies to cow's milk, hen's egg, peanut, tree nut, fish, and shellfish. These studies included 1 meta-analysis on incidence and prevalence; 18 studies on diagnosis; and 53 studies on management and prevention (28 studies on management, 4 meta-analyses, and 21 studies on prevention).

Definition of Food Allergy

Food allergy has no universally accepted definition. The NIAID has suggested that food allergy be defined as an "adverse immune response that occurs reproducibly on exposure to a given food and is distinct from other adverse responses to food, such as food intolerance, pharmacologic reactions, and toxin-mediated reactions."[3] To assess agreement with this definition, we retrieved 85 reviews of food allergy, 73 of which did not otherwise meet inclusion criteria (eReferences). Seventy-one of these articles (82%) provided a definition of *food allergy*. Generally, definitions overlapped considerably with the NIAID definition: 62 reviews (87%) included the phrase *immune response*, 22 (31%) included the concept of reproducibility, 32 (45%) included the concept of a particular food, and 35 (49%) required distinction from food intolerance, pharmacologic, or toxin-mediated reactions. Furthermore, 56 reviews (79%) stated that food allergy involved IgE-mediated reac-

tions and 47 (66%) included non–IgE-mediated immunologic reactions.

Prevalence of Food Allergies

We identified an existing systematic review on the prevalence of food allergies[4] that identified 51 relevant studies that provided population-based estimates of prevalence. Studies varied in how food allergy was diagnosed. Some used self-report, other studies used skin prick testing (SPT) or food-specific IgE determinations, and a few studies used double-blind, placebo-controlled food challenges. In general, studies that used self-report found a higher prevalence of food allergies than studies that used the other 3 methods. For cow's milk allergy, the pooled estimate of prevalence was 3.5% (95% CI, 2.9%-4.1%) from self-report and 0.6% to 0.9% from the other 3 methods. For the other common foods, the pooled estimates for self-report and other methods were for egg allergies, 1.3% (95% CI, 1.0%-1.6%) vs 0.3% to 0.9%; for peanut allergies, 0.75% (95% CI, 0.6%-0.9%) vs 0.75%; for fish allergies, 0.6% (95% CI, 0.5%-0.7%) vs 0.2% to 0.3%; and for shellfish allergies, 1.1% (95% CI, 1.0%-1.2%) vs 0.6%. The authors noted that the precision of these latter estimates was very poor and that more standardized methods for diagnosis are needed to minimize this source of variability across studies. The self-reported prevalence of allergy to cow's milk and hen's egg (but not peanut, fish, or shellfish) was higher in children than in adults.

Changes in the Prevalence of Food Allergies

We identified 3 population-based studies (1 each from the United States, Canada, and the United Kingdom) that assessed whether food allergies are changing over time.[10-14] The parentally-reported prevalence of peanut allergy among children living on the Isle of Wight increased from 0.5% in 1989 to 1.0% in 1994-1996 ($P=.20$), and the prevalence of IgE antibodies increased from 1.1% to 3.3% ($P=.001$).[10] A response rate of 43% in the 1994-1996 sample is a limitation of this study. The prevalence of peanut allergy among schoolchildren in Montreal (assessed using an algorithm that included parental self-report, SPT, food-specific IgE, and food challenge) was 1.5% in 2000-2002 and increased to 1.63% in 2005-2007, a difference that was not statistically significant.[11,12] The authors noted that the width of the CIs on these estimates prevented identifying the true change in prevalence. The US studies used administrative data from hospital discharges, self-report, and food-specific IgE to estimate changes in food allergy prevalence over time and estimated that 3.3% of US children had food allergies in 1997 vs 3.9% in 2007, a statistically significant difference.[13,14] However, these authors noted that this increase could be due to increased awareness and reporting rather than a true increase in disease.

