

413 for adults and children, respectively, to any of these five foods. Pooled results
 414 are far lower (about 3 percent), however, when assessed by sensitization
 415 alone, sensitization with symptoms, or by double-blind, placebo-controlled
 416 food challenge. These data emphasize the fact that food allergies are over-
 417 reported by patients and that objective measurements are necessary to
 418 establish a true FA diagnosis. For specific foods, pooled results show that
 419 prevalence is highest for milk (3 percent by symptoms alone, 0.6 percent for
 420 symptoms plus positive skin prick test (SPT), and 0.9 percent for symptoms
 421 plus food challenge).

422 **Table 2.1: Prevalence of allergy to peanut, milk, egg, fish, and crustacean shellfish²⁰**

Diagnostic Criteria	Overall prevalence	Peanut	Milk	Egg	Fish	Crustacean Shellfish
Self-reported symptoms: Children	12%					
Self-reported symptoms: Adults	13%					
Self-reported symptoms: All Ages		0.6%	3%*	1%	0.6%	1.2%
Symptoms plus skin test or serum IgE: All Ages	3%	0.75%	0.6%	0.9%	0.2%	0.6%
Food Challenge: All ages	3%	NE	0.9%	0.3%	0.3%	NE†

423 *Greater prevalence in children than adults, not specifically estimated but it appears to be about 6–7% in
 424 children and 1–2% in adults.

425 †NE: Not estimated

426 ○ The paper by Zuidmeer et al.,²¹ which includes data from 33 publications,
 427 presents an epidemiological data review for fruits, vegetables/legumes, tree
 428 nuts, wheat, and soy. The results, summarized in Table 2.2 below,
 429 demonstrate that the reported prevalence for these foods is generally lower
 430 than for the five foods reported in Table 2.1. Once again, the prevalence of FA
 431 was much higher when assessed using self-reporting than when using
 432 sensitization or food challenge.

433

434 **Table 2.2: Prevalence of allergy to fruits, vegetables/non-peanut legumes, tree nuts,**
 435 **wheat, and soy²¹**

Diagnostic Criteria	Fruits	Vegetables / Non-Peanut Legumes	Tree Nuts	Wheat	Soy
Self-reported Symptoms	0.02–8.5%	0.01–13.7%	0–4.1%	0.2–1.3%	0–0.6%
Skin Test	0.02–4.2%	0.01–2.7%	0.04–4.5%	0.2–1.2%	0.03–0.2%
Challenge test	0.1–4.3%	0.1–0.3%	0.1–4.3%	0–0.5%	0–0.7%
Meta-analysis: Adult Studies	1.22% (symptoms)	0.1% (symptoms)	NE†	0.4% (symptoms) 2% (sensitization)	NE
Meta-analysis: Children Studies	NE	NE	0.5% (symptoms)	0.4% (sensitization)	NE

436 NE: Not estimated

- 437 ○ The Center for Disease Control and Prevention (CDC) reviewed the
 438 International Classification of Diseases (ICD) codes in the US for food allergy
 439 in 2007 and found that approximately 3 million children under age 18 years
 440 (3.9 percent) reported a FA in the previous 12 months. From 2004 to 2006,
 441 this review noted that there were approximately 9,500 hospital discharges per
 442 year with a diagnosis related to FA among children under age 18 years.¹⁸
 443 ○ Another US study analyzed national data from the Infant Feeding Practices
 444 Study II, a longitudinal mail survey from 2005 to 2007 of pregnant women
 445 who gave birth to a healthy single child of at least 35 weeks duration,
 446 beginning in the third trimester of pregnancy and periodically thereafter up to
 447 age 1 of the infant.²² In this analysis, probable FA was defined as a
 448 doctor-diagnosed FA, or food-related symptoms of swollen eyes or lips or
 449 hives. Of 2,441 mothers, 60 percent completed all serial questionnaires with
 450 detailed questions about problems with food. About 500 infants were
 451 characterized as having a food-related problem, and 143 (6 percent) were
 452 classified as probable FA cases by one year of age.

453 **2.3.2 PREVALENCE RATES FOR SPECIFIC FOODS AND ANAPHYLAXIS**

- 454 ● **Peanut and tree nuts allergy**
 455 Investigators from the United States and several other countries have published
 456 prevalence rates for allergy to peanut and tree nuts. The results are presented in
 457 Tables 2.3 and 2.4 and include sensitization rates and other clinical results. Where
 458 prevalence and sensitization were measured in the same study, prevalence is
 459 always less than sensitization.

- 460 **Peanut summary**
- 461 ○ US prevalence of peanut allergy ranges from 0.4 to 0.8 percent of the
- 462 population
- 463 ○ Prevalence of peanut allergy in Australia, France, Germany, Israel, Sweden,
- 464 and the United Kingdom varies between 0.6 and 5.9 percent.
- 465 **Tree nuts summary**
- 466 ○ US prevalence of tree nuts allergy is 0.4 percent of the population
- 467 ○ Prevalence of tree nut allergy in France, Germany, Israel, Sweden, and the
- 468 United Kingdom varies between 0.17 and 8.5 percent.

469 **Table 2.3: Peanut allergy prevalence studies**

First author ^{Ref #}	Age (years)	Country	Prevalence (%)	Sensitized (%)	Oral challenge + SPT
Sicherer ²³	1–65	US	0.4 % (48/12032)	-	-
Sicherer ²³	1–65	US	0.8 % (108/13493)	-	-
Liu ²⁴	1–85	US	-	7.6 % (625/8203)	-
Woods ²⁵	20–45	Australia	-	-	0.6 %(7/1141)
Rance ²⁶	2–14	France	0.74 % (20/2716)	-	-
Penard-Morand ²⁷	9–11	France	0.3 % (21/6672)	1.1 % (70/6672)	-
Schafer ²⁸	25–74	Germany	2.1 % (33/1537)	11.1 % (137/1537)	-
Dalal ²⁹	0–2	Israel	0.6 % (6/9040)	-	0.4 % (4/9040)
Marklund ³⁰	13–21	Sweden	5.9 % (86/1451)	-	-
Tariq ³¹	4	UK	-	1.1 % (13/1218)	0.5 % (6/1218)
Grundy ³²	3–4	UK	-	3.3 % (41/1246)	1.4 % (18/1273)
Venter ³³	3	UK	-	2.0 % (13/642)	1.2 % (11/1273)
Venter ³⁴	6	UK	-	2.6 % (18/700)	1.8 % (15/798)
Pereira ³⁵	11	UK	1.9 % (14/775)	3.7 % (26/699)	1 % (8/775)
Pereira ³⁵	15	UK	2.5 % (19/757)	2.6 % (17/649)	0.8 % (6/757)
Du Toit ³⁶	4–18	UK	UK: 1.85 % (73/3942) Israel: 0.17 % (8/4657)	-	-

470 **Table 2.4: Tree nut allergy prevalence studies**

Study	Age (years)	Country	Prevalence (%)	Sensitized	Oral challenge +SPT
Sicherer ²³	1–65	US	0.4 % (48/12032)	-	-
Sicherer ²³	1–65	US	0.4 % (54/13493)	-	-
Rance ²⁶	2–14	France	0.74 % (20/2716)	-	-
Schafer ²⁸	25–74	Germany	8.5 % (130/1537)	17.8 % (274/1537)	-
Dalal ²⁹	0–2	Israel	0.3 % (6/9040)	-	0.2 % (4/9040)
Marklund ³⁰	13–21	Sweden	5.9 % (86/1451)	-	-
Tariq ³¹	4	UK	-	0.2 percent (2/1218)	0.2 %
Venter ³³	3	UK	-	-	0.5 % (6/1273)
Venter ³⁴	6	UK	1.3 % (13/798)	-	N/A
Pereira ³⁵	11	UK	1.1 % (9/775)	-	1 % (8/775)
Pereira ³⁵	15	UK	2.2 % (17/757)	-	0.8 % (6/757)

- 471 ● Seafood allergy
- 472 ○ Sicherer et al.³⁷ in the US used random digit dialing of a national sample to
- 473 estimate lifetime prevalence rate for reported seafood allergy.
- 474 – Rates were significantly lower for children than for adults: fish allergy,
- 475 0.2 percent versus 0.5 percent (p=0.02); crustacean shellfish allergy,
- 476 0.5 percent versus 2.5 percent (p<0.001); any seafood allergy, 0.6 percent
- 477 versus 2.8 percent (p=0.001)
- 478 – Rates were higher for women than men: crustacean shellfish allergy,
- 479 2.6 percent versus 1.5 percent (p<0.001); any fish, 0.6 percent versus
- 480 0.2 percent (p<0.001)
- 481 ○ Liu et al.,²⁴ using National Health and Nutrition Survey (NHANES) data from
- 482 2005–2006, estimated clinical food allergy to shrimp was 0.99 percent of the
- 483 population and sensitization to shrimp was 5.9 percent.
- 484 ● Milk and egg allergy
- 485 ○ Liu et al.,²⁴ using the NHANES data, estimated the prevalence of milk and
- 486 egg sensitization (not allergy) in the United States.
- 487 – 5.7 percent of the population was sensitive to milk and 3.9 percent
- 488 sensitive to egg

- 489 ○ In a Danish cohort of 1,749 children followed from birth through age 3,
490 children were evaluated by history, milk elimination, oral challenge, and skin
491 tests or sIgE.³⁸
- 492 – Milk allergy was suspected in 117 children (6.7 percent) and confirmed in
493 39 (2.2 percent). Of those, 21 had IgE-mediated allergy and the remaining
494 18 were classified as non-IgE-mediated.
- 495 ○ In a Norwegian cohort of 3,623 children followed from birth until the age of
496 two, parents completed questionnaires regarding adverse food reactions at
497 6 month intervals.^{38,39}
- 498 – The cumulative incidence of adverse food reactions was 35 percent by age
499 2, with milk, the single food item most commonly associated with an
500 adverse food reaction, at 11.6 percent.
- 501 – In the second phase of the study, those children who had persistent
502 complaints of milk or egg allergy underwent a more detailed evaluation at
503 the age of 2 years, including skin testing and open and double-blind oral
504 challenges.⁴⁰⁻⁴¹ The prevalence of cow's milk and egg allergy or
505 intolerance at the age of 2½ years were estimated to be 1.1 percent and
506 1.6 percent, respectively. Most milk reactions were not IgE mediated and
507 only 33 percent of parental reports of adverse milk reactions were
508 confirmed. Most egg reactions were IgE mediated and 56 percent of
509 parental reports were confirmed.

- 510 ● **Anaphylaxis:** Five US studies assessed the incidence of anaphylaxis related to
511 food; all used administrative databases or medical record review to identify cases
512 of anaphylaxis.⁴²⁻⁴⁶
- 513 ○ These studies found wide differences (from 1/100,000 population to as high as
514 70/100,000 population) in the rates of hospitalization or Emergency
515 Department visits for anaphylaxis, as assessed by ICD codes or medical
516 record review. These variations may be due to differences in the study
517 methods or differences in the populations (Florida, New York, Minnesota).
- 518 ○ The proportion of anaphylaxis cases thought to be due to foods also varied
519 between 13 percent and 65 percent, with the lowest percentages found in
520 studies that used more stringent diagnostic criteria for anaphylaxis.
- 521 ○ One study reported that the number of hospitalizations for anaphylaxis
522 increased with increasing age, while another study reported total cases of
523 anaphylaxis were almost twice as high in children as in adults.

524 The EP agreed that any estimate of the overall U.S. incidence of anaphylaxis is
525 unlikely to have utility because such an estimate fails to reflect the substantial
526 variability in patient age, geographic distribution, criteria used to diagnose
527 anaphylaxis, and the study methods used.

- 528 ● **Incidence and prevalence of co-morbid conditions**
- 529 ○ According to a recent CDC study, children with FA are about two to four
530 times more likely to have other related conditions such as asthma (2.3 fold),
531 AD (2.3 fold), and respiratory allergies (3.6 fold), compared with children
532 without FA.⁴⁷

- 533 ○ Several studies report on the co-occurrence of other allergic conditions in
- 534 patients with FA,⁴⁸⁻⁵⁰ such as
- 535 – 35 to 71 percent with evidence of AD
- 536 – 33 to 40 percent with evidence of allergic rhinitis
- 537 – 34 to 49 percent with evidence of asthma
- 538 ○ In patients with both AD and FA⁵¹
- 539 – 75 percent had another atopic condition
- 540 – 44 percent had allergic rhinitis and asthma
- 541 – 27 percent had allergic rhinitis
- 542 – 4 percent had asthma, without another atopic condition
- 543 ○ The prevalence of FA in individuals with moderate to severe AD is 30 to
- 544 40 percent and these patients have clinically significant IgE-mediated FA (as
- 545 assessed by some combination of convincing symptoms, skin tests, sIgE
- 546 levels, or oral food challenges)⁵² or a definite history of immediate reactions
- 547 to food.⁵³
- 548 ○ A retrospective review of the records of 201 children with an ICD-9 diagnosis
- 549 of asthma found 88 (44 percent) have concomitant food allergy.⁵⁴

550 Thus, children with food allergy may be especially likely to develop other allergic
 551 diseases. However, the above studies should be interpreted with caution since they may
 552 be subject to selection bias.

553 2.4 KNOWLEDGE GAPS

554 Studies on the incidence, prevalence, and epidemiology of food allergy are lacking,
 555 especially in the United States. It is essential that studies using consistent and appropriate
 556 diagnostic criteria be initiated to understand the incidence, prevalence, natural history,
 557 and temporal trends of food allergy and associated conditions.

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620 35:167–72.

768 **Table 3.1: Summary of U.S. studies of natural history of peanut allergy in children**

Ref #	Clinical site	Criteria for Diagnosis	Sample Size	Years of Study	Population Characteristics	Natural History
1	National Jewish Medical & Research Center	<ul style="list-style-type: none"> History of clinical peanut hypersensitivity and/or a positive food challenge test Positive SPT 	102 (83 contributed data to the analysis)	Mean duration of follow-up 5.9 years	<ul style="list-style-type: none"> 2–4 years old at start of study Male 69 % Initial symptoms non-life-threatening in 73 % 	<ul style="list-style-type: none"> 60% had accidental exposure to peanut during follow up and the severity of the initial reaction did not predict the severity of the subsequent reactions 0–33/year was the mean adverse reactions due to unintentional exposure 4 children selected on the basis of a low peanut sIgE had food challenges that were negative at ages 10, 8, 6 and 4 years
20	95% from Johns Hopkins University	<ul style="list-style-type: none"> History of acute reaction to peanut, and positive skin test, RAST, or challenge In some cases positive results to RAST or skin test with no history of ingesting peanuts 	223	1998–2000	<ul style="list-style-type: none"> > 4 years old Male 63% Median age at diagnosis 1.5 years Median age at evaluation 6.5 years 	<ul style="list-style-type: none"> Based on the history and a low level of peanut sIgE, 85 patients underwent either open peanut challenge or DBPCFC with 48 (57%) passing the challenge. 8 patients selected due to low peanut-specific IgE had negative food challenges at a median age 6 years
18	88% from Johns Hopkins University	<ul style="list-style-type: none"> History of acute reaction to peanut, and positive skin test, RAST, or challenge In some cases positive results to RAST or skin test with no history of ingesting peanuts 	68	1997–2003	<ul style="list-style-type: none"> > 4 years Male 59 % Median age at diagnosis 1.1 years Median age at evaluation 8.5 years 	<p>Tolerance to peanut developed in some children as follows:</p> <ul style="list-style-type: none"> Tolerance 69% (47/68) Possible tolerance 26% (18/68) Recurrence 4% (3/38)
2	Duke University pediatric clinic	<ul style="list-style-type: none"> Convincing clinical history and food-specific IgE or food challenge 	140	2000–2006	<ul style="list-style-type: none"> Male 66 % Median age at first visit 28 months 	<ul style="list-style-type: none"> Unintentional exposure to peanuts after diagnosis 39 % Developed tolerance 3%
17	National Jewish Center for Immunology and Respiratory Medicine	<ul style="list-style-type: none"> All had symptoms and a positive double blind oral food challenge 	32	1973–1985	<ul style="list-style-type: none"> 2–14 years old Median age at diagnosis 7 years 	<ul style="list-style-type: none"> No patient developed tolerance

769

770

771 **3.1.4 TREE NUTS**

772 In an evaluation²³ of 278 patients with a positive tree nut (TN)-specific IgE

- 773 ● 36 percent (101) had a history of acute reactions to TN, 12% (12) of whom had
774 reactions to multiple TN and 63% (73) of whom had a history of moderate-to-
775 severe reactions.
- 776 ● Double blind placebo-controlled food challenge (DBPCFC) were offered to
777 subjects if all current sIgE levels were less than 10 kU(A)/L. Nine of 20 patients
778 who had previously reacted to TN, including some who had prior severe
779 reactions, passed food challenges. Thus, 9% of 101 patients with a history of prior
780 TN reactions outgrew TN allergy.
- 781 ● 74 percent (14/19) of patients who had never ingested TN, but had detectable
782 TN-specific IgE levels, passed challenges.
- 783 ● Looking at specific sIgE cutoffs in these 14 patients, 58 percent with sIgE levels
784 of 5 kU(A)/L or less and 63 percent with sIgE levels of 2 kU(A)/L or less passed
785 challenges. Although an ideal sIgE cutoff for challenge cannot be firmly
786 determined on the basis of these data, the authors concluded that patients aged
787 4 years or older with all sIgE levels of 5 kU(A)/L or less should be considered for
788 challenge.