Diagnosis of Food Allergies

There are no well-accepted criteria for diagnosing food allergies. Numerous diagnostic tests have been proposed as useful adjuncts to the clinical history for establishing the diagnosis. The most commonly studied are SPT, serum food-specific IgE determinations, and atopy patch testing (APT), although APT is not in widespread clinical use. The placebo-controlled food challenge is usually considered the criterion standard. Most authorities consider it necessary to perform the food challenge under double-blind conditions, although at least 1 study has shown that open challenges give the same results.[15] Unfortunately, the need for specialized personnel, time, expense, risk of anaphylaxis, and lack of criteria for what constitutes a positive food challenge limits the widespread use of this test.

We identified 18 studies of diagnostic tests that were prospective, had an identified patient population, compared SPT, serum food-specific IgE, or APT with a food challenge reference standard, and reported both sensitivity and specificity (**TABLE**).[15-32] In general, the quality of these studies was fair (eFigure 2). Of these studies, 13 studied SPT,[15,17-24,29-32] 11 studied serum food-specific IgE,[16,18,20-26,29,31] and 8 studied APT.[15,18,20,22,24,25,27,28] The **FIGURE** presents the summary ROC curves comparing SPT and serum food-specific IgE to a food challenge overall, and separately for cow's milk and hen's egg. There were no statistically significant differences for the diagnostic tests overall or for the specific foods. There were insufficient data to calculate summary ROC curves for the APT or for peanut or tree nut or fish or shellfish allergies. Ten studies attempted to improve diagnostic accuracy by combining tests, but results were generally inconclusive.[3] Other proposed tests for diagnosing food allergy (eg, histamine, tryptase, and chymase assays) were either not assessed or had too few studies meeting inclusion criteria to allow conclusions regarding their use for diagnosing food allergies.

Management of Food Allergies

We identified 25 studies of 7 food allergy management strategies[33-57] (elimination diets [1 study[33]]; immunotherapy [7 studies[34-40]]; food substitutions or alterations [8 studies[41-48]]; diets in breastfeeding women [1 study[49]]; medical or pharmacologic therapies [5 studies[50-54]]; probiotics [2 studies[55,56]]; and education [1 study[57]]) (eTable 1). Overall study quality was fair. The variability of the studies did not allow for pooling of results or for a clear consensus regarding the most effective management strategies.

Elimination Diets. Only 1 study[33] evaluated the effects of an elimination diet and reported improvement in atopic dermatitis in patients on elimination diets compared with those who were not on elimination diets.

Immunotherapy. In immunotherapy, the immune response to allergen exposure is altered using protocols designed to administer increasing doses of the causative allergen over time. Immunotherapy may result in desensitization or tolerance to the specific allergen. Desensitization refers to a temporary clinical state in which allergen exposure fails to cause allergic symptoms, whereas tolerance indicates clinical nonreactivity to allergen exposure even after long periods of abstinence. Five studies gave oral immunotherapy[34-36,38,39] and 2 studies gave subcutaneous immunotherapy.[37,40] Immunotherapy was somewhat effective for desensitization but tolerance and safety were inadequately evaluated.

Food Substitutions or Alterations. Five studies[41-45] reported feeding infants with presumed cow's milk allergy with alternatives to cow's milk formula. These studies did not present sufficient data to conclude which formula was most beneficial. Three studies[46-48] treated cow's milk allergy by substituting non–cow's milk, but methodological limitations of these studies prevent conclusive determination of the benefits of these substitutes for cow's milk.

Table. Studies of Diagnosis of Food Allergies

Source	Population	Reference Test	Diagnostic Tests Used	Foods Evaluated				
				CM	HE	P	F	O
Sampson,[16] 2001	100 consecutive children (ages 0.4-14.3 y)	FC	sIgE: Pharmacia CAP-FEIA	✔	✔	✔	✔	✔
Wananukul,[17] 2005	100 consecutive patients with urticaria, university hospital pediatric dermatology clinic in Bangkok over 2 y	DBPCFC or OFC in 22 patients, recent history of anaphylactic reaction (n = 5)	SPT: cutoff not reported	✔	✔		✔	✔
Mehl,[18] 2006	437 German consecutive children (3 mo-17 y), specialist for suspected food allergy; 391 patients with AD	DBPCFC (except patients <1 y with history of immediate reactions) guided by SPT, sIgE, and clinical history	SPT: fresh food samples, positive tests not reported; sIgE: RAST APT: 1 drop fresh CM/HE (white and yolk) put on filter paper and applied to back with aluminum cups; occlusion time 48 h; results at 48 and 72 h	✔	✔			✔
Calvani,[19] 2007	104 consecutive children, Italian pediatric allergy clinic for suspected CMA	FC (70 OFC and 34 DBPCFC): 28/104 positive tests	SPT: lactalbumin, casein, BLG, and fresh milk; positive tests defined as mean wheal diameters 3 mm ≥ negative control	✔	✔			
Canani,[20] 2007	60 children (3-48 mo), pediatric gastroenterology center in Naples for suspected food allergy–related symptoms	OFC with fresh CM, HE, or wheat powder based on reactions to SPT, APT, and sIgE (31/55 OFC positive for CM; 19/28 OFC positive for HE)	SPT: positive reaction ≥3 mm with no reaction to control APT: occlusion time 48 h; results at 72 h; positive test defined as minimum of erythema and slight infiltration	✔	✔			✔
Osterballe,[21] 2004	495 children, Danish birth cohort (3 y) with and without AD	OFC to assess both early and late reactions (3/8 positive for CM; 8/14 positive for HE)	SPT: cutoff ≥3mm Magic Lite: cutoff 1.43 U/mL	✔	✔			
Isolauri,[15] 1996	183 Finnish children (2-36 mo) with AD and suspected CMA	DBPCFC (n = 118) or OFC (n = 65); 99/183 confirmed with CMA by oral challenge	SPT: commercial CM allergen and milk powder; reactions at 15 min; wheals >half the histamine reaction size were positive APT: humidified skim CM applied with aluminum cups; occlusion time 48 h; results at 48 and 72 h	✔				
Keskin,[22] 2005	37 consecutive children (1.5-84 mo) with suspected CMA, Turkish allergy clinic at a tertiary care center, excluding children with chronic disease	DBPCFC preceded by ≥2 wk of CM elimination (except 6 patients with anaphylactic reaction to CM); reactions were categorized as early (within 2 h of test) or late (23/37 had positive challenges or history of anaphylaxis)	SPT: commercial allergen with wheal ≥3 mm larger than negative control was positive sIgE: Immuno CAP-FEIA APT: CM powder mixed with saline, applied with aluminum cups; cups removed after 48 h; read 72 h after application	✔				
García-Ara,[23] 2001	170 consecutive infants (1-12 mo), Madrid children's hospital allergy service for suspected CMA	OFC (n = 161 infants), remaining 9 had severe allergic reaction to CM protein and evidence of milk sIgE	SPT: ALA, BLG, whole milk, and casein; positive test defined as a net wheal diameter 3 mm > negative control sIgE: CAP-FEIA using milk, ALA, BLG, and casein; positive test defined as sIgE ≥0.35	✔				
Saarinen,[24] 2001	239 infants (6-7 mo), prospective Finnish birth cohort study, effect of infant formula on CMA with symptoms that disappeared on withdrawal of milk	239 OFC (118/239 positive)	SPT: CM formula, whole milk, or CM protein fractions; positive test was defined as wheal diameter ≥3 mm sIgE: CAP using whole CM and/or CM protein fractions APT: CM formula powder, bovine serum albumin, crystallized bovine BLG, and bovine casein each dissolved in saline; filter papers soaked in solutions before applied to back under aluminum cup; occlusion time 48 h; results at 48 h	✔				
De Boissieu,[25] 2003	35 children (2-57 mo), diagnosis of nonspecific persistent digestive symptoms	FC	sIgE: CAP-RAST APT: blotting paper soaked with 50% skimmed CM applied to uninvolved skin on back with aluminum cup; occlusion time 48 h; results at 48 and 72 h	✔				
Tainio,[26] 1990	34 children (3-51 mo) with suspected CMA	Elimination diet and FC (19 confirmed with FC)	sIgE: RAST	✔				
Cudowska,[27] 2005	34 children (5 mo-16 y), 20 (<3 y), and 14 (≥3 y) with suspected CMA	FC	APT: isotonic saline mixed with CM powder and applied to skin on back with aluminum cup; occlusion time 48 h; results at 48 and 72 h	✔				