789 **3.1.5 WHEAT**

790 In a study²⁴ of 103 patients with wheat allergy (IgE mediated, not celiac disease), rates of
791 resolution were

- 792 ● 29 percent by 4 years
- 793 ● 56 percent by 8 years
- 794 ● 65 percent by 12 years

795 Higher wheat sIgE levels were associated with poorer outcomes. The peak wheat IgE
796 level recorded was a useful predictor of persistent allergy ($P < 0.001$), although many
797 children outgrew wheat allergy with even the highest levels of wheat-specific IgE. The
798 median age of resolution of wheat allergy was approximately 6½ years in this population.
799 In a significant minority of patients, wheat allergy persisted into adolescence.

800 **3.1.6 SEAFOOD**

801 There are few studies systematically assessing the natural history of allergy to seafood,
802 which commonly has onset in adult life. In one study,²⁵ sera collected sequentially during
803 a 24-month interval from 11 individuals, each with a clinical history suggesting allergy to
804 shrimp, and 10 control subjects were evaluated for shrimp-specific IgE. Those with
805 suggestive histories and positive tests underwent DBPCFC to shrimp.

- 806 ● Seven subjects exhibited positive challenges based on objective signs and
807 symptoms.
- 808 ● Four subjects reported the subjective symptom of oropharyngeal pruritus.

- 809 • Shrimp-specific IgE levels in all subjects were relatively constant during the
810 24 months of the study and not affected by shrimp challenge.

811 **3.2 NATURAL HISTORY OF LEVELS OF SPECIFIC IgE (sIgE)** 812 **TO FOODS**

813 **In summary: For many patients, sIgE to foods appears within the first two years of**
814 **life. Levels may increase or decrease; a decrease is often associated with the ability**
815 **to tolerate the foods.**

816 Based on the previously discussed studies pertaining to individual foods (Section 3.1),
817 sIgE to a food commonly appears within the first two years of life, with the levels
818 increasing or decreasing over time depending on the food. In a study¹⁶ of patients with
819 allergy to cow's milk and hen's egg and who had repeated DBPCFC, sIgE levels to cow's
820 milk and hen's egg were retrospectively determined from stored serum samples obtained
821 at the time of the food challenges.

- 822 • 42 percent (28 of 66) egg-allergic and 48percent (16 of 33) milk-allergic patients
823 lost their allergy over time.
- 824 • For egg, decreases in sIgE levels were significantly related to the probability of
825 developing clinical tolerance (P=0.0014).
- 826 • For milk, there also was a significant relationship between the decrease in sIgE
827 levels and the probability of developing the ability to tolerate to milk (P=0.0175).
- 828 • Stratification into those below versus above 4 years of age at the time of first
829 challenge revealed that in the younger age group the rate of decrease in sIgE
830 levels over time was more predictive of the likelihood to develop clinical
831 tolerance.
- 832 • The median level of sIgE at diagnosis was significantly lower for the group
833 developing tolerance to egg (P <0.001), and a similar trend was seen for milk
834 allergy (P=0.06).

835 These results were used to develop a model for predicting the likelihood of developing
836 tolerance in milk and egg allergy based on the decrease in food sIgE over time.

837 **3.3 DIFFERENCES IN NATURAL HISTORIES OF PEDIATRIC** 838 **AND ADULT FOOD ALLERGY**

839 **In summary: FA in adults can reflect persistence of pediatric food allergies, (e.g.,**
840 **cow's milk, peanut, and tree nuts) or *de novo* sensitization to food allergens**
841 **encountered after childhood. Although there is a paucity of data from U.S. studies,**
842 **FA that start in adult life tends to persist and not resolve.**

843 The data presented below is extracted from studies of FA with mixed age groups.

- 844 • In a retrospective study²⁶ of 601 cases of anaphylaxis with a mean age of
845 37 years, there were 133 cases of food-related anaphylaxis. The causative foods in
846 descending order of frequency were crustacean shellfish, peanuts, food additives

847 or spices, tree nuts, beef, almonds or peaches. It should be noted in this study that
848 anaphylaxis (in this study, this includes non-life threatening and largely cutaneous
849 reactions) is used as a surrogate for the incidence of FA as measured by food
850 challenge.

- 851 ● A non-U.S. study²⁷ compared 30 cow's milk-allergic adults to 25 milk-sensitized,
852 but tolerant, controls. The investigators found that
 - 853 ○ The majority of milk-allergic patients, 67% (20/30), reported severe
854 symptoms on milk ingestion.
 - 855 ○ Milk-allergy was confirmed in all 11 patients participating in a DBPCFC.
 - 856 ○ The dose of milk protein (0.3 to 300 mg) that elicited subjective symptoms
857 was significantly lower than the dose that elicited objective signs of reaction
858 (300 to 9000 mg).
 - 859 ○ The severity of milk allergy by history and eliciting dose was not correlated
860 with the size of the skin prick test (SPT) wheal or the level of milk-specific
861 sIgE.
 - 862 ○ Patients with allergy had larger SPT reactivity than tolerant controls for whole
863 cow's milk, alpha-lactalbumin, and beta-lactoglobulin (P=0.002, P=0.014,
864 P=0.004, respectively) but not for casein. In contrast, sIgE to casein was
865 higher in patients than in controls (P=0.016). No difference was observed for
866 sIgE to alpha-lactalbumin and beta-lactoglobulin.
- 867 ● Allergy to milk, egg, wheat, and soy generally resolves, thus becoming less
868 prevalent in adults. In contrast, allergies to peanut, tree nuts, are more likely to
869 persist.²⁸ Allergy to seafood most commonly develops in adulthood, and it usually
870 persists.^{46,47}

871 **3.4 NATURAL HISTORY OF CONDITIONS THAT CO-EXIST** 872 **WITH FOOD ALLERGY**

873 **In summary: FA may coexist with asthma, AD, eosinophilic esophagitis (EoE), and**
874 **exercise-induced anaphylaxis. The presence of FA can be a predictor of acute,**
875 **severe asthma. Moreover, food may be a trigger for exercise-induced anaphylaxis.**
876 **Elimination of food allergens in sensitized individuals can improve symptoms of**
877 **some concomitant co-morbid conditions.**

878 **3.4.1 ASTHMA**

879 Four U.S. studies^{10,29-31} assessed the relationship of food allergies to asthma. In addition,
880 two studies^{8,9} dealing with fatal or near fatal anaphylaxis to foods in U.S. children
881 reported that all or almost all patients who died also had asthma. Furthermore, as already
882 noted in numerous studies, concomitant asthma is highly prevalent among patients
883 diagnosed with FA. These studies also drew several additional conclusions.

- 884 ● Food-allergic asthmatics were more likely than the non-food allergic asthma
885 patients to have had a hospitalization for asthma, and had increased emergency
886 department visits for asthma.

- 887 • Sensitized (e.g., to milk, wheat, peanut, or egg) asthmatic children had a higher
888 rate of hospitalization than non-sensitized asthmatic children and also required
889 more steroid use.
- 890 • The presence of self-reported FA was significantly more likely in patients
891 admitted to the ICU compared to ambulatory care asthma patients or those
892 admitted to the hospital, but not to the ICU.
- 893 • The presence of FA is a risk factor for asthma severity. Moreover, the presence of
894 asthma may substantially increase the risk of death from anaphylaxis to food
895 proteins.

896 3.4.2 ATOPIC DERMATITIS

897 **In summary: AD and FA are highly associated. When a FA is outgrown, the**
898 **re-introduction of the food in the diet will not result in recurrence or worsening of**
899 **the AD.**

900 As noted previously, up to 37 percent of children under 5 years of age with moderate to
901 severe AD will have IgE-mediated FA.⁵ Whether FA can exacerbate AD is still
902 controversial in part because the signs and symptoms of food allergen exposure are so
903 pleomorphic and because well-designed relevant food allergen avoidance trials have
904 rarely been done in AD subjects. A systematic review of nine randomized controlled
905 trials,³² which assessed the effects of dietary exclusions for the treatment of established
906 AD in unselected subjects, found little evidence to support the role for food avoidance.
907 However, several studies³³⁻³⁵ found an improvement in pruritus when egg-allergic AD
908 subjects were placed on an egg-free diet.

909 In a U.S. study³⁶ of the natural history of FA in children with AD, 75 children with a
910 mean age of 8 months (range 3 to 18 months) were diagnosed using a DBPCFC. Patients
911 had other atopic diseases as described above in section 2.3.2. In addition

- 912 • 60 percent were allergic to a single food
913 • 28 percent were allergic to two foods
914 • 8 percent were allergic to three foods
915 • 4 percent were allergic to four foods
916 • Milk, peanut, and egg were the most likely to produce positive food challenges

917 After their initial diagnosis, all children were placed on allergen-restricted diets, with a
918 history of compliance of 90 percent. After one or two years, the patients underwent repeat
919 food challenge tests.

- 920 • 26 percent of patients lost all evidence of symptomatic FA.
921 • Overall, 31 percent of the 1,221 food allergies were outgrown after one year of
922 food avoidance.
923 • All patients who outgrew their reactivity to a specific food had the food
924 reintroduced into their diets with no recurrence of symptoms and no worsening of
925 AD at a follow-up from six months to four years.

- 926 ● Patients who developed both skin and respiratory tract symptoms at the initial
927 food challenge were much less likely to outgrow their FA than patients whose
928 initial symptoms were limited to skin only or skin and gastrointestinal tract
929 symptoms.

930 **3.4.3 EOSINOPHILIC ESOPHAGITIS**

931 **In summary: Eosinophilic esophagitis (EoE) is commonly associated with**
932 **sensitization to foods. The natural history of EoE is that of a chronic relapsing**
933 **condition. There is insufficient data to judge the impact of food sensitization on the**
934 **natural history of EoE, and vice versa. There are data to support the beneficial**
935 **effect of food elimination diets on the clinical course of EoE in patients who also**
936 **have FA.**

937 Three U.S. studies³⁷⁻³⁹ examined the natural history of EoE in children, and the results
938 are summarized in 3.2. Briefly,

- 939 ● Most children were diagnosed within the first three years of life, with symptoms
940 including emesis, abdominal pain, heartburn, dysphagia, airway symptoms,
941 cough, and chest.³⁷
- 942 ● In one study,³⁹ symptoms were grouped into age-related categories as “refusal to
943 eat” in toddlers, gastroesophageal reflux or vomiting in young school-age
944 children, and dysphasia and food impaction in older children.
- 945 ● In two studies with adequate follow-up, most patients remained symptomatic and
946 resolution was uncommon. (14 percent³⁷ and 2 percent³⁹). However, progression
947 of eosinophilia to other parts of the gastrointestinal tract was very different.
948 (77 percent³⁷ and 0 percent³⁹).

949

950 **Table 3.2: U.S. Studies of the Natural History of EoE**

Ref #	Clinical Site	Sample Size	Years of Study	Population Characteristics	Sensitization	Clinical EoE
38	Mayo Clinic	71	1992–2003	<ul style="list-style-type: none"> • Male 65% • Age at diagnosis <ul style="list-style-type: none"> ○ Mean 10.5yr ○ Mode 12yr 	60 % of patients had food allergies, most common foods: <ul style="list-style-type: none"> • Milk, • Peanuts • Soy beans 	<ul style="list-style-type: none"> • 17 of 26 patients treated with fluticasone had “complete response.”
37	Cincinnati’s Children’s Hospital	89 (57 to data follow-up)	1997–2004	<ul style="list-style-type: none"> • Male 79 % • White 94% • Age at diagnosis <ul style="list-style-type: none"> ○ Mean 6yr ○ Mode 1yr 	<ul style="list-style-type: none"> • 39% to egg • 39% to peanut • 34% to soy • 29% to beans • 29% to cow’s milk • 29% to pea • 26% to mustard 	<ul style="list-style-type: none"> • 14% resolved • 53% resolved with relapse • 33% persisted • 77% had mucosal eosinophilia or non eosinophilic histopathology in stomach, duodenum, and colon
39	Children’s Hospital in Philadelphia	562	1996–2006	<ul style="list-style-type: none"> • Male 75% • White 90% • Age at diagnosis <ul style="list-style-type: none"> ○ Mean 6yr ○ Mode 1–3 yr 	<ul style="list-style-type: none"> • 17% to Milk • 11% to egg • 10% to wheat • 8% to soy • 8% to corn • 5% to peanut 	<ul style="list-style-type: none"> • 2% resolved • 6% partial resolution • 0% progression to eosinophilia in colon or stomach

951 Two other studies^{40, 41} evaluated the effect of an elimination diet in treating EoE and
 952 found

- 953 • A decrease in the number of esophageal eosinophils per high power field in
 954 78 percent (112/146) of patients.⁴⁰
- 955 • A reduction in clinical symptoms in 57% (75/132) patients. Almost all patients
 956 (160/164) who underwent complete dietary elimination with an amino-acid based
 957 formula showed clinical improvement.⁴¹

958 The influence of concomitant EoE on the natural history of FA is poorly understood. As
 959 discussed above, EoE is associated with a frequent sensitization to food allergens, as
 960 evidenced by the presence of IgE by skin prick tests, or delayed reactions to food
 961 antigens by atopy patch tests. Patients who present with EoE often have either a medical
 962 history of, or ongoing, clinical FA. Food sensitization in patients with EoE is mainly
 963 against the most common food allergens. Some studies in children have shown that
 964 removal of the sensitizing foods may lead to resolution of EoE.⁴⁸ The natural history of
 965 clinical FA in patients with EoE has not been well studied, but clinical experience
 966 suggests that it is the same as in patients with clinical FA without EoE. The influence of
 967 food avoidance on the ability to tolerate food in both pediatric and adult EoE patients
 968 remains to be fully defined.

969 **3.4.4 EXERCISE-INDUCED ANAPHYLAXIS**

970 **In summary: Exercise-induced anaphylaxis in adults is triggered by foods in about a**
971 **third of patients and has a natural history marked by frequent recurrence of the**
972 **episodes.**

973 A U.S. study⁴² of the natural history of exercise-induced anaphylaxis comes from a
974 survey of 279 patients aged 18 or older identified at a single center from 1980 until 1993.

- 975 • Thirty seven percent of patients reported a food trigger, most commonly
976 crustacean shellfish (16 percent), alcohol (11 percent), tomatoes (8 percent),
977 cheese (8 percent), and celery (7 percent).
- 978 • All patients met criteria for exercise-induced anaphylaxis (anaphylactic
979 symptoms, urticaria, and/or angioedema with symptoms consistent with upper
980 respiratory obstruction) or had cardiovascular collapse during exercise.
- 981 • 75 percent of the patients were female.
- 982 • The mean age was 37 years with an onset of symptoms at age 26, and the mean
983 duration of symptoms was 10.6 years.
- 984 • The average number of episodes per year at the time of initial presentation was
985 14.5, but this frequency decreased to 8.3 at the time of the survey.
- 986 • Approximately 33 percent of patients had no attacks in the 12 months prior to the
987 survey.
- 988 • The most frequently occurring symptoms were pruritus (92 percent), urticaria
989 (86 percent), angioedema (72 percent), flushing (70 percent), and shortness of
990 breath (51 percent).
- 991 • About 50 percent of the patients reported seasonal rhinitis or dust allergies,
992 19 percent also reported having asthma, and 10 percent had eczema.

993 Although this study suggests a role for FA in the pathophysiology of exercise-induced
994 anaphylaxis, the results must be interpreted cautiously since the diagnosis of FA was not
995 based on objective testing.