(continued)

Table. Studies of Diagnosis of Food Allergies (continued)

Source	Population	Reference Test	Diagnostic Tests Used	Foods Evaluated				
				CM	HE	P	F	O
Järvinen,[28] 2003	90 children (2.5-36 mo) with CMA controlled via elimination but with residual symptoms not responding to elimination of eggs, nuts, fruits, chocolate, or fish	Elimination diet then OFC; immediate reactions were within 1 h of last dose; each child only tested with 1 cereal (30/44 OFC were positive for wheat; 66/90 OFC were positive for all cereals)	APT: wheat flour mixed with isotonic saline applied to back with aluminum cups; cups removed after 48 h and reactions at 72 h after cups were applied; presence of edema or eczema were positive reaction	✔				✔
Monti,[29] 2002	107 children (1-19 mo) with AD and no prior egg exposure, Italian allergy clinic for AD	OFC and monitoring for early and late reactions (<8 d) (72/107 children were positive)	SPT: commercial extracts of albumin and yolk; reported absolute measure of the wheal diameter
sIgE: RAST		✔			
Diéguez,[30] 2008	104 patients (12-15 mo) with IgE-mediated CMA (by history and SPT/sIgE) with no prior egg exposure, Spanish allergy clinic	OFC with egg components (38/104 were positive)	SPT: egg white, yolk, OVA, OVM, OVT, and lysozyme; wheal diameter ≥3 mm regarded as positive		✔			
Rancé,[31] 2002	393 consecutive children, French hospital with suspected peanut allergy	DBPCFC preceded by elimination diet; patients monitored for reactions for 4 h following test (177/393 peanut allergic by FC)	SPT: fresh peanut mix with wheals 3 mm >negative control defined as positive
sIgE: Pharmacia CAP-FEIA			✔		
Wainstein,[32] 2007	84 consecutive children, Sydney pediatric hospital allergy clinic with positive SPT (defined as a wheal 3 × 3 mm > control)	DBPCFC or documented recent reaction to peanut (51/84 peanut allergic by FC)	SPT: commercial whole peanut extract; 2 wheal diameter cutoffs of ≥8 and ≥15 mm used to calculate sensitivity and specificity			✔		

Abbreviations: AD, atopic dermatitis; ALA, alpha-lactalbumin; APT, atopy patch test; BLG, beta-lactoglobulin; CAP-FEIA, fluorenzymeimmunoassay; CAP-RAST, radioallergosorbic test; CM, cow's milk; CMA, cow's milk allergy; DBPCFC, double-blind, placebo-controlled food challenge; F, shellfish/fish; FC, food challenge; HE, hen's egg; O, other; OFC, open food challenge; OVA, ovalbumin; OVM, ovomucoid; OVT, ovotransferrin; P, peanut/tree nut; RAST, radioallergosorbic test; sIgE, serum food-specific IgE; SPT, skin prick test.

Diets in Breastfeeding Women. One study[49] evaluated hypoallergenic diets in nursing women to reduce food allergy–related colic in their children and found a statistically significant improvement in the low allergen group, with an adjusted relative risk of 37% (95% CI, 18%-56%).

Medical or Pharmacologic Therapies. An elimination diet combined with either thymomodulin[50] or cromolyn[51] appeared to improve food allergy–related skin lesions, whereas cromolyn without an elimination diet did not.[52] Two studies[53,54] evaluated pharmacologic management of peanut or tree nut allergy. One study[53] found that a 450-mg dose of TNX-901, a humanized IgG1 monoclonal antibody, increased the sensitivity from one-half a peanut to almost 9 peanuts, and the other study[54] found that aztemizole decreased symptom severity in an oral provocation test.

Probiotics. Probiotics did not improve atopic dermatitis outcomes, either standardized measures of disease severity or rectal bleeding, in infants with suspected food allergies.[55,56]

Education. After giving patients with a peanut allergy advice on nut avoidance and self-recognition of reactions, 1 study[57] found 88 of 567 patients (15%) had a follow-up reaction of reduced severity and 3 of 567 patients (0.5%) had a severe follow-up reaction compared with an initial 12% of patients.

Prevention of Food Allergies and Atopic Eczema

In general, studies addressing food allergy prevention outcomes enrolled pregnant women, their newborns, or both with a history of allergic disease and randomized them to receive special diets (or formula) or receive placebo (to be given with or without breast milk), and followed up the children to compare the cumulative incidence of allergic disease in the intervention and placebo groups. We identified 6 systematic reviews[58-63] and 47 RCTs[33,64-109] that evaluated methods to prevent food allergies. Twenty of the included RCTs were evaluated in 1 or more of these systematic reviews and were not analyzed further.[64-83] Two publications[84,85] reporting information on the same population were excluded because they did not report data comparing the intervention and control groups. We also excluded studies by Chandra et al[65], given published reports that question the validity of those data.[87,88] The studies meeting inclusion criteria evaluated 5 prevention strategies: breastfeeding and delayed introduction of solids (2 studies[89,90]), maternal diet during pregnancy or lactation (3 studies[58,91,92]), exclusive breastfeeding (3 studies[93,95,110]), special diets in infants and young children (12 studies[59-61,94,96-100,106-108]), and probiotics (5 studies[101-105]) (eTable 2).

Breastfeeding and Delayed Introduction of Solids. Both of the included studies found some association between delayed solids and incidence of atopic symptoms (parents reported decreased food intolerance[89] and nonsignificant higher incidence of atopy in controls[90]). However, their findings should be interpreted with caution given the multimodal nature[89] and poor quality.[90]

Maternal Diet During Pregnancy or Lactation. Maternal diet during preg-

nancy, lactation, or both demonstrated conflicting effects on atopic disease among children at high risk. One systematic review[58] reported no evidence to support a protective effect of maternal diet; 2 studies[91,92] reporting on 1 nonrandomized comparative study (115 patients evaluated at 10 months and at 4 years) found a significantly reduced incidence of atopic dermatitis in children whose mothers had a restricted diet during lactation (free from cow's milk, hen's egg, and fish product for 3 months' postpartum).

Exclusive Breastfeeding. Three analyses[93,95,110] of data from the same population provided conflicting evidence on the prevention of atopic disease by exclusive breastfeeding, depending on which control group was used (2 of these studies reported decreased atopic dermatitis among children who were exclusively breastfed compared with children who were not).

Special Diets in Infants. Hydrolyzed formulas, soy formulas, and early exposure to cow's milk have been tested for prevention of allergy development. Two systematic reviews[60,61] and 5 RCTs[96-100] evaluated the effects of hydrolyzed formulas on the development of food aller-

gies in children. The effects of soy formula were evaluated by 1 systematic review[59] and 1 RCT.[94] Three RCTs[106-108] evaluated neonatal exposure to cow's milk on 2 distinct populations.

Hydrolyzed formulas (particularly extensively and partially hydrolyzed formulas) may reduce infant and childhood cow's milk allergy in high-risk infants when compared with cow's milk formula. However, the terms *partially* and *extensively* hydrolyzed as well as *high risk* were not well-defined in the literature. There was little difference between soy formula and cow's milk formula for the prevention of allergies in high-risk infants. The benefits and harms of early exposure to cow's milk remain uncertain.

Probiotics. Two studies[101,102] evaluated probiotics in combination with breastfeeding, and 3 studies[103-105] evaluated probiotics in pregnant women and their newborn infants. The use of probiotics in the perinatal period may be associated with mild reductions in the cumulative incidence of allergic skin disease in children. However, these results are interpreted with caution because the trials with the most significant results used

probiotics in conjunction with breastfeeding, hypoallergenic formula, or both, and the independent effects of probiotics could not be established.

COMMENT

This systematic review of food allergies found that the evidence on the prevalence, diagnosis, management, and prevention of food allergies is voluminous, diffuse, and critically limited by the lack of uniformity for the diagnosis of a food allergy, severely limiting conclusions about best practices for management and prevention.