996 **3.4.5 ALLERGIC RHINITIS**

997 IgE-mediated FA does not commonly manifest as rhinitis. Similarly, allergic rhinitis is
998 not thought to be a risk factor for the development of FA.⁴³

999 **3.5 RISK FACTORS FOR THE DEVELOPMENT OF FOOD**
1000 **ALLERGY**

1001 **In summary: Family history of atopy and the presence of atopic dermatitis (AD) are**
1002 **risk factors for the development of both sensitization and confirmed FA.**

1003 A family history of atopy is a risk factor for FA as well as all other atopic disorders, as
1004 illustrated by the following three studies:

- 1005 ● A fourth to a third of children seen in a referral clinic under 5 years of age with
- 1006 moderate to severe AD will have IgE-mediated FA as determined by both the
- 1007 presence of sIgE to one of the six most common food allergens (milk, egg, wheat,
- 1008 soy, peanut, and fish) **and** either a positive DBPCFC, positive open food
- 1009 challenge, or a strong history of food reaction to food product.⁵
- 1010 ● Eighty two percent of 138 peanut allergic patients seen in a referral clinic had
- 1011 AD.²
- 1012 ● AD patients who developed severe dermatitis within the first 3 months of age
- 1013 most commonly had sIgE to cow's milk, egg, and peanut, suggesting that this
- 1014 group is at risk for manifesting IgE-mediated FA⁶.

1015 These studies strongly suggest that FA and moderate to severe AD occur frequently in the
 1016 same child and that early-onset severe AD is associated with risk for the sensitization to
 1017 food.

1018 The mechanism of early sensitization to foods is unclear. Recent publications⁷ have
 1019 suggested that peanut sensitization is independently associated with

- 1020 ● Intake of soy milk or soy formula
- 1021 ● Dermatitis over joints and skin creases (clinical features of AD)
- 1022 ● Household consumption of peanut
- 1023 ● Use of peanut-oil-containing skin preparations

1024 **3.6 RISK FACTORS FOR SEVERITY OF ALLERGIC** 1025 **REACTIONS**

1026 **In summary: The severity of allergic reactions to foods is multi-factorial and**
 1027 **variable.⁸⁻¹² The severity of a reaction cannot be accurately predicted by the degree**
 1028 **of severity of past reactions (also discussed in Section 3.7). The factor most**
 1029 **commonly identified with the most severe reactions is the co-existence of asthma.**

1030 The severity of allergic reactions to food varies on

- 1031 ● The amount ingested
- 1032 ● The food form (cooked, raw, or processed)
- 1033 ● The co-ingestion of other foods

1034 The severity also may be influenced by

- 1035 ● The age of the patient
- 1036 ● The degree of sensitization at the time of ingestion
- 1037 ● The rapidity of absorption, based on whether
 - 1038 ○ The food is taken on an empty stomach
 - 1039 ○ The ingestion is associated with exercise
 - 1040 ○ The patient has other co-morbid conditions (e.g., asthma or AD)

- 1041 Most patients who have had near-fatal or fatal reactions also had
- 1042 ● Concomitant asthma, especially severe asthma with adrenal suppression caused
 - 1043 by chronic glucocorticoid therapy
 - 1044 ● Delayed administration of epinephrine
 - 1045 ● Lack of skin symptoms
 - 1046 ● Denial of symptoms
 - 1047 ● Concomitant intake of alcohol (which may increase absorption of the food
 - 1048 allergen)
 - 1049 ● Reliance on oral antihistamines alone to treat symptoms

1050 **3.7 INCIDENCE, PREVALENCE AND CONSEQUENCES OF**

1051 **UNINTENTIONAL EXPOSURE TO FOOD ALLERGENS**

1052 **In summary: Self-reported food allergic reactions frequently occur in patients with**

1053 **a known diagnosis of FA. Although a subset of these reactions is due to intentional**

1054 **exposure, most are due to unintentional exposure. Both types of exposure can be life**

1055 **threatening. There is no evidence that unintentional or intentional exposures to the**

1056 **food allergen alter the natural history of the FA.**

1057 Data on incidence/prevalence and consequences of unintentional exposures of a patient to

1058 their food allergen is derived from several longitudinal studies of individual food

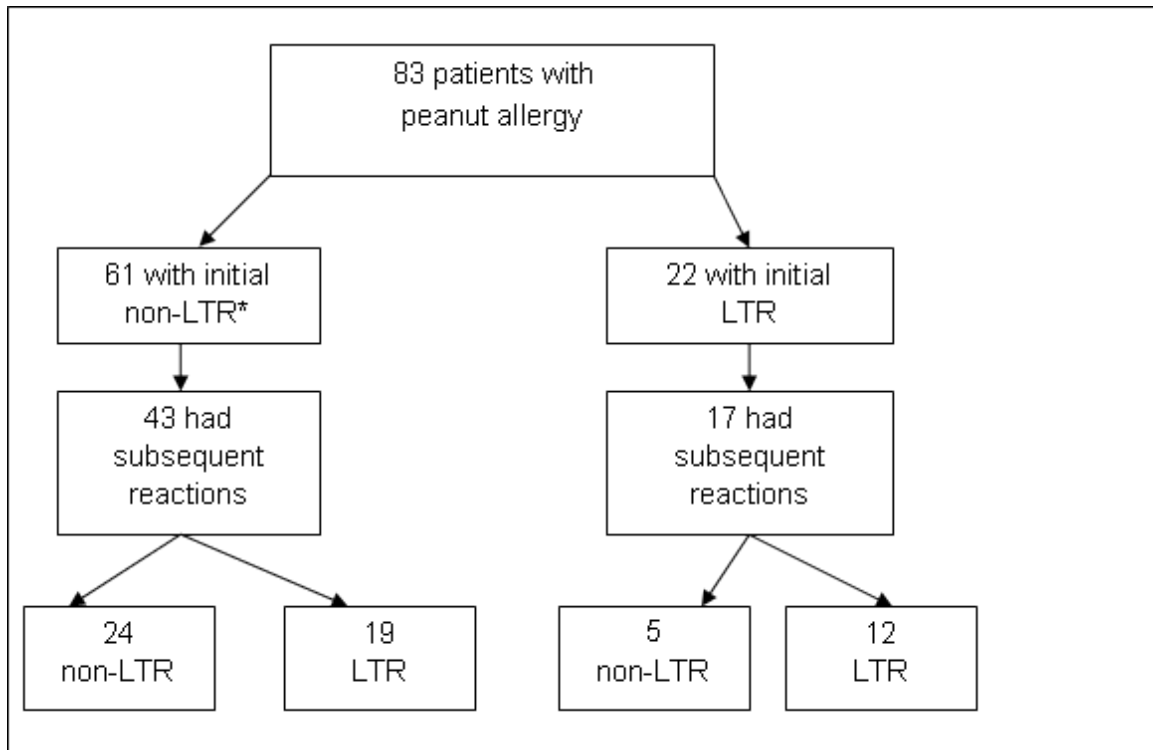
1059 allergies, as follows:

- 1060 ● A study¹ of 83 patients with adverse reactions to peanuts prior to age 4 years,
- 1061 60 percent (50/83) reported a total of 115 unintentional exposures to peanuts with
- 1062 adverse reactions, for a rate of 0.33 adverse reactions due to unintentional
- 1063 exposure per year. When the 83 patients were followed over time, the severity of
- 1064 the initial reaction to peanut did not predict the severity of subsequent reactions
- 1065 on unintentional exposures to peanut, as shown in Fig 3.1.
- 1066 ● Among these subsequent reactions, the rate of life-threatening reactions was high.
- 1067 In patients who had an initial reaction that was not life-threatening, and had a
- 1068 subsequent reaction, 44 percent (19/43) had potentially life-threatening reactions
- 1069 during at least one of these subsequent reactions.
- 1070 ● In patients who had an initial reaction that was life-threatening, and had a
- 1071 subsequent reaction, 71 percent (12/17) had potentially life-threatening symptoms
- 1072 during at least one of these subsequent reactions.

1073

1074

Figure 3.1: The severity of the subsequent reactions to peanuts¹.



1075
1076

*LTR Life threatening reaction

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- A retrospective chart review study² of pediatric patients with peanut allergy seen in a university practice between 2000 and 2006 found that unintentional ingestions occurred in 39 percent of 140 patients, with a mean of 1.8 unintentional ingestions per patient and a range of 1 to 10 ingestions. The median time to first unintentional ingestion was 12.5 months after diagnosis and 25 percent of patients reported a subsequent reaction that was more severe than the first one. A telephone survey³ about unintentional exposures to peanuts in 252 children found 35 unintentional exposures occurred in 29 children over a period of 244 patient-years, yielding an annual incidence rate of 14.3 percent. Eighty five percent of the children attended schools prohibiting peanuts.
- A survey study⁴ of college students with FA found that 42.2 percent (121/278) reported having had a food reaction while enrolled in a university and 27 percent (75/278) had the reaction while on campus. The reactions occurred in restaurants (21.3 percent), residence halls (19.9 percent), parent’s house (18.8 percent), apartment (17.1 percent), friend’s house (16.7 percent), dining hall (13.6 percent) and other (5 percent).

1093 **3.8 KNOWLEDGE GAPS**

1094 There are many gaps in the published literature on the natural history of FA. In particular,
1095 while there are several follow-up studies from single clinics, there are no data from
1096 community-based populations in the United States. Thus, the true natural history of

1097 symptoms, co-morbid conditions, and the frequency and impact of inadvertent exposures
1098 are largely unknown.

1099 Little is known about

- 1100 ● The factors that may cause higher morbidity and mortality from FA (aside from
1101 the association with asthma).
- 1102 ● The natural history of IgE-mediated FA in adults with the exception that
1103 crustacean shellfish allergy is thought to be more common in this age group and
1104 possibly the most common recognized food allergen.
- 1105 ● The differences in the range of symptoms of FA based on the age of the patient,
1106 their co-morbidities (e.g., other atopic disorders), the food allergen, its mode of
1107 preparation, or the dose of allergen.
- 1108 ● The differences and similarities between pediatric and adult FA
- 1109 ● The natural history of non-IgE but immunologic FA.

1110 No information is available on

- 1111 ● The impact of treatment for ongoing asthma on the outcome of anaphylaxis

1112 Other important areas that need to be addressed include

- 1113 ● The clinical and immunopathogenic impact of relevant allergen avoidance in
1114 atopic individuals with FA.
- 1115 ● The clinical and immunopathogenic impact of asthma on the clinical course of
1116 AD and EoE.
- 1117 ● The use of more aggressive management of FA (e.g., therapeutic use of anti-IgE,
1118 targeted food elimination diet, newer immunotherapeutics) to determine if it
1119 would alter the severity or magnitude of the other co-morbid conditions.

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1230 *Supplementary document identified by the EP
1231

1232 **SECTION 4 DIAGNOSIS OF FOOD ALLERGY**

1233 **4.1 WHEN SHOULD FOOD ALLERGY BE SUSPECTED?**

1234 **Guideline 1:** The Expert Panel (EP) recommends that food allergy (FA) should be
1235 considered

- 1236 ● In individuals presenting with anaphylaxis or any combination of symptoms listed
1237 in Table 4.1 that occur within minutes to hours of ingesting food, especially in
1238 young children and/or if symptoms have followed the ingestion of a specific food
1239 on more than one occasion
- 1240 ● In infants and young children diagnosed with certain disorders such as moderate
1241 to severe atopic dermatitis (AD), eosinophilic esophagitis (EoE), enterocolitis,
1242 enteropathy, and allergic proctocolitis
- 1243 ● In adults diagnosed with EoE

1244 **Rationale:** There is sufficient evidence to support the evaluation of food allergy in
1245 patients presenting with specific allergic signs and symptoms following the ingestion of
1246 food or with certain disorders frequently associated with allergic reactions to food, even
1247 in some cases without an apparent relationship to eating.

1248 **Balance of Benefits and Harms:** Identification and avoidance of foods responsible for
1249 food allergic reactions improve quality of life and potentially prevent life-threatening
1250 reactions and disorders. With the appropriate evaluation, there is a low risk of labeling
1251 someone as food allergic and adversely affecting their nutritional well-being and social
1252 interactions.

1253 **Quality of Evidence:** Moderate

1254 **Contribution of Expert Opinion:** Significant

1255

1256 **Table 4.1 Symptoms of Food-allergic Reactions**

Target Organ	Immediate Symptoms	Delayed Symptoms
Cutaneous	<ul style="list-style-type: none"> • Erythema • Pruritus • Urticaria • Morbilliform eruption • Angioedema 	<ul style="list-style-type: none"> • Erythema • Flushing • Pruritus • Morbilliform eruption • Angioedema • Eczematous rash
Ocular	<ul style="list-style-type: none"> • Pruritus, • Conjunctival erythema • Tearing • Periorbital edema 	<ul style="list-style-type: none"> • Pruritus • Conjunctival erythema • Tearing • Periorbital edema
Upper Respiratory	<ul style="list-style-type: none"> • Nasal congestion • Pruritus • Rhinorrhea • Sneezing 	-
Lower Respiratory	<ul style="list-style-type: none"> • Cough • Chest tightness • Dyspnea • Wheezing • Intercostal retractions • Accessory muscle use 	<ul style="list-style-type: none"> • Cough, dyspnea, and wheezing
Gastrointestinal (Oral)	<ul style="list-style-type: none"> • Angioedema of the lips, tongue, and/or palate • Oral pruritus • Tongue swelling • Swelling in the throat • Hoarseness • Dry staccato cough 	-
Gastrointestinal (Lower)	<ul style="list-style-type: none"> • Nausea • Colicky abdominal pain • Reflux • Vomiting • Diarrhea 	<ul style="list-style-type: none"> • Nausea • Abdominal pain • Reflux • Vomiting • Diarrhea • Hematochezia • Irritability and food refusal with weight loss (young children)
Cardiovascular	<ul style="list-style-type: none"> • Tachycardia (occasionally bradycardia in anaphylaxis) • Hypotension • Dizziness • Fainting • Loss of consciousness 	-

1257

1258 When an individual presents with any combination of the symptoms listed in Table 4.1
1259 shortly after ingesting food, a diagnosis of food allergy should be considered, especially
1260 if symptoms have followed the ingestion of a specific food on more than one occasion.
1261 Note that upper airway symptoms (e.g., nasal congestion and/or ocular pruritus) in the
1262 absence of other allergic symptoms are rarely due to a food allergy.¹

1263 4.1.1 TIMING OF FOOD ALLERGIC REACTIONS

1264 Allergic reactions to food or a food additive may present with a variety of symptoms (see
1265 Table 4.1). These reactions may be

- 1266 ● **Immediate**, occurring within minutes to a few hours, and typically involve
1267 IgE-mediated mechanisms
- 1268 ● **Delayed**, occurring within several hours to a few days, and are thought to
1269 typically involve cellular mechanisms

1270 4.1.2 IgE-MEDIATED REACTIONS TO FOOD

1271 IgE-mediated reactions to foods are more common in young children, affecting up to
1272 6 percent of children under 5 years of age, and are more frequently seen in children with
1273 certain atopic disorders, such as AD. For example, approximately 35 percent of children
1274 with moderate to severe AD have FA². In another study, investigators found that the
1275 younger the child and the more severe the AD, the greater likelihood that the child has a
1276 FA.⁷ Although any food may cause an allergic reaction, symptoms following the
1277 ingestion of certain foods should raise greater suspicion of food allergy, especially in
1278 atopic individuals. For example

- 1279 ● Milk, egg, and peanut account for the vast majority of allergic reactions in young
1280 children
- 1281 ● Peanut, tree nuts, and seafood (fish and crustacean shellfish) account for the vast
1282 majority of reactions in teenagers and adults.

1283 Symptoms of FA should occur consistently following the ingestion of the causative food
1284 allergen, although small, sub-threshold quantities of a food allergen or extensively baked,
1285 heat-denatured foods may sometimes be ingested without inducing symptoms.

1286 When evaluating older patients, certain complementary factors must be considered, such
1287 as exercise, alcohol consumption and use of non-steroidal anti-inflammatory drugs. Some
1288 individuals will only experience allergic reactions if they ingest specific foods in
1289 association with these factors. For example, anaphylaxis that occurs following exercise is
1290 associated with sensitization to specific foods in approximately 30 percent of cases.

1291 Sensitization to food proteins and allergic reactions to food are much more prevalent in
1292 individuals with certain clinical disorders. For example, more than 95 percent of children
1293 and adolescents with EoE experienced marked clinical and histological improvement
1294 when placed on an allergen elimination (often elemental) diet,⁷⁴ although the causative
1295 role of IgE-mediated mechanisms in EoE is unclear.

1296 **4.1.3 MIXED IgE- AND NON-IgE-MEDIATED REACTIONS TO FOOD**

1297 Mixed IgE- and non-IgE-mediated mechanisms should be suspected when symptoms,
1298 which generally involve the gastrointestinal (GI) tract, are of a more chronic nature, do
1299 not resolve quickly, and are not closely associated with ingestion of an offending food
1300 (e.g., food protein-induced enterocolitis syndrome (FPIES) and EoE). Thus, the presence
1301 of food allergy should be suspected but the differential diagnosis will be broader as
1302 compared to IgE-mediated food allergy.

1303 FA should be suspected when an esophageal biopsy as part of an evaluation for
1304 chronic/intermittent symptoms of gastroesophageal reflux reveals EoE, as evidenced by
1305 eosinophilia in the proximal 2/3 of the esophagus.⁸ EoE can be seen at any age, but is
1306 most common in infants, children, and adolescents. In adults, symptoms of EoE include
1307 abdominal pain, dysphagia and/or food impaction. Allergic eosinophilic gastroenteritis
1308 can manifest at any age and present as chronic abdominal pain, emesis, poor appetite,
1309 failure to thrive, weight loss, anemia, or protein-losing enteropathy.

1310 **4.1.4 NON-IgE-MEDIATED REACTIONS TO FOOD**

1311 Some gastrointestinal disorders in children are frequently provoked by exposure to food
1312 proteins and thought to be caused by delayed, immune but not IgE-mediated reactions to
1313 foods, for example

- 1314 • Food protein-induced enterocolitis syndrome (FPIES) (milk, soy, rice, cereal
- 1315 grains)³⁻⁵
- 1316 • Food protein-induced enteropathy syndrome
- 1317 • Food protein-induced allergic proctocolitis syndrome (milk, soy, egg)⁶

1318 Adults may also develop these disorders, but they appear to be much less common than in
1319 children. Celiac disease is the exception among non-IgE-mediated reactions to food
1320 because it occurs with similar frequency in children and adults.

1321 Two examples of non-IgE-mediated disorders are allergic proctocolitis and FPIES.^{4-6,9}
1322 The former can manifest in young infants who frequently are breastfed and presents as
1323 blood-streaked or hemoccult-positive stools in an otherwise healthy appearing infant. The
1324 latter also usually occurs in young infants and manifests as chronic emesis, diarrhea, and
1325 failure to thrive. Upon re-exposure to the offending food after a period of elimination, a
1326 subacute syndrome can present with repetitive emesis and dehydration. There are also
1327 reports of adults (IgE-negative) experiencing crampy abdominal pain, severe vomiting,
1328 light-headedness, and lethargy two to three hours following the ingestion of crustacean
1329 shellfish.⁷³

1330 **4.1.5 DIFFERENTIAL DIAGNOSIS OF FOOD ALLERGY**

1331 In a meta-analysis of studies evaluating FA, up to 35 percent of individuals reporting a
1332 food reaction believe they have FA,⁶⁷ whereas studies confirming FA by oral food
1333 challenge suggest a prevalence of about 3.5 percent.⁶⁸ Much of this discrepancy is due to
1334 a misclassification of adverse reactions to foods that are not allergic in origin, for

1335 example lactose intolerance causing bloating, abdominal pain, and diarrhea after
1336 consuming milk products. There are many causes of reactions to foods that are not
1337 allergic in origin.

1338 In the differential diagnosis of food allergies, allergic disorders from other causes, such
1339 as drugs, as well as disorders that are not immunologic in nature must be considered. The
1340 medical history is vital in excluding these alternative diagnoses, for example

- 1341 ● Acute allergic reactions initially attributed to a food may have been triggered by
1342 other allergens (e.g., medications, insect stings).
- 1343 ● In children with atopic dermatitis, eczematous flares erroneously attributed to
1344 foods are often precipitated by irritants, humidity, temperature fluctuations, and
1345 bacterial infections of the skin (e.g., *Staphylococcus aureus*).
- 1346 ● Chronic gastrointestinal symptoms may result from reflux, infection, anatomical
1347 disorders, metabolic abnormalities, e.g. lactose intolerance, and other causes.
- 1348 ● Chemical effects and irritant effects of foods may mimic allergic reactions. For
1349 example, gustatory rhinitis may occur from hot or spicy foods due to neurologic
1350 responses to temperature or capsaicin.⁶⁹
- 1351 ● Tart foods may trigger an erythematous band on the skin of the cheek along the
1352 distribution of the auriculotemporal nerve in persons with gustatory flushing
1353 syndrome.⁷⁰
- 1354 ● Food poisoning, due to bacterial toxins such as toxigenic *E. coli* or scombroid
1355 poisoning caused by spoiled dark-meat fish such as tuna and mahi-mahi, can
1356 mimic an allergic reaction.⁷¹
- 1357 ● For persons with eosinophilic gastrointestinal disorders, alternative diagnoses
1358 such as parasite infections, gastroesophageal reflux disease, systemic eosinophilic
1359 disorders and vasculitis should be considered.
- 1360 ● Behavioral and mental disorders may result in food aversion (e.g., anorexia
1361 nervosa).
- 1362 ● Pharmacological effects of foods, such as tryptamine (in tomatoes) and food
1363 additives may mimic some allergic symptoms of the skin and gastrointestinal
1364 tract.⁷²

1365 **4.2 DIAGNOSIS OF IgE-MEDIATED FOOD ALLERGY**

1366 **4.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATION**

1367 **Guideline 2:** Medical history and physical examination

- 1368 ● Medical History: The EP recommends utilizing a detailed medical history to help
1369 focus the evaluation of a food allergy. Although the medical history often
1370 provides evidence for the type of food allergic reaction and the potential causative
1371 food(s) involved, history alone cannot be considered diagnostic of food allergy.
- 1372 ● Physical Examination: The EP recommends performing a physical examination of
1373 the patient, which may provide signs consistent with an allergic reaction or
1374 disorder often associated with FA. However, by itself, the physical examination
1375 cannot be considered diagnostic of a FA.

1376 **Rationale:** Medical history is useful for identifying food allergens that may be
1377 responsible for IgE-mediated allergic reactions, but it lacks sufficient sensitivity and
1378 specificity to definitively make a diagnosis of FA. Moreover, medical history is more
1379 useful in diagnosing “acute” food allergic reactions compared to “delayed” reactions, but
1380 usually requires further evaluation to confirm a diagnosis of FA; such as laboratory
1381 studies and/or oral food challenges.

1382 **Balance of benefits and harms:** The medical history and physical examination provide
1383 evidence for suspecting FA and focus the evaluation. However, basing the diagnosis of
1384 FA on either history or physical examination alone may lead to an erroneous diagnosis of
1385 FA and may lead to unnecessarily restrictive diets that could have adverse nutritional and
1386 social consequences.

1387 **Quality of Evidence:** Low

1388 **Contribution of Expert Opinion:** Significant

1389 In evaluating a patient with suspected FA, a thorough medical history is very important in
1390 identifying symptoms associated with FA (see Table 4.1) and focusing the diagnostic
1391 work-up, but alone cannot be considered diagnostic.^{10,1} The nature of the reaction often
1392 suggests the underlying mechanism, either IgE-mediated (immediate) or non-IgE-
1393 mediated (delayed), and will determine the diagnostic tests to be utilized. Since none of
1394 the symptoms of FA are pathognomonic for the disorder, the medical history may be used
1395 to help identify causative allergens or to differentiate the reaction from non-allergic
1396 disorders, even though history alone does not provide sufficient sensitivity or specificity
1397 to make a diagnosis of FA.¹²

1398 Critical questions should include the following:

- 1399 • What are the symptoms of concern?
1400 • When do they occur in relation to exposure to a given food?
1401 • Can the food ever be eaten without these symptoms occurring?
1402 • Have the symptoms been present at times other than after exposure to a given
1403 food?
1404 • What treatment was given and how long did the symptoms last?

1405 There are no findings in a physical examination that are diagnostic of food allergy. The
1406 presence of physical signs at the time of the physical examination may verify the
1407 diagnosis of an atopic disorder (e.g., urticaria, AD), or suggest prolonged symptoms (e.g.,
1408 loss of body weight in patient with EoE). Physical examination may also reveal findings
1409 more suggestive of a non-allergic disorder that would require further investigation and
1410 testing.

1411 **Guideline 3:** The EP recommends that parent and patient reports of food allergy must be
1412 confirmed since multiple studies demonstrate that 50 to 90 percent of presumed food
1413 allergies are not actually allergies.

1414 **Rationale:** Given the low positive predictive value of self-reported symptoms, it is
1415 important that all suspected food allergy be confirmed by appropriate evaluation (e.g.,
1416 food challenge, tests for allergic sensitization).

1417 **Balance of Benefits and Harm:** Since unnecessary food avoidance affects quality of life
1418 and nutrition, there is possible harm in over-diagnosing FA.

1419 **Quality of Evidence:** High

1420 **Contribution of expert opinion to the recommendation:** Minimal

1421 As described in Section 2.3, (see Tables 2.1 and 2.2) two systematic reviews/meta-
1422 analyses found that the prevalence of FA based on self-reported symptoms of FA was
1423 several fold higher compared to when the diagnosis was based on sensitization alone,
1424 sensitization with symptoms, or by double-blind placebo-controlled food challenge
1425 (DBPCFC).

1426 **4.2.2 METHODS TO IDENTIFY THE CAUSATIVE FOOD**

1427 When evaluating a patient for FA, the diagnostic tests selected are based upon a
1428 comprehensive medical history. The history should suggest the possible allergic
1429 mechanism involved (i.e., IgE-mediated or non-IgE-mediated), which then determines
1430 the types of testing to be pursued, and the possible foods involved. Tests selected to
1431 evaluate FA should be based on the medical history and **not** be comprised of general
1432 large panels of food allergens. In addition, diagnostic tests for non-allergic disorders may
1433 be needed depending on the differential diagnosis.

1434 **4.2.2.1 Skin Prick (Puncture) Test**

1435 **Guideline 4:** The EP recommends performing a skin prick test (SPT) to assist in the
1436 identification of foods that may be provoking IgE-mediated food allergic reactions, but
1437 the SPT alone cannot be considered diagnostic of FA.

1438 **Rationale:** SPTs are safe and useful for identifying foods potentially provoking IgE-
1439 mediated food allergic reactions, but they have a low positive predictive value for the
1440 clinical diagnosis of FA.

1441 **Balance of Benefits and Harms:** The reagents and methods for performing SPTs are not
1442 standardized. Nevertheless, SPTs effectively detect the presence of food-specific IgE
1443 antibodies (sIgE), but many patients have sIgE without clinical FA. Compared to oral
1444 food challenge, SPTs have low specificity and low positive predictive value for making
1445 an initial diagnosis of FA. Thus, use of SPTs in this clinical setting may lead to over-
1446 diagnosis. However, in a patient with confirmed FA, SPTs are valuable in identifying the
1447 food(s) responsible for IgE-mediated food allergy. In this clinical setting, compared to
1448 oral food challenge, SPTs have high sensitivity and high negative predictive values.

1449 **Quality of Evidence:** Moderate

1450 **Contribution of Expert Opinion:** Significant

1451 SPTs provide immediate results and are the most commonly performed procedure in the
1452 evaluation of IgE-mediated FA.¹³⁻¹⁶ However, no international standards exist for
1453 standardization of reagents for skin testing, administering, or interpreting SPTs.¹³

1454 A positive SPT is generally considered a wheal with a mean diameter 3 mm or greater
1455 than the negative control.¹⁴ Various studies use different methods to define a positive test,
1456 from measuring the absolute wheal size to measuring the wheal size relative to the

1457 negative (diluent) and positive (histamine) controls. A positive SPT simply correlates
1458 with the presence of allergen-specific IgE bound to the surface of cutaneous mast cells.
1459 Although the larger the mean wheal diameter provoked, the more likely that a food
1460 allergen will be of clinical relevance, the SPT alone is not diagnostic of FA.¹⁷⁻²⁰

1461 When diagnosing the oral allergy syndrome, or in cases where SPTs with commercial
1462 extracts do not correlate with clinical histories, the prick technique with fresh foods,
1463 especially fruits and vegetables, may prove more sensitive.^{21,22}

1464 Negative SPTs occasionally occur in patients with IgE-mediated FA. Therefore, in cases
1465 where history is highly suggestive, further evaluation (e.g., physician-supervised oral
1466 food challenge) is necessary before telling a patient that he or she is not food allergic and
1467 may ingest the suspected food.

1468 4.2.2.2 Intradermal Tests

1469 **Guideline 5:** The EP recommends that intradermal testing should **not** be used to make a
1470 definitive diagnosis of FA.

1471 **Rationale:** There is insufficient evidence to support the use of intradermal skin testing
1472 for the diagnosis of FA. Moreover, intradermal skin tests carry a higher risk of adverse
1473 reactions than SPT.

1474 **Balance of Benefits and Harms:** Although intradermal testing has been suggested to be
1475 more sensitive than SPT for the diagnosis of IgE-mediated FA, there is no evidence to
1476 support such claims for protein-induced FA and insufficient evidence to support its
1477 routine use in diagnosing carbohydrate-induced food allergy. In addition, there is a
1478 greater risk of systemic adverse allergic reactions from intradermal skin tests compared to
1479 SPT.

1480 **Quality of Evidence:** Low

1481 **Contribution of Expert Opinion:** Significant

1482 Intradermal testing for food allergy does not provide increased sensitivity in detecting
1483 food protein-induced allergic reactions.¹⁴ There is suggestive but unconfirmed evidence
1484 to support its use in diagnosing a form of carbohydrate-induced IgE-mediated allergy that
1485 is a characteristic of some types of red meat allergy.²³

1486 4.2.2.3 Total Serum IgE

1487 **Guideline 6:** The EP recommends that the routine use of measuring total serum IgE
1488 should **not** be used to make a definitive diagnosis of FA.

1489 **Rationale:** There is insufficient evidence to support the proposal that measurements of
1490 total serum IgE levels can be a sensitive and specific test for FA.

1491 **Balance of Benefits and Harms:** Although an elevated total serum IgE is frequently
1492 found in atopic individuals and some investigators suggest that it may be useful when
1493 interpreting allergen-specific IgE levels, the EP could find no studies to support such a
1494 claim. In addition, the sensitivity and specificity of this test compared to the outcome of
1495 oral food challenges is insufficient to warrant routine use in evaluating FA.

1496 **Quality of Evidence:** Low

1497 **Contribution of Expert Opinion:** Significant

1498 Mehl et al. looked at the predictive value of the ratio of sIgE to total IgE for the diagnosis
1499 of FA compared to the DBPCFC and concluded that the ratio offered no advantage over
1500 sIgE alone in diagnosing FA.²⁴

1501 **4.2.2.4 Food Allergen-Specific Serum IgE (sIgE)**

1502 **Guideline 7:** The EP recommends sIgE tests for identifying foods that potentially
1503 provoke IgE-mediated food allergic reactions, but alone these tests are not diagnostic of
1504 FA.

1505 **Rationale** sIgE tests are useful for identifying foods potentially provoking IgE-mediated
1506 food allergic reactions, and specified “cut-off” levels may be more predictive than SPTs
1507 of clinical reactivity in certain populations, but when used alone they are not diagnostic
1508 of FA.

1509 **Balance of Benefits and Harms:** sIgE tests are very useful for detecting the presence of
1510 sIgE antibodies, which indicate the presence of allergic “sensitization.” Fluorescence-
1511 labeled antibody assays have been shown to have comparable sensitivity to that of SPTs,
1512 and the absolute levels of sIgE antibodies may directly correlate with likelihood of
1513 clinical reactivity when compared to oral food challenges for the identification of foods
1514 provoking IgE-mediated food allergy.

1515 **Quality of Evidence:** Moderate

1516 **Contribution of Expert Opinion:** Significant

1517 Specific IgE testing and skin testing both depend on the presence of allergen-specific
1518 antibodies. Because the former test measures sIgE in the serum and the latter reflects IgE
1519 bound to cutaneous mast cells, their results may not correlate. Serum testing can be
1520 especially useful when SPTs cannot be done (e.g., extensive dermatitis or
1521 dermatographism), or when antihistamines cannot be discontinued.

1522 Specific IgE levels were originally measured using the radioallergosorbent test (RAST),
1523 but this test has been replaced by more sensitive fluorescence enzyme-labeled assays and
1524 the term “RAST” should be abandoned.

1525 It is important to note that results from different laboratories or different assay systems
1526 may not be comparable.²⁵ Wang et al. examined 50 patients who were between 2 and
1527 20 years of age and used three different systems (Phadia ImmunoCAP, Turbo-MP, and
1528 Immulite 2000) to assess for allergy to cow’s milk, hen’s egg, peanut, as well as three
1529 aeroallergens.²⁵ Each system used slightly different forms of the antigens (e.g., skimmed
1530 cow’s milk versus freeze-dried cow’s milk versus whole cow’s milk). Of the 50 patients,
1531 42 had diagnosed FA. Each system provided significantly different measurements of sIgE
1532 for the same serum samples. Thus, the predictive values associated with clinical evidence
1533 of allergy for ImmunoCAP (which is a second generation in vitro assay for IgE antibody)
1534 cannot be applied to the third generation instruments, Turbo-MP and Immulite.

1535 The presence of sIgE reflects allergic sensitization and not necessarily clinical allergy.
1536 Several studies comparing the quantity of sIgE to oral food challenges have reported that

1537 the greater the levels of sIgE, the higher the probability that ingestion of the food will
1538 lead to an allergic reaction. However, the predictive values varied from one study to
1539 another.²⁶⁻³⁴

1540 4.2.2.5 Atopy Patch Tests (APT)

1541 **Guideline 8:** The EP suggests that APT should **not** be used to make a definitive
1542 diagnosis of non-contact FA.

1543 **Rationale:** There is insufficient evidence to support the use of APT for the evaluation of
1544 FA.

1545 **Balance of Benefits and Harms:** While a number of studies have reported that the APT
1546 may be useful in the evaluation of FA in patients with AD and EoE, there is no agreement
1547 on the appropriate reagents, methods, or interpretation of these tests. When compared to
1548 oral food challenges, APTs show highly variable sensitivity and specificity among
1549 different studies.

1550 **Quality of Evidence:** Low

1551 **Contribution of Expert Opinion:** Significant

1552 The APT is a specific type of patch test. In general, a patch test is used to determine
1553 allergic sensitivity by applying small pads soaked with allergen to the unbroken skin. The
1554 only difference between the APT and the regular patch test is the antigen that is being
1555 tested. The APT utilizes allergens (e.g., food allergens) that are typically used only for
1556 IgE-mediated reactions while the patch test utilizes antigens that are typically used for T
1557 cell-mediated reactions. The tests are both performed the same way.

1558 The APT is an investigational tool for diagnosing FA and is generally used to assess
1559 delayed, or non-IgE-mediated, reactions to an allergen. There are no standard reagents
1560 and no studies specifically addressing the methodology of APTs, although test material is
1561 typically applied to the skin for 48 hours and read at 72 hours following application.^{37,38}
1562 No studies of APT methodology met the RAND inclusion criteria, although most studies
1563 report applying foods (fresh or from powders) in aluminum discs to the skin with
1564 occlusion times of 48 hours and final reading at 72 hours after application of the food.
1565 The sensitivity and specificity of the test varies between studies and may be affected by
1566 the presence of AD and the age of the patient. No studies compared the use of different
1567 food allergen preparations. Two large studies concluded that there was no significant
1568 clinical value in using APTs for diagnosing FA.^{16, 39}

1569 4.2.2.6 Use of SPT, sIgE, and APT in Combination

1570 **Guideline 9:** The EP suggests **not** using the combination of SPTs, sIgE levels, and APTs
1571 for the routine diagnosis of FA.

1572 **Rationale:** There is no literature to support the proposal that the use of SPTs, allergen-
1573 specific sIgE levels, and APTs in combination for the evaluation of FA provides any
1574 significant advantage over the use of SPTs or sIgE tests alone.

1575 **Balance of Benefits and Harms:** Combining the results of SPTs, sIgE levels and APTs
1576 may provide higher positive and negative predictive values than any test alone, but use of

1577 all three tests is time consuming, inconvenient for the patient, and provides marginally
1578 improved positive and negative predictive values that may not be clinically relevant.

1579 **Quality of Evidence:** Low

1580 **Contribution of Expert Opinion:** Significant

1581 A few studies show that various combinations of APT, SPT and sIgE, improved the
1582 sensitivity and specificity over the use of individual tests.^{16,39,40} However, the small
1583 number of studies that calculated the proportion of patients for whom two or more tests
1584 could obviate the need for a DBPCFC found these proportions to be quite small.

1585 4.2.2.7 Food Elimination Diets

1586 **Guideline 10:** The EP suggests that elimination of one or a few specific foods from the
1587 diet may be useful in the diagnosis of FA, especially in identifying foods responsible for
1588 some non-IgE-mediated food allergic disorders, such as FPIES and proctocolitis, EoE,
1589 and Heiner's Syndrome.

1590 **Rationale:** The use of an elimination diet in combination with a convincing history may
1591 be sufficient to diagnose FA in several food allergic disorders, including FPIES and
1592 proctocolitis, EoE, and Heiner's Syndrome.

1593 **Balance of Benefits and Harms:** In several non-IgE-mediated food allergies, a
1594 suggestive medical history plus the elimination of the suspected food resulting in the
1595 resolution of symptoms provides compelling evidence for the diagnosis of FA. In these
1596 situations, there are no known laboratory tests that are diagnostic of the causative food,
1597 and the oral food challenge, while a potentially useful diagnostic test, may provoke
1598 significant morbidity. Thus, many physicians base the initial diagnosis on history and
1599 clearing of symptoms while on the elimination diet, and reserve the oral food challenge
1600 for evaluating the eventual "outgrowing" of the disorder.

1601 **Quality of Evidence:** Low

1602 **Contribution of Expert Opinion:** Significant

1603 The EP did not find specific studies to support the diagnostic value of using dietary
1604 elimination trials or of food/symptoms diaries for the diagnosis of FA. Given the
1605 morbidity of oral food challenges in some non-IgE mediated food allergic disorders,
1606 some investigators believe that a convincing history plus clearing of symptoms with the
1607 initiation of an elimination diet is sufficient to make the diagnosis of FA. However,
1608 prolonged elimination diets consisting of multiple foods have been reported to induce
1609 severe malnutrition,⁴¹⁻⁴³ so confirmatory diagnostic studies must be performed in such
1610 cases to confirm the diagnosis of FA.

1611 4.2.2.8 Oral Food Challenges

1612 **Guideline 11:** The EP recommends using oral food challenges for diagnosing FA. The
1613 DBPCFC is the "gold standard" but the single-blind and open food challenge may be
1614 considered diagnostic in the clinical setting when the food challenge elicits no symptoms
1615 (i.e., negative challenge), or when there are objective symptoms (i.e., positive challenge)
1616 that correlate with medical history and are supported by laboratory tests.

1617 **Rationale:** DBPCFC is the most specific test for diagnosing food allergy. However, due
1618 to the expense and inconvenience of DBPCFCs, single-blind and open food challenges
1619 may be used in the clinical setting if strict criteria are met.

1620 **Balance of Benefits and Harms:** The DBPCFC eliminates potential bias of patients and
1621 supervising physicians that may interfere with the appropriate interpretation of food
1622 challenges, and corresponds most closely to the natural ingestion of food. Other
1623 diagnostics tests lack specificity and may lead to the unnecessary exclusion of foods from
1624 patients' diets. However, the DBPCFC is time consuming, expensive, and, like any form
1625 of oral food challenge, subjects the patient to potential severe allergic reactions. Single-
1626 blind and open food challenges are frequently used to screen patients for FA. When
1627 negative, they may be considered diagnostic in ruling out FA, and when positive (i.e.
1628 when "immediate" objective allergic symptoms are elicited), may be considered
1629 diagnostic in patients who also have a convincing medical history and supportive
1630 laboratory data.

1631 **Quality of Evidence:** High

1632 **Contribution of Expert Opinion:** Moderate

1633 A positive SPT and/or sIgE test result are indicative of allergic sensitization, but these
1634 findings alone may or may not be clinically relevant. Most investigators in the field agree
1635 that verification of clinical reactivity requires well designed oral food challenge
1636 testing.^{14,15,44-48}

1637 Prior to initiating an oral food challenge, suspected foods are eliminated from the diet for
1638 two to eight weeks depending upon the type of food allergic reaction being examined.^{48,49}
1639 All foods in question must be strictly avoided simultaneously. A young infant's diet can
1640 be limited to a hypoallergenic formula. For exclusively breastfed infants, either the
1641 suspected food is eliminated from the mother's diet or the baby is fed a hypoallergenic
1642 formula until the allergic food is identified.

1643 After documenting significant improvement on dietary elimination, the challenge test is
1644 carried out while the patient is on minimal or no symptomatic medication. The test
1645 should be designed and performed under medical supervision to document the dose that
1646 provoked the reaction and to administer symptomatic treatment, which may require
1647 management of anaphylaxis (Section 6), and the medical personnel should have
1648 experience in carrying out such challenges. Food challenge begins with a low dose
1649 (intended to be lower than a dose that can induce a reaction^{51,52}), which is then gradually
1650 increased, while monitoring for any symptoms, until a cumulative dose at least equal to
1651 the usually eaten quantity is reached. The challenge may be carried out in an open fashion
1652 in infants but in older children, single-blind or DBPCFCs may be necessary to minimize
1653 the bias.

1654 Using DBPCFC, several studies have shown that only about a third of the suspected
1655 foods are found to be truly allergic. In addition to verifying FA, challenge testing
1656 prevents unnecessary dietary avoidance and enhances compliance with the elimination
1657 diet. Nevertheless, because of the risk of a severe reaction, intentional challenge should
1658 be avoided in patients who have recently experienced a life-threatening reaction to a

1659 particular food, particularly if it occurred more than once. In the case of post-prandial
1660 exercise-induced reactions, food challenge should be followed by exercise.⁵⁰

1661 There is currently no internationally-accepted, standardized protocol for performing and
1662 interpreting DBPCFCs, although reviews outlining benefits and deficiencies have been
1663 published.⁵¹⁻⁵²

1664 4.2.2.9 Non-standardized and Unproven Procedures

1665 **Guideline 12:** The EP does **not** recommend the use of any of the following non-
1666 standardized tests for the routine evaluation of food allergy

- 1667 ● Basophil histamine release/activation^{53,54}
- 1668 ● Lymphocyte stimulation^{55,56}
- 1669 ● Facial thermography⁵⁷
- 1670 ● Gastric juice analysis⁵⁸
- 1671 ● Endoscopic allergen provocation⁵⁹⁻⁶¹
- 1672 ● Allergen-specific IgG
- 1673 ● Allergen-specific IgG₄
- 1674 ● Cytotoxic assays
- 1675 ● Electrodermal test (Vega)
- 1676 ● Mediator Release Assay (LEAP diet)

1677 **Rationale:** These non-standardized tests have not been shown to be of value in the
1678 diagnosis of food allergy.

1679 **Balance of Benefits and Harms:** The utility of these tests has not been validated for the
1680 diagnosis of FA and may result in false positive or false negative diagnoses, leading to
1681 unnecessary dietary restrictions or delaying the appropriate diagnostic
1682 workup, respectively.

1683 **Quality of Evidence:** Low

1684 **Contribution of Expert Opinion:** Significant

1685 4.3 DIAGNOSIS OF NON-IgE-MEDIATED IMMUNOLOGIC 1686 ADVERSE REACTIONS TO FOOD

1687 The diagnosis of non-IgE-mediated FA can be challenging. Prior to a diagnostic workup,
1688 it may be difficult to distinguish an IgE-mediated from a non-IgE-mediated allergy based
1689 on history and physical examination alone. There are some distinct non-IgE-mediated
1690 conditions associated with FA. T cells have been shown to play a central role in celiac
1691 disease. Studies have shown that T cells may mediate the pathogenesis of some other
1692 non-IgE-mediated adverse reactions to food. Diagnostic tools available for non-IgE-
1693 mediated reactions include DBPCFC, contact dermatitis patch testing, APT, intradermal
1694 skin testing, lymphocyte activation assays, food-specific IgG testing, and endoscopic
1695 biopsy.

1696 Specific non-IgE-mediated adverse reactions to foods include:

- 1697 ● Eosinophilic gastrointestinal diseases (EGIDs)
- 1698 ● Food protein-induced enterocolitis syndrome (FPIES)

- 1699 ● Allergic proctocolitis (AP)
- 1700 ● Contact urticaria
- 1701 ● Allergic contact dermatitis (ACD)
- 1702 ● Systemic contact dermatitis
- 1703 ● Heiner's syndrome

1704 4.3.1 EOSINOPHILIC GASTROINTESTINAL DISEASES (EGIDS)

1705 **Guideline 13:** The EP suggests using SPTs, sIgE tests, and APTs to help identify foods
1706 that may be responsible for EoE, but these tests alone are not sufficient to make the
1707 diagnosis of FA. The role of these tests in the diagnosis of other EGIDs has not been
1708 established.

1709 **Rationale:** SPTs, sIgE, and APTs alone are insufficient to establish a causal role for FA
1710 in EoE, but they may be useful in identifying foods that should be investigated further
1711 with other diagnostic tests, such as dietary elimination, oral food challenges, and
1712 endoscopy and esophageal biopsy.

1713 **Balance of Benefits and Harms:** Some studies suggest that SPTs, sIgE levels, and APTs
1714 may be of value in identifying foods that cause symptoms of EoE. However, the utility of
1715 these tests has not been validated for the diagnosis of FA in EoE or other EGIDs and may
1716 result in false positive or false negative diagnoses.

1717 **Quality of Evidence:** Low

1718 **Contribution of Expert Opinion:** Significant

1719 EGIDs are a diverse group of intestinal diseases that require endoscopic analysis with
1720 mucosal biopsy to make the diagnosis. The diagnosis of EoE is defined by an esophageal
1721 biopsy with the finding of >15–20 eosinophils per high power field. The gold standard
1722 for establishing FA as the cause of EoE is resolution of symptoms and esophageal
1723 eosinophilia following dietary elimination, and recurrence of esophageal eosinophilia
1724 with reintroduction of the suspected food.⁸

1725 Because food allergens are thought to play a large role in the pathogenesis of these
1726 diseases, sIgE tests and SPTs are used to identify potentially causative foods and design
1727 an optimal elimination diet. However, little evidence supports the use of these tests in
1728 predicting the severity of EGID symptoms,⁶² and no studies have systematically assessed
1729 the positive and negative predictive values of SPT or sIgE results in evaluating the
1730 potential causal role of food allergy in EoE. Results of APT from one study suggest some
1731 benefit in their use for identifying suspect food allergens,⁶² but this has not been
1732 confirmed in other studies.

1733 4.3.2 FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME (FPIES)

1734 **Guideline 14:** The EP recommends using the medical history and oral food challenge to
1735 establish a diagnosis of FPIES. However, given the potential morbidity provoked by the
1736 oral food challenge, a diagnosis may be based on a definitive history and absence of
1737 symptoms when the causative food is eliminated from the diet.

1738 **Rationale:** FPIES is diagnosed based on a supportive medical history, resolution of
1739 symptoms with the elimination of the causative food, and in many cases, provocation of
1740 symptoms following an open or single-blind oral food challenge.

1741 **Balance of Benefits and Harms:** There are no laboratory studies with demonstrated
1742 specificity and sensitivity to diagnose FPIES, so an oral food challenge is necessary to
1743 establish the diagnosis. Although the food challenge may induce significant symptoms,
1744 there are no alternative methods with adequate predictability to diagnose FPIES.
1745 However, when the history is very compelling (e.g., two or more reactions with classic
1746 symptoms to the same food in a six-month period and symptoms are eliminated when the
1747 causative food is removed from the diet), a food challenge may not be necessary to make
1748 the diagnosis. Since this disorder often lasts only a few years, however, subsequent oral
1749 food challenges are warranted to determine when FPIES has resolved and food allergen
1750 elimination diets can be terminated.

1751 **Quality of Evidence:** High

1752 **Contribution of Expert Opinion:** Moderate

1753 FPIES is a severe systemic response to food protein that typically occurs one to four
1754 hours after the ingestion of the causative food and frequently develops in the first few
1755 years of life. Symptoms include vomiting, diarrhea, acidosis, and in some cases
1756 shock.^{4,5,63}

1757 Since FPIES occurs when the infant's diet is quite limited, history is often helpful in
1758 identifying food triggers. Because FPIES is a non-IgE-mediated disorder, sIgE tests and
1759 SPT are typically negative. Endoscopy may reveal a mixed eosinophilic and neutrophilic
1760 infiltrate but is not required to make the diagnosis. When young infants develop FPIES to
1761 one formula or food they are at greater risk of developing allergic reactions to other
1762 whole protein formulas. Therefore, hypoallergenic formulas are recommended.^{4,64}
1763 Because hypotension may develop in up to 15 percent of cases, children should be
1764 challenged in a setting where intravenous hydration is readily available.⁴⁸

1765 4.3.3 ALLERGIC PROCTOCOLITIS (AP)

1766 **Guideline 15:** The EP recommends using the clinical history, resolution of symptoms
1767 when the causative food is eliminated from the diet, and recurrence of symptoms
1768 following an oral food challenge to diagnose allergic proctocolitis.

1769 **Rationale:** The evidence supports the conclusion that food protein-induced AP can be
1770 diagnosed based on a supportive medical history, resolution of symptoms with the
1771 elimination of the causative food, and provocation of symptoms following an oral food
1772 challenge.

1773 **Balance of Benefits and Harms:** There are no laboratory studies with sufficient
1774 specificity and sensitivity to diagnose food protein-induced AP, so an oral food challenge
1775 is necessary to establish the diagnosis. Although the food challenge may induce blood in
1776 the stools, symptoms of AP are generally benign and there are no alternative methods
1777 with adequate predictability to diagnose allergic colitis. In cases with a classic history of
1778 AP, a normal physical examination and resolution of symptoms following elimination of
1779 the causative food leads many investigators to believe that an oral food challenge is not
1780 required to establish the diagnosis. Since this disorder often lasts only a few years,

1781 repeated challenges are warranted to determine when food allergen elimination diets can
1782 be terminated.

1783 **Quality of Evidence:** Moderate

1784 **Contribution of Expert Opinion:** Significant

1785 AP is a common transient disease of infancy that manifests itself as the passage of
1786 mucoid, blood-streaked stools in an otherwise healthy infant.⁶ Typically AP is associated
1787 with the ingestion of cow's milk, soy milk, or human breast milk during infancy. Because
1788 AP is a non-IgE-mediated food allergy, sIgE and SPTs are typically negative. Although
1789 colonoscopy and biopsy are not generally necessary to make the diagnosis, the procedure
1790 will reveal lesions that are confined to the large bowel and consist of mucosal edema with
1791 infiltration of eosinophils in the epithelium and lamina propria. In severe lesions with crypt
1792 destruction, polymorphonuclear leukocytes are also prominent.⁶⁵

1793 **4.3.4 CONTACT URTICARIA**

1794 **Guideline 16:** The EP suggests using the clinical history including the absence of
1795 symptoms while the causative food is avoided, positive sIgE or SPTs, and positive
1796 immediate epicutaneous skin tests to establish the diagnosis of food-induced contact
1797 urticaria.

1798 **Rationale:** There are a limited number of well-controlled studies to demonstrate the
1799 utility of these methods in diagnosing contact urticaria, but traditionally they have been
1800 used and found to correlate with clinical symptoms.

1801 **Balance of Benefits and Harms:** Although, there are few well-controlled studies to
1802 demonstrate the benefits of these methods in diagnosing contact urticaria, the potential
1803 harm of avoiding contact with foods provoking such symptoms appears to be minimal.

1804 **Strength of Recommendation:** Moderate

1805 **Contribution of Expert Opinion:** Significant

1806 Contact urticaria can be of two types, either IgE mediated or non-IgE mediated. In
1807 IgE-mediated contact urticaria, substances present in foods interact with allergen-specific
1808 IgE bound to cutaneous mast cells, leading to the release of histamine and other
1809 inflammatory mediators. Localized or generalized urticaria, as well as systemic
1810 symptoms may result. In non-IgE-mediated adverse reactions to food, systemic
1811 symptoms are rarely seen. Immunologic contact urticaria may be assessed with patch
1812 tests, SPT or sIgE testing, although there is no standardization of diagnostic
1813 methodology.

1814 **4.3.5 ALLERGIC CONTACT DERMATITIS (ACD)**

1815 **Guideline 17:** The EP recommends using the clinical history, which includes the absence
1816 of symptoms while the causative food is avoided, and positive patch tests to diagnose
1817 ACD.

1818 **Rationale:** There are a limited number of well-controlled studies demonstrating the
1819 utility of these methods in diagnosing ACD. However, the concept that patch testing can
1820 be useful in establishing the diagnosis of ACD is based on both the underlying

1821 immunologic mechanism involved in the disease and observations from general medical
1822 practice.

1823 **Balance of Benefits and Harms:** Traditionally patch testing has been used to support
1824 history in diagnosing ACD. While there are insufficient well-controlled studies to
1825 demonstrate the benefits of these methods in diagnosing ACD, the testing method largely
1826 reflects the immunopathogenic mechanism involved and the harm of avoiding contact
1827 with the food identified by this method appears minimal.

1828 **Quality of Evidence:** Moderate

1829 **Contribution of Expert Opinion:** Significant

1830 ACD is a cell-mediated allergic reaction and may be triggered by foods or contaminants
1831 in foods. The immediate reactions in ACD may be initiated by contact with chemical
1832 moieties in the food, such as oleoresins in fruits and vegetables or spices. Examples
1833 include touching garlic causing contact dermatitis of the hands, mango causing perioral
1834 dermatitis, or raw chestnut causing hand and perianal dermatitis.⁶⁶ A detailed history will
1835 aid in the diagnosis of ACD. Patch testing may be performed with standardized contact
1836 allergens or suspected allergens (i.e., food allergens) applied to a healthy area of the skin
1837 with eczematous reactions assessed 48 to 72 hours later.⁶⁷ Positive reactions must be
1838 distinguished from simple irritant reactions. Furthermore, positive tests are a sign of
1839 sensitization to the allergen, but the clinical relevance of such sensitization needs to be
1840 assessed in the context of other clinical signs.

1841 4.3.6 SYSTEMIC CONTACT DERMATITIS

1842 **Guideline 18:** The EP suggests using the clinical history including the resolution of
1843 symptoms while the causative food is avoided, and positive patch tests to establish the
1844 diagnosis of systemic contact dermatitis.

1845 **Rationale:** There are insufficient well-controlled studies to demonstrate the utility of
1846 these methods in diagnosing systemic contact dermatitis.

1847 **Balance of Benefits and Harms:** Traditionally patch testing has been used to support a
1848 suggestive history in diagnosing this rare condition. Although there are insufficient well-
1849 controlled studies to demonstrate the benefits of these methods in diagnosing systemic
1850 contact dermatitis, the harm of eliminating a small number of foods on this basis appears
1851 minimal.

1852 **Quality of Evidence:** Low

1853 **Contribution of Expert Opinion:** Significant

1854 Systemic contact dermatitis is a rare disorder consisting of generalized eczematous
1855 dermatitis associated with systemic symptoms such as fever, headache, rhinitis, and
1856 gastrointestinal complaints that develop after oral or parenteral allergen exposure to a
1857 food allergen, to which the individual has been sensitized through the skin. Metals and
1858 fragrances are allergens that play an important role in food-associated systemic contact
1859 dermatitis. Metals found in foods and associated with systemic contact dermatitis include
1860 nickel, cobalt, and chrome. Balsam of Peru, a fragrance associated with systemic contact
1861 dermatitis, consists of several chemicals, including cinnamic acid, cinnamaldehyde,
1862 cinnamic alcohol, vanillin, eugenol, methyl cinnamate, and benzyl cinnamate. This
1863 fragrance may be present in alcohol, chocolate, citrus fruits, pickled vegetable, spices,

1864 and tomatoes.⁶⁶ Patch testing with standardized contact allergens or suspected allergens
1865 may assess contact allergen sensitization, but sIgE testing is usually negative. Clinical
1866 relevance of positive patch testing requires assessment of the clinical context, and may
1867 require food elimination or food challenges.

1868 **4.3.7 HEINER'S SYNDROME**

1869 Heiner's Syndrome is a rare syndrome in infants and young children characterized by
1870 chronic or recurrent lower respiratory symptoms often associated with pulmonary
1871 infiltrates, often associated with upper respiratory symptoms, gastrointestinal symptoms,
1872 failure to thrive, and iron-deficiency anemia.^{66,67} Symptoms are associated with non-IgE-
1873 mediated immune responses to cow's milk with precipitating antibodies to cow's milk
1874 protein fractions, and often evidence of peripheral eosinophilia, iron deficiency, and
1875 deposits of immunoglobulins and C3 in lung biopsies in some cases. Milk elimination
1876 leads to marked improvement in symptoms within days and clearing of pulmonary
1877 infiltrates within weeks.⁶⁷ The immunopathogenesis of this disorder is not understood,
1878 but seems to combine cellular and immune-complex reactions causing alveolar vasculitis.
1879 In severe cases, alveolar bleeding leads to pulmonary hemosiderosis. There is no
1880 evidence for involvement of milk-specific IgE in this disease.

1881 **4.4 KNOWLEDGE GAPS**

1882 At the current time, oral food challenges provide the "gold standard" for diagnosing FA.
1883 These tests are accurate and sensitive, but they also present the greatest risk to the patient.
1884 Other laboratory tests used to diagnose FA, while safer for the patient, all have significant
1885 drawbacks, for example

- 1886 • SPTs and measurements of allergen-specific IgE antibodies to detect sensitization
1887 to foods provide very sensitive means of identifying foods that **may be**
1888 responsible for IgE-mediated food allergic reactions. However, these tests have
1889 poor specificity and show relatively poor overall correlation with clinical
1890 reactivity. Consequently, if used alone, they lead to a gross over-diagnosis of
1891 clinical allergic reactivity.
- 1892 • Assays based upon food allergen epitope specificity^{75,76} or component protein-
1893 based assays⁷⁷ may prove to be more specific, but further studies are necessary to
1894 determine their efficacy.
- 1895 • Sensitive and specific laboratory tests for diagnosing non-IgE-mediated food
1896 allergy are almost completely lacking.

1897 The lack of objective data available to adequately evaluate existing tests to diagnose FA
1898 is reflected in the fact that of 18 guidelines proposed in this section, 15 are heavily
1899 dependent on expert opinion and only three are based on evidence of "high quality."

1900 In conclusion, studies to identify sensitive and specific biomarkers that correlate with
1901 clinical reactivity to both IgE- and non-IgE-mediated food allergic reactions and clinical
1902 FA will be needed for the development of newer and safer laboratory tests.

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2096 **SECTION 5 MANAGEMENT OF NON-ACUTE**
2097 **ALLERGIC REACTIONS AND PREVENTION OF FOOD**
2098 **ALLERGY**

2099 This section of the Guidelines addresses the management and prevention of non-acute
2100 (and non-severe) allergic reactions to food in individuals diagnosed with food allergy
2101 (FA). Management of individuals at risk for developing FA and specific concerns about
2102 vaccination in patients with egg allergy are also addressed.

2103 **5.1 MANAGEMENT OF INDIVIDUALS WITH FA**

2104 **5.1.1 DIETARY AVOIDANCE OF SPECIFIC ALLERGENS IN IgE-**
2105 **MEDIATED FA**

2106 **Guideline 19:** The Expert Panel recommends that patients with documented
2107 IgE-mediated FA should avoid ingesting their specific allergen or allergens.

2108 **Rationale:** The EP recognizes that allergen avoidance is a strategy that is unproven in
2109 randomized controlled trials. However, allergen avoidance is currently the safest strategy
2110 for managing FA.

2111 **Balance of benefits and harm:** For patients with FA, ingesting food allergens can cause
2112 allergic reactions ranging in severity from mild to life threatening. Carefully planned
2113 allergen-free diets can provide sufficient nutrients to maintain a healthy and active life. In
2114 addition, there is no evidence that strict food avoidance (compared to less strict
2115 avoidance) has any effect on the rate of natural remission to a specific food allergen.

2116 **Quality of evidence:** Low

2117 **Contribution of expert opinion to the recommendation:** Significant

2118 **5.1.2 DIETARY AVOIDANCE OF SPECIFIC ALLERGENS IN**
2119 **NON-IgE-MEDIATED FA**

2120 **Guideline 20:** The EP recommends that individuals with non-IgE-mediated FA should
2121 avoid ingesting their specific allergen or allergens.

2122 **Rationale:** The literature cannot readily be divided on the basis of IgE-mediated and
2123 non-IgE-mediated reactions. In general, the management of non-IgE-mediated FA is
2124 similar to IgE-mediated FA in that the clinical history, the age of the individual, and the
2125 specific food allergen are all-important considerations in developing the management
2126 plan. Although there are relatively few high-quality studies regarding treatment for non-
2127 IgE-mediated FA, the bulk of the evidence suggests that food avoidance is the best
2128 management plan.

2129 **Balance of benefits and harm:** For patients with FA, ingesting trigger foods can cause
2130 reactions ranging in severity from mild to life threatening. Carefully planned allergen-
2131 free diets can provide sufficient nutrients to maintain a healthy and active life. In
2132 addition, there is no evidence that strict food avoidance (compared to less strict
2133 avoidance) has any effect on the rate of natural remission to a specific food allergen.

2134 **Quality of evidence:** Low

2135 **Contribution of expert opinion to the recommendation:** Significant

2136 **5.1.3 EFFECTS OF DIETARY AVOIDANCE ON ASSOCIATED AND CO-**
2137 **MORBID CONDITIONS SUCH AS ATOPIC DERMATITIS (AD), ASTHMA,**
2138 **AND ESOPHAGEAL ESOPHAGITIS (EoE)**

2139 **Guideline 21:** In patients with documented or proven FA, who also have AD, asthma, or
2140 EoE, the EP recommends avoidance of the food allergen.

2141 **Rationale:** There is only limited study data on this issue. In appropriately diagnosed
2142 individuals with FA, food allergen avoidance may reduce the severity of AD or EoE.
2143 Current evidence is not available to indicate whether food allergen avoidance will alter
2144 the course of asthma, AD, or EoE.

2145 **Balance of benefits and harm:** This approach is not a further burden for patients already
2146 practicing food avoidance to manage FA.

2147 **Quality of evidence:** Low

2148 **Contribution of expert opinion to the recommendation:** Significant

2149 In a nonrandomized comparative study, Agata et al.¹² concluded that an elimination diet
2150 is a good treatment for AD associated with FA and that specific IgE to food antigens
2151 were useful as indices of the effect of elimination diets. However, it is important to note
2152 that the study was conducted in a small number of patients and the evidence quality is
2153 considered low.

2154 **Guideline 22:** In patients without documented or proven FA, the EP does **not**
2155 recommend avoiding potentially allergenic foods as a means of managing AD, EoE, or
2156 asthma.

2157 **Rationale:** There is no evidence to suggest avoiding food allergens reduces the severity
2158 of AD, EoE, or asthma in patients who are not sensitized and have not demonstrated
2159 specific clinical reactivity to foods.

2160 **Balance of benefits and harm:** Unnecessary food avoidance could place patients at risk
2161 for nutritional deficiencies and growth deficits. There is no known benefit to avoiding
2162 potentially allergenic foods (e.g., egg, milk, peanut, tree nut, fish, crustacean shellfish).

2163 **Quality of evidence:** Moderate

2164 **Contribution of expert opinion to the recommendation:** Moderate

2165 The EP identified two systematic, high-quality reviews that evaluated the effect of dietary
2166 exclusion for treating AD.

- 2167
- 2168 • The review by Kramer et al.¹⁰ assessed whether maternal dietary antigen
2169 avoidance during lactation by mothers of infants with AD could reduce severity.
2170 One small trial (n=17) that met inclusion criteria for this part of the review found
2171 no significant reduction in eczema area score (mean difference -0.8; 95% CI -4.43
2172 - 2.83) or eczema activity score (mean difference -1.4; 95% CI -7.18 to 4.38)
2173 between infants whose mothers avoided dietary antigens and those whose mothers
2174 followed a usual diet.
 - 2175 • The review by Bath-Hextall et al.¹¹ evaluated the effect of dietary exclusion by
2176 patients for treating established AD. Nine low-quality randomized controlled
2177 trials (RCTs) were found, of which only two were sufficiently similar to combine.
Six of the RCTs examined milk and egg exclusion, one was a study of a diet

2178 including only a few foods, and two evaluated elemental diets. The authors found
2179 no evidence to support the use of these dietary exclusion strategies for treating
2180 AD in an unselected population.

2181 Similarly, the EP did not find any studies specifically addressing food allergen avoidance
2182 in other co-morbid conditions, such as asthma and EoE, when patients do not have
2183 documented or proven FA.

2184 **5.1.4 FOOD AVOIDANCE AND NUTRITIONAL STATUS**

2185 **Guideline 23:** The EP recommends nutritional counseling and regular growth monitoring
2186 for all children with FA.

2187 **Rationale:** Although few studies have evaluated whether food allergen avoidance results
2188 in nutritional deficiency, the EP acknowledges that obtaining adequate nutrition is a
2189 concern in this population.

2190 **Balance of benefits and harm:** Avoidance of specific allergens can limit the availability
2191 of nutritious food choices. Nutrition counseling can help patients plan and consume an
2192 allergen-free, yet nutritionally adequate diet.

2193 **Quality of evidence:** Low

2194 **Contribution of expert opinion to the recommendation:** Significant

2195 No randomized clinical studies have been undertaken to address whether food allergen
2196 avoidance diminishes nutritional status. However, studies^{1,2} in which growth
2197 measurements were evaluated against diet records suggest children with FA are at risk for
2198 inadequate nutritional intake.

2199 Christie et al.¹ estimated energy and nutrient intakes based on 3-day diet records. The
2200 age-matched, consecutive sampling, cross-sectional study had 98 children with FA and
2201 99 without. The study found that

- 2202 ● Children with two or more FAs were shorter than those with one FA ($p < 0.05$),
2203 based on height-for-age percentiles.
- 2204 ● More children with cow's milk allergy or multiple food allergies consumed
2205 dietary calcium that was less than the age- and gender-specific recommendations
2206 compared with children without cow's milk allergy and/or one FA.
- 2207 ● The possibility of consuming a less-than-recommended intake of calcium and
2208 vitamin D in children with FA was less if the child received nutrition counseling
2209 ($p < 0.05$) or consumed a safe infant/toddler commercial formula or
2210 calcium-fortified soy beverage.

2211 Tiainen et al.² collected 6-day food records for 18 children with cow's milk allergy and
2212 20 healthy children, and found

- 2213 ● There was no difference in caloric intake between the two groups.
- 2214 ● Protein intake by the allergic children was lower (39 g versus 48 g; $p < 0.05$) and
2215 fat intake was higher (47 g versus 39 g; $p < 0.05$) than that of the healthy children.

- 2216 ● While no overt nutritional problems were found, the height-for-age was lower in
2217 the children with cow’s milk allergy (-0.6 versus 0.2 SD units; $p < 0.05$) as
2218 compared with healthy children.

2219 5.1.5 FOOD LABELING IN FA MANAGEMENT

2220 **Guideline 24:** The EP suggests that patients with FA and their caregivers receive
2221 education and training on how to interpret ingredient lists on food labels and how to
2222 recognize incomplete labeling of ingredients.

2223 **Rationale:** Current standards under the Food Allergen Labeling and Consumer
2224 Protection Act (FALCPA) include the use of precautionary ingredient labeling (e.g., “this
2225 product may contain trace amounts of allergen”), and such precautionary labeling is
2226 meant to communicate potential risk. Nevertheless, ingredient labeling is not completely
2227 effective in preventing unintentional exposure to allergens.

2228 **Balance of benefits and harm:** Ingredient lists on food packages can help consumers
2229 identify the contents of products, but are often incomplete or difficult to interpret. No
2230 studies specifically evaluating the effectiveness of FALCPA were found. Incomplete or
2231 difficult-to-interpret ingredient labeling places patients at risk for unintentional exposure
2232 to allergens.

2233 **Quality of evidence:** Low

2234 **Contribution of expert opinion to the recommendation:** Significant

2235 FALCPA, which was passed by the U.S. Congress in 2004, identified eight major food
2236 allergens (peanut, tree nuts, egg, milk, soy, wheat, fish, and crustacean shellfish) that are
2237 responsible for 90 percent or more of serious adverse food reactions in the United States.
2238 Under FALCPA, products containing these major food allergens must clearly list the
2239 food allergen on the label in simple English. The one exemption is for protein from
2240 highly refined oils and their derivatives. Food labels containing disclaimers that the food
2241 “may contain” trace amounts of a major food allergen can leave consumers without
2242 adequate knowledge to make objective decisions.

2243 The EP identified ten studies that examined whether standards for food labeling are
2244 effective in preventing food allergic reactions. No study explicitly attempted to infer a
2245 cause-and-effect relationship between changes in frequency of severe symptoms from
2246 unintentional exposure (e.g., peanut) as a consequence of implementing food labeling.
2247 The identified studies mostly assessed knowledge and preferences for food labeling.

2248 Three studies, however, undertaken prior to FALCPA were particularly helpful in
2249 evaluating food labels.

- 2250 ● The first study involved 91 parents of children attending the pediatric allergy
2251 clinic at Mt. Sinai Medical Center in New York. The parents were asked to review
2252 23 food product labels and name the food allergens to which their child was
2253 allergic and which were also present in the particular product.³
- 2254 ○ 7 percent of parents (4/60) correctly identified all 14 products containing milk.
 - 2255 ○ 22 percent of parents (6/17) correctly identified all seven products containing
2256 soy.

- 2257 ○ 54 percent of parents (44/82) correctly identified all five products containing
- 2258 peanut.
- 2259 ○ Identification was much better for products containing wheat and egg.

- 2260 ● The second relevant study assessed 489 respondents (84 percent response rate)
- 2261 from attendees at a Food Allergy and Anaphylaxis Network (FAAN)
- 2262 Conference.⁴
- 2263 ○ Survey results indicated that ingredient labels were “always” or “frequently”
- 2264 read before purchasing a product by 99 percent of consumers doing the
- 2265 shopping and by 94 percent of people doing the cooking for food allergic
- 2266 patients.
- 2267 ○ Adverse reactions were attributed to misunderstanding of the food label in
- 2268 16 percent of cases and to ingredients not declared on the label in 22 percent
- 2269 of cases.

- 2270 ● A third study⁹ sought to determine the frequency and language used in voluntary
- 2271 advisory labels among commercially available products and to identify labeling
- 2272 ambiguities affecting consumers with allergy. Trained surveyors performed a
- 2273 supermarket survey of 20,241 unique manufactured food products (from an
- 2274 original assessment of 49,604 products) for use of advisory labels. Overall,
- 2275 17 percent of the products surveyed contained advisory labels. As described in the
- 2276 review by Sicherer and Burks,¹⁰¹ it is clear that numerous products have advisory
- 2277 labeling and ambiguities that present challenges to consumers with food allergy.

2278 Similar problems in identification were reported in a study of parents of children with
 2279 cow’s milk allergy in Brazil,⁵ and difficulties interpreting labels and general
 2280 dissatisfaction with current labels were noted in studies from the United States, the
 2281 United Kingdom, the Netherlands, and Greece.^{6,7,8}

2282 With global variations in culinary practices, labeling laws vary among geographic
 2283 regions. In the European Union, for example, celery, mustard, sesame, lupine, and
 2284 molluscan shellfish have been identified as major allergens. In Japan, buckwheat is an
 2285 important allergen. The globalization of the food supply and exposure of Americans to
 2286 new foods or culinary practices may lead to increases in the number of major food
 2287 allergens in the United States.

2288 **5.1.6 WHEN TO REEVALUATE PATIENTS WITH FA**

2289 **Guideline 25:** The EP suggests follow-up testing for individuals with FA depending on
 2290 the specific food to which the individual is allergic. Whether testing is done annually or
 2291 at other intervals depends on the food in question, the age of the child, and the
 2292 intervening clinical history.

2293 **Rationale:** There is insufficient evidence to make a strong recommendation as to the
 2294 timing for reevaluating individuals for FA.

2295 **Balance of benefits and harm:** It is recognized that children will likely outgrow certain
 2296 food allergies (i.e., milk, egg, soy, wheat) and be less likely to outgrow other food
 2297 allergies (i.e., peanut, tree nuts, fish, crustacean shellfish). Results of follow-up testing

2298 can guide decision-making regarding whether it is safe to introduce or re-introduce
2299 allergenic food into the diet.

2300 **Quality of evidence:** Low

2301 **Contribution of expert opinion to the recommendation:** Significant

2302 There is insufficient evidence for the EP to recommend a specific optimal interval for FA
2303 follow-up testing for each food. It is known is that allergy to some foods is outgrown
2304 quickly (e.g. milk, egg), while allergy to other foods are not (e.g. peanuts, tree nuts). If
2305 the patient has had a recent FA reaction, then there is little reason to re-test for several
2306 years. Annual testing is often the practice for determining whether allergy to milk, egg,
2307 wheat, and soy have been outgrown and the testing interval is extended to 2 to 3 years for
2308 allergy to peanut, tree nuts, fish, and crustacean shellfish. However, the EP noted that
2309 these testing schedules are not supported by objective evidence.

2310 **5.1.7 PHARMACOLOGICAL MANAGEMENT OF FA**

2311 **5.1.7.1 IgE-Mediated Reactions**

2312 **Guideline 26** There are **no** medications currently recommended by the EP to prevent
2313 IgE-mediated food allergic reactions.

2314 **Rationale:** There is insufficient evidence to recommend the use of pharmacologic
2315 therapy in preventing food allergic reactions.

2316 **Balance of benefits and harm:** Pharmacological agents have the potential to prevent or
2317 lessen the severity of food allergic reactions, but these agents may display significant side
2318 effects and predispose individuals to an increased risk for infection. Only limited safety
2319 and cost-effectiveness data are currently available.

2320 **Quality of evidence:** Moderate

2321 **Contribution of expert opinion to the recommendation:** Significant

2322 Drug therapy has been used to manage FA in cases where allergen avoidance is
2323 extremely difficult or results in nutritional deficiencies. Drugs that alter the immune
2324 response to the allergen are commonly considered the most likely candidates for such
2325 therapy.

2326 The EP identified five RCTs that evaluated immune-altering drugs to treat FA,¹³⁻¹⁷ such
2327 as

- 2328 ● The effect of astemizole on oral allergy syndrome induced by consumption of
2329 hazelnuts in patients with positive SPT to birch pollen. The treatment group
2330 ingested astemizole (10 mg each morning for 14 days) and the control group
2331 ingested placebo for 14 days. Treatment was followed by two open oral
2332 provocations. The reduction in symptom severity from baseline to the final oral
2333 provocation was significantly greater in the astemizole versus placebo group
2334 (p=0.004).¹³
- 2335 ● The effect of cromolyn in children with AD and documented allergy to egg. All
2336 patients had AD as defined by Hanifin and Rajka,¹⁹ had positive SPT, and were
2337 on a strict egg-avoidance diet for one year. Patients were treated for a week with

2338 either cromolyn or placebo, and then were evaluated. A washout period of three to
2339 five weeks occurred before patients were crossed over to the other arm (cromolyn
2340 or placebo) for a week, and again evaluated. After one week of treatment with
2341 either cromolyn or placebo, there was no statistically significant difference in the
2342 symptom score for AD or in the response to a DBPCFC.¹⁴
2343 ● The effect of anti-IgE therapy in patients with peanut allergy. The administration
2344 of TNX-901, a humanized IgG₁ monoclonal antibody against IgE, increased the
2345 threshold of sensitivity to peanut on oral food challenge from a level equal to one
2346 peanut to almost nine peanuts.¹⁵

2347 Given the heterogeneity of the pharmacologic interventions and allergic conditions
2348 evaluated, the EP concludes that there is insufficient evidence to recommend the use of
2349 pharmacologic therapy in preventing food allergies. However, promising results from
2350 early studies support further evaluation of astemizole and anti-IgE therapies in managing
2351 FA. Lastly, the use of antihistamines, as needed, remains the mainstay of managing (as
2352 opposed to preventing) non-severe food allergic reactions.

2353 5.1.7.2 Non-IgE-Mediated Reactions

2354 **Guideline 27:** There are **no** medications currently recommended by the EP to prevent
2355 non-IgE-mediated food allergic reactions.

2356 **Rationale:** There is insufficient evidence to recommend consideration of pharmacologic
2357 therapy in patients with non-IgE-mediated FA reactions.

2358 **Balance of benefits and harm:** The use of swallowed corticosteroids has the potential to
2359 lessen the severity or prevent future food allergic reactions, but these agents may display
2360 significant side effects and predispose individuals to an increased risk for infection.
2361 Nevertheless, swallowed corticosteroids have been shown to be beneficial in the
2362 treatment of EoE.

2363 **Quality of evidence:** Moderate

2364 **Contribution of expert opinion to the recommendation:** Significant

2365 5.1.8 IMMUNOTHERAPY FOR FA MANAGEMENT

2366 5.1.8.1 Allergen-Specific Immunotherapy

2367 **Guideline 28:** The EP does **not** recommend using allergen-specific immunotherapy to
2368 treat FA in clinical practice settings.

2369 **Rationale:** Allergen-specific immunotherapy improves clinical symptoms of FA while
2370 on treatment. However, it is currently difficult to draw conclusions on the safety of such
2371 an approach and whether clinical tolerance (i.e., improvement in clinical symptoms that
2372 persists even after allergen immunotherapy is discontinued) will develop with long-term
2373 treatment.

2374 **Balance of benefits and harm:** Allergen-specific immunotherapy can improve clinical
2375 symptoms of FA for some patients; however, because of the risk of severe reaction, the
2376 approach has been used only in highly controlled settings.

2377 **Quality of evidence:** Low

2378 **Contribution of expert opinion to the recommendation:** Significant

2379 5.1.8.2 Immunotherapy with Cross-Reactive Allergens

2380 **Guideline 29:** The EP does **not** recommend immunotherapy with cross-reactive allergens
2381 for treating FA.

2382 **Rationale:** Although there is evidence to suggest that specific immunotherapy with
2383 cross-reactive allergens is beneficial in treating FA, additional safety and efficacy data is
2384 needed before such treatment can be recommended.

2385 **Balance of benefits and harm:** It has been hypothesized that immunotherapy with cross-
2386 reactive antigens could benefit patients with FA, yet the safety of this approach has been
2387 evaluated in only one study to date.

2388 **Quality of evidence:** Low

2389 **Contribution of expert opinion to the recommendation:** Significant

2390 Immunotherapy alters the immune response to allergens as a means to treat FA.

2391 Immunotherapy can be accomplished by using small amounts of the allergic food

2392 (allergen-specific immunotherapy), or cross-reactive allergens (specific immunotherapy

2393 with cross-reactive allergens) to desensitize the patient.

2394 **Allergen-Specific Immunotherapy**

2395 • **Oral Immunotherapy**

2396 Seven RCT studies used desensitization protocols with the allergic food to induce
2397 tolerance.²⁰⁻²⁶

2398 ○ Staden et al.²⁰ assigned children with allergy to either milk or hen's egg to
2399 oral tolerance induction or an elimination diet.

2400 – 64 percent (16/25) achieved tolerance in the group that received oral
2401 tolerance compared with 35 percent (7/20) in the group that adhered to an
2402 elimination diet (p=0.05).

2403 ○ Morisset et al.²¹ performed a randomized study to examine an oral
2404 desensitization protocol in children with IgE-mediated milk or egg allergies.

2405 – 11 percent (3/27) of the oral desensitized group for milk allergy reacted to
2406 a single (S)BPCFC compared to 40 percent (12/30) of the continued
2407 avoidance group, a significant improvement, (p<0.025). The size of the
2408 SPT wheal also decreased (p<0.002).

2409 – 31 percent (15/49) of the group desensitized for egg allergy reacted to a
2410 SBPCFC compared with 49 percent (17/35) of the continued avoidance
2411 group showing a trend toward improvement (p<0.10). The size of the SPT
2412 wheal also decreased (p<0.05).

2413 ○ Skripak et al.²² studied milk oral immunotherapy in treating cow's milk
2414 allergy in patients aged 6 to 21 years. Once the immunotherapy dose of 15 mL
2415 of milk was reached, patients were then treated for 13 weeks. The milk dose
2416 threshold was higher in the group receiving oral immunotherapy (p=0.002). In
2417 a follow-up analysis, 15 participants who successfully completed the double-
2418 blind portion of the study were continued on measured dairy intake at home
2419 daily.²⁷ Initial milk doses ranged from 500 to 4,000 mg daily. After 13 to
2420 75 weeks (median=17) of open-label dosing, 13 participants underwent food

2421 challenge, at which time 46 percent (6) tolerated 16,000 mg with no reaction,
 2422 and 54 percent (7) reacted at 3,000 mg to 16,000 mg.
 2423 ○ Longo et al.²³ studied 60 children 5 years or older with cow's milk allergy;
 2424 half were assigned to an oral desensitization regimen and half kept on a milk-
 2425 free diet. After 1 year
 2426 – 36 percent in the immunotherapy regimen were completely milk tolerant
 2427 – 54 percent could take limited amounts of milk (5 to 150 mL)
 2428 – 10 percent were not able to complete the protocol because of persistent
 2429 respiratory or abdominal complaints.
 2430 – 0 percent on a milk-free diet could tolerate 5 mL of milk.
 2431 – Patriarca et al.²⁴ evaluated oral desensitization protocols in patients with a
 2432 wide variety of allergies, including milk, hen's egg, wheat, bean, and cod.
 2433 – 75 percent (36/48) people assigned to the desensitization arm had a
 2434 negative DBPCFC, compared with none of the control patients.

2435 Non-randomized trials of egg and peanut oral immunotherapy also suggest the
 2436 approach can be successful in desensitizing patients.

2437 ○ In a study by Buchanan et al.²⁸ seven subjects with egg allergy completed a
 2438 24-month protocol for egg oral immunotherapy.
 2439 – 57 percent (4/7) of the subjects passed a DBPCFC to 10 g egg at the
 2440 conclusion of therapy.
 2441 – 43 percent (3/7) had significantly increased threshold to egg.
 2442 – As the study continued enrolling, the senior authors noted that of 21 new
 2443 subjects, 2 were unable to reach the goal of 300 mg daily.²⁹
 2444 ○ 93 percent (27/29) children who completed a peanut oral immunotherapy
 2445 protocol were able to ingest 3.9 g peanut protein during subsequent food
 2446 challenge.³⁰

2447 ● Sublingual immunotherapy (SLIT)
 2448 ○ In a study of the effect of sublingual hazelnut extract on patients with a
 2449 hazelnut FA, the mean hazelnut quantity that provoked symptoms increased in
 2450 the group receiving hazelnut extract but not in the placebo group (p=0.02).²⁵

2451 ● Injection immunotherapy
 2452 ○ In a study of the effect of injections of subcutaneous peanut extract on patients
 2453 with peanut allergy, there was a decreased peanut sensitivity at one month
 2454 (p=0.0002) but no effect on SPT or peanut-specific IgE as compared to
 2455 patients with peanut allergy who did not receive subcutaneous injections. The
 2456 study was suspended early for safety reasons before longer-term data could be
 2457 evaluated.²⁶

2458 ● **Safety issues of immunotherapy**
 2459 Injections with peanut extract can result in repeated systemic reactions when
 2460 administered in a “rush” protocol and are thus considered unsafe.²⁸ Oral and
 2461 sublingual immunotherapy have been generally well tolerated and are safe in
 2462 highly controlled clinical settings. However, few studies have provided extensive

2463 safety data, and systemic reactions can occur at previously tolerated doses of
2464 allergen, especially after exercise or viral illness.³⁰

2465
2466 A non-randomized study of peanut oral immunotherapy extensively evaluated
2467 safety data for 20 patients who completed all phases of therapy.³¹ Subjects most
2468 often experienced significant allergic symptoms during the initial escalation,
2469 which occurred in a clinical setting. During the initial escalation day, upper
2470 respiratory tract (79 percent) and abdominal (68 percent) symptoms were most
2471 likely experienced. The risk of reaction with any home dose was 3.5 percent, and
2472 treatment was given with 0.7 percent of home doses. Two subjects received
2473 epinephrine after one home dose each.

2474 **Specific Immunotherapy with Cross-Reactive Allergens**

2475 The EP found four RCTs that used immunotherapy with cross-reactive allergens to treat
2476 food allergies.³²⁻³⁵ A fifth study was not directed at specific food allergies but evaluated
2477 the oral allergy syndrome (OAS) in the setting of natural rubber latex allergy.³⁵

- 2478 ● Patients with apple allergy received birch pollen extract immunotherapy. There
2479 was no statistically significant change in OAS response to an open apple food
2480 challenge after treatment with placebo, sublingual, or subcutaneous birch pollen
2481 extracts.³²
- 2482 ● Patients with OAS to apple and hazelnuts were treated with subcutaneous
2483 immunotherapy with tree pollen extract. Improvement of OAS occurred in
2484 67 percent (10/15) patients receiving subcutaneous immunotherapy and only
2485 17 percent (2/12) control patients (p<0.05).³³
- 2486 ● Birch pollen-sensitive patients with apple-induced OAS received injection
2487 immunotherapy with birch pollen extract. This treatment was found to reduce
2488 clinical apple sensitivity (p<0.001) but not apple-specific IgE.³⁴
- 2489 ● A study of the safety and efficacy of sublingual immunotherapy with a latex
2490 extract in patients with food allergies found no significant difference in SPTs for
2491 food allergies after treatment.³⁵

2492 **5.1.9 QUALITY OF LIFE ISSUES ASSOCIATED WITH FA**

2493 **Guideline 30:** The EP recommends that patients with FA and their caregivers be
2494 provided with age- and culturally-appropriate information on food allergen avoidance and
2495 emergency management.

2496 **Rationale:** Food-allergen avoidance and the risk of severe allergic reactions can have
2497 substantial daily consequences for patients and their caregivers.

2498 **Balance of benefits and harm:** Patients with FA and their caregivers (especially
2499 mothers) can experience anxiety and diminished quality of life because of the risk of
2500 anaphylaxis and the burden of selecting or preparing allergen-free foods. Concerns may
2501 change as FA patients mature. Knowledge and skills related to management of food
2502 allergies may improve patient and caregiver self-efficacy, quality of life, and allergen
2503 avoidance and management.

2504 **Quality of evidence:** Low

2505 **Contribution of expert opinion to the recommendation:** Significant

2506 **Effects of FA on Anxiety and Quality of Life**

2507 A survey by King et al.³⁶ of 46 families who had a child with peanut allergy, which asked
2508 members of the family to complete quality of life, anxiety, and perceived stress scales,
2509 found

- 2510 ● Mothers rated their own psychological ($p < 0.01$) and physical ($p < 0.05$) quality
2511 of life significantly worse than fathers rated theirs and also had higher scores than
2512 fathers for anxiety ($p < 0.05$) and stress ($p < 0.001$).
- 2513 ● Children with peanut allergy had significantly poorer physical health-related
2514 quality of life ($p < 0.05$), quality of life within school ($p < 0.01$), and general
2515 quality of life ($p < 0.05$) than their siblings did, as well as greater separation
2516 anxiety ($p < 0.05$).

2517 Another survey by Ostblom et al.³⁷ compared 212 children who were 9 years old with FA
2518 to 221 children with allergic diseases and no FA. The survey found

- 2519 ● Children with FA exhibited significantly lower scores on the subscales physical
2520 functioning and social limitations within the Child Health Questionnaire Parental
2521 Form 28.
- 2522 ● Children with food-related symptoms from the lower airways scored lower on
2523 self-esteem and family cohesion.

2524 As children transition into adolescence and adulthood, they have increased responsibility
2525 regarding food selection. Their vigilance in avoiding allergens may depend in part upon
2526 whether or not they remember experiencing anaphylaxis.

- 2527 ● Food-allergic young adults aged 18 to 22 years who reported having experienced
2528 an anaphylactic reaction described their disease as more severe, reported more
2529 worry about their disease, and rated their parents as more overprotective than food
2530 allergic young adults who reported never having experienced anaphylaxis.³⁸
- 2531 ● In contrast, 7 teenagers interviewed when they were 13 to 16 year old and who
2532 had a history of clinically diagnosed anaphylaxis, reported perceiving anaphylaxis
2533 as “no big deal.”³⁹ However, most of the teens did not remember experiencing
2534 anaphylaxis. Interviewed parents reported anxiety about “handing over”
2535 responsibility for avoidance and emergency management to their children.

2536 **Effects of Food Allergy Management Plans for Patients with FA**

2537 Bollinger et al.⁴⁰ asked caregivers of food-allergic children to complete a questionnaire
2538 that evaluated their perception of the impact of their child’s FA on family activities.
2539 Among the 87 families who completed the study

- 2540 ● More than 60 percent of caregivers reported that FA significantly affected meal
2541 preparation.
- 2542 ● 49 percent or more indicated that FA affected family social activities.

2543 • 10 percent chose to home school their children because of FA.

2544 **5.1.10 VACCINATIONS IN PATIENTS WITH EGG ALLERGY**

2545 Several vaccines are grown in chick embryos or embryonic tissues and may contain
2546 small, but variable, amounts of egg protein. Recommendations for administering such
2547 vaccines to patients with egg allergy vary on the basis of the amount of egg protein in the
2548 vaccine and patient history of reaction.

2549 **5.1.10.1 Measles, Mumps, Rubella, Varicella**

2550 **Guideline 31:** The EP recommends that children with egg allergy, even those with a
2551 history of severe reactions, receive vaccines for measles, mumps, rubella (MMR), and
2552 varicella (V).

2553 **Rationale:** MMR and MMRV vaccines are safe for children with egg allergy, even for
2554 those with a history of severe reactions.

2555 **Balance of benefits and harm:** Vaccinations can prevent severe disease and generally,
2556 proof of MMR vaccination is required for school entry. Varicella vaccine is also required
2557 in most states. The measles component of the vaccine is produced in chicken-embryo
2558 fibroblasts, which may be of concern to parents with egg-allergic children. However, the
2559 MMR and MMVR vaccines are safe to administer to egg-allergic subjects because the
2560 egg protein content of these vaccines is very low.

2561 **Quality of evidence:** Moderate

2562 **Contribution of expert opinion to the recommendation:** Significant

2563 Although the measles component of the MMR vaccine is produced in chicken-embryo
2564 fibroblast culture, the vaccine is safe for children with egg allergy, even those with a
2565 history of anaphylaxis.⁹⁷ The monovalent varicella vaccine does not contain preservatives
2566 or egg protein. Therefore, children with egg allergy may be given MMR or the
2567 quadrivalent MMRV vaccine without previous skin testing.⁹⁸ Many reactions to the
2568 MMR and other vaccines originally attributed to egg have been shown to be due to
2569 gelatin in the vaccine.⁹⁷ Ovalbumin is one of the egg proteins present in egg-based
2570 vaccines, and can be used as a surrogate marker for the relative levels of egg allergens
2571 present in a particular vaccine.

2572 **5.1.10.2 Influenza**

2573 **Guideline 32:** The EP recommends **against** administering either inactivated or live-
2574 attenuated influenza vaccines to children with a history of hives, angioedema, egg allergy
2575 plus allergic asthma, or systemic anaphylaxis to egg proteins, unless either (a) the vaccine
2576 contains less than 1.2 mcg/mL of ovalbumin; or (b) an evaluation, for allergy to the
2577 vaccine, is done first, if the vaccine's ovalbumin content is greater than 1.2 mcg/mL, or is
2578 unknown. For all children with asthma, the EP recommends using only inactivated
2579 influenza vaccine as the live attenuated influenza vaccine is contraindicated in these
2580 children.

2581 **Rationale:** In the past, both the inactivated and live-attenuated influenza vaccines have
2582 been contraindicated in children with the following known allergic reactions to egg

2583 proteins: hives, angioedema, allergic asthma, or systemic anaphylaxis. However, less
2584 severe or local manifestations of allergy to egg or feathers were not contraindications.
2585 More recent information indicates that, as long as the ovalbumin content is less than
2586 1.2 mcg/mL, this vaccine can be safely given to individuals with egg allergy, even with a
2587 history of asthma or systemic anaphylaxis.

2588 **Balance of benefits and harm:** Both the inactivated and live-attenuated influenza
2589 vaccines that are manufactured using embryonated hen eggs pose a risk of allergic
2590 response in patients with egg allergy. Influenza vaccination can prevent severe disease in
2591 susceptible individuals with asthma and egg allergy.

2592 **Quality of evidence:** Moderate

2593 **Contribution of expert opinion to the recommendation:** Significant

2594 Because both the trivalent inactivated and live-attenuated influenza vaccines are
2595 developed using embryonated hen eggs, the American Academy of Pediatrics (AAP),⁹⁹
2596 the Advisory Committee on Immunization Practices (ACIP),¹⁰² and the British Medical
2597 Journal (BMJ)¹⁰³ have concluded that both vaccines are contraindicated in children with
2598 the following known allergic reactions to egg proteins: hives, angioedema, allergic
2599 asthma, or systemic anaphylaxis. However, the AAP believes that less severe or local
2600 manifestations of allergy to egg or feathers are not contraindications.⁹⁹

2601 **The EP recommendations differ from those of the AAP, the ACIP, and the BMJ,**
2602 **based on recent clinical experience and discussions.** Patients with egg allergy, even
2603 those with a history of severe allergic reactions including anaphylaxis, should receive the
2604 vaccine if they are considered at risk for complications from influenza. Such a group
2605 includes patients with asthma, who should receive only the inactivated vaccine because
2606 the live-attenuated vaccine is contraindicated.

2607 Before giving a patient the influenza vaccine, healthcare providers should first determine
2608 the amount of ovalbumin in the vaccine.

- 2609
- 2610 ● If the egg protein (ovalbumin) is less than 1.2 mcg/mL, the vaccine can be given
2611 without allergy testing.
 - 2612 ● If the egg protein (ovalbumin) is unknown, or is equal to or greater than
2613 1.2 mcg/mL, the patient should undergo SPT with the vaccine prior to
2614 administration.
 - 2615 ○ If the result is negative, the vaccine may be given.
 - 2616 ○ If the result is positive, the vaccine can be given, but in divided doses (e.g.,
2617 50µL followed by 450µL if the initial dose is tolerated, to deliver a 0.5ml
2618 dose) and under the supervision of a healthcare provider experienced in
dealing with anaphylaxis.

2619 A recent publication demonstrates the variability in ovalbumin content of vaccines and
2620 also demonstrates that the actual concentrations of ovalbumin are well within the
2621 manufacturers' labeling of ovalbumin content.¹⁰⁴

2622 **5.1.10.3 Rabies and Yellow fever**

2623 **Guideline 33:** The EP recommends **against** administering either rabies or yellow fever
 2624 vaccines to patients with a history of hives, angioedema, allergic asthma, or systemic
 2625 anaphylaxis to egg proteins, unless an allergy evaluation and testing to the vaccine is
 2626 done first.

2627 **Rationale:** Both rabies and yellow fever vaccines may contain egg protein. There are no
 2628 data available on whether there are concentrations of ovalbumin in these vaccines that are
 2629 low enough to administer without allergy evaluation and testing.

2630 **Balance of benefits and harms:** Both vaccines are manufactured in eggs, and therefore
 2631 pose a risk of allergic reactions in egg-allergic people. FA evaluation and testing can
 2632 provide insight into the potential for risk to an individual. Vaccination can prevent severe
 2633 disease in susceptible individuals with egg allergy.

2634 **Quality of evidence:** Low

2635 **Contribution of expert opinion to the recommendation:** Significant

2636 **Table 5.1: Vaccines That May Contain Egg Protein**

Vaccine	Grown in	Recommendation summary
MMR and MMRV	Measles and mumps components in chick embryo fibroblasts	Administer in usual manner, even to patients with history of severe reaction to egg ^{97,98}
Influenza (inactivated)	Chick extraembryonic allantoic fluid	Egg-allergic patients, at risk for complications from influenza (e.g., patients with concomitant asthma) <ul style="list-style-type: none"> • For vaccines with less than 1.2 micrograms/mL ovalbumin, give the vaccine without allergy testing. • For vaccines with unknown content or with equal to or more than 1.2 micrograms/mL of ovalbumin, do SPT test with the vaccine before administration <ul style="list-style-type: none"> ○ If the SPT is negative, the vaccine may be given. ○ If the SPT is positive, the vaccine can be given in divided doses, by a healthcare provider experienced in dealing with anaphylaxis.
Influenza (live attenuated)	Chick extraembryonic allantoic fluid	Contraindicated for children with asthma. Otherwise, recommendation as for inactivated vaccine as above.
RabAvert	Chick embryo fibroblasts	For patients with egg allergy, test the vaccine prior to administration.
Yellow fever	Chick embryos	For patients with egg allergy, test the vaccine prior to administration.

2637 The overall exposure of patients to other food allergens that might be present in
 2638 preventive vaccines is unknown. There is some suggestion that cow’s milk proteins are
 2639 present in some vaccines, such as diphtheria, tetanus, and pertussis. No recommendations
 2640 can be made concerning other vaccines without further studies.

2641 **5.2 MANAGEMENT OF INDIVIDUALS AT RISK FOR FA**

2642 **5.2.1 NON-FOOD ALLERGEN AVOIDANCE IN AT-RISK PATIENTS**

2643 **Guideline 34:** The EP suggests that patients at risk for developing FA do **not** limit
2644 exposure to potential, non-food allergens (e.g., dust, pollen, or pet dander). Patients at
2645 risk for developing FA are defined as those with a biological parent or sibling with
2646 existing, or history of, allergic rhinitis, asthma, atopic dermatitis or food allergy. This
2647 definition of “at risk” is used throughout Section