Our review found several key results. First, food allergies affect more than 1% or 2% but less than 10% of the US population. Whether the prevalence of food allergies is increasing is not well established. Second, food challenges, SPT, and serum food-specific IgE all have a role to play in making the diagnosis but no one test has sufficient ease of use or sensitivity or specificity to be recommended over the other tests. Numerous other proposed diagnostic tests are of uncertain value due to lack of evidence.

Third, although elimination diets are the mainstay of therapy, we identified

Figure. Summary ROC Curves for the Diagnosis of All Food Allergies, Cow's Milk Allergy, and Hen's Egg Allergy Comparing SPT With sIgE Testing
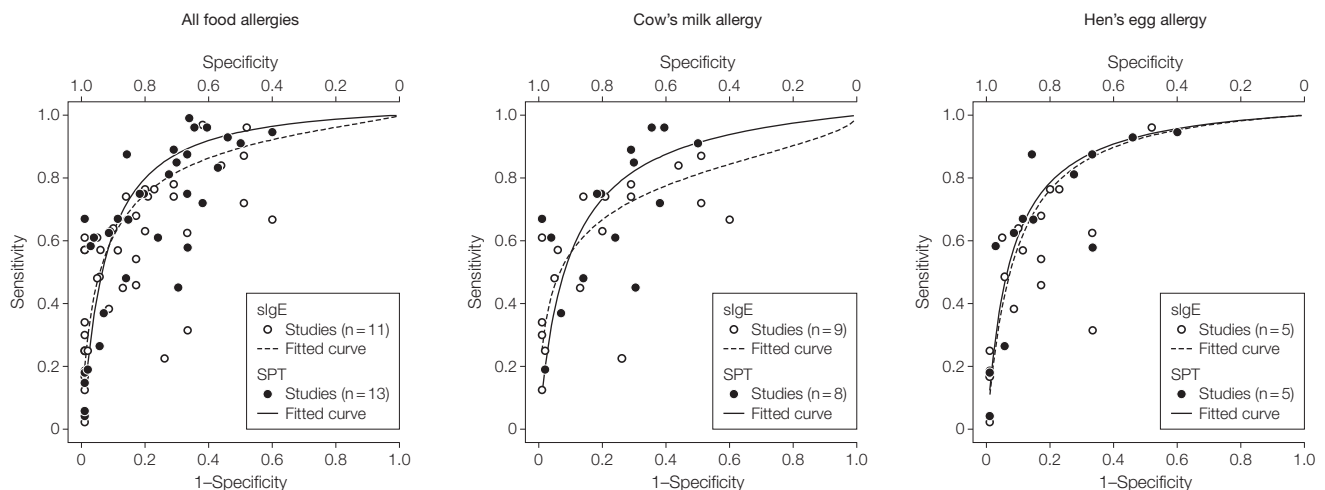
ROC indicates receiver operator characteristic; SPT, skin prick testing; sIgE, serum food-specific IgE. Each of the individual circles represents the sensitivity/specificity pair from an individual study. More than 1 data point may be shown for each study due to a study reporting multiple thresholds for sensitivity/specificity. For all food allergies, the area under the curve for SPT and sIgE was 0.87 (95% confidence interval [CI], 0.81-0.93) and 0.84 (95% CI, 0.78-0.91), respectively (mean difference, 0.03; 95% CI, −0.05 to 0.11). For cow's milk allergy, 0.84 (95% CI, 0.75-0.92) and 0.78 (95% CI, 0.70-0.86), respectively (mean difference, 0.06; 95% CI, −0.06 to 0.18). For hen's egg allergy, 0.87 (95% CI, 0.76-0.97) and 0.85 (95% CI, 0.62-1.09), respectively (mean difference, 0.01; 95% CI, −0.25 to 0.27).

only 1 RCT of an elimination diet. Many authorities would consider RCTs of elimination diets for serious life-threatening food allergy reactions unnecessary and unethical; however, it should be recognized that such studies are generally lacking for other potential food allergic conditions, such as atopic dermatitis and eosinophilic esophagitis. In these instances, the benefits of an elimination diet are uncertain based on published evidence, and potential benefits need to be weighed against the potential nutritional risks of such a diet, particularly in children. More controlled studies of elimination diets in patients with non–anaphylactic food allergy symptoms are needed.

Fourth, immunotherapy, although currently not a licensed method for the treatment of food allergy, may be effective in generating desensitization, but whether this treatment can also generate long-term tolerance remains to be determined. The safety of immunotherapy is likely to vary with the food allergen and the route of therapy administration (eg, oral, sublingual) and, to date, it has been inadequately studied.

Fifth, among high-risk infants, hydrolyzed formula may prevent against cow's milk allergy but standardized definitions of *high risk* and *hydrolyzed formula* do not exist. Probiotics in conjunction with breastfeeding, hypoallergenic formula, or both may help prevent food allergy but their independent effects remain unclear.

A clinical consequence of our findings regarding lack of uniformity of criteria for diagnosis and the limited sensitivity and specificity of existing office-based tests for IgE sensitization is the potential for overdiagnosis of food allergy in the general population. Patients with nonspecific symptoms (rash, abdominal complaints) who have positive SPT or serum food-specific IgE studies to foods have less than a 50% likelihood of actually having a food allergy (given the sensitivity, specificity, and prevalence). Inappropriately diagnosing such individuals with food allergy may unnecessarily subject them to broad dietary restrictions, the risk of

nutritional problems from elimination diets (eg, milk or egg elimination in children), significant anxiety and worry, and the social challenges food allergies cause.[1] Proper interpretation of SPT and serum food-specific IgE results requires evaluation of the data within the context of the clinical history and physician understanding of symptoms consistent with clinical food allergy to separate out false positives from true positives for food allergy. Furthermore, the overdiagnosis or misdiagnosis of food allergy by medical practitioners obscures the substantial morbidity caused in patients truly affected by immune-mediated food allergy and serves to perpetuate some public misperceptions that food allergy is a trivial medical condition.

The limitations of our study reflect the limitations of the included articles in terms of the quality of the original studies. We have attempted to limit our conclusions accordingly. In addition to the need for greater rigor in the design, execution, and reporting of food allergy studies, a key limitation of these studies is the heterogeneity in the criteria used for the diagnosis of food allergy. This makes comparisons of prevalence across studies dependent on the methods used for the diagnosis, limits all studies of diagnostic tests by the lack of a consistent criterion standard, and introduces heterogeneity into studies of management, making comparisons across studies more challenging. Another key limitation of our analysis was that we were unable to perform formal evaluations for publication bias due to the heterogeneity of the included studies. The potential for publication bias may be magnified in a review of food allergy, because *food allergy* is not a PubMed index term, and there is no good agreement on the conditions that constitute a food allergy. This makes searching for the relevant literature particularly challenging. Consideration should be given to creating a *food allergy* index term to facilitate future searches for relevant evidence. Our restriction to

English-language–only articles also may have excluded some relevant studies. Even with these limitations, we screened more than 12 000 citations and reviewed in detail more than 1000 full-text articles. However, food allergy is a subject of much current study. Three abstracts[111-113] have recently been presented (1 regarding the prevalence in different racial groups of symptoms and serum food-specific IgE sensitization in a nationally-representative US sample[111] and 2 more on preliminary positive early results of desensitization[112,113]). We expect the evidence base about food allergy to change more rapidly in the near future than it has in the past.

In conclusion, there is a voluminous literature related to food allergy, but high-quality studies are few. Prime needs for advancement of the field are uniformity in the criteria for what constitutes a food allergy and a set of evidence-based guidelines on which to make this diagnosis.

the development of search terms, strategies for this systematic review, and comments. Julie Schwaninger, MS (NIAID), and Joshua Boyce, MD, provided comments on the Evidence Report. Jerome Hawkins, BA, Breanne Johnsen, BS, Aneesa Motala, BA, Yee-Wei Lim, PhD, and Elizabeth Roth, MA (Southern California Evidence Based Practice Center, Rand Health, Santa Monica, California), provided contributions to the Evidence Report prepared for NIAID. John Adams, PhD (Southern California Evidence Based Practice Center, Rand Health), provided help constructing the receiver operator characteristic curves.

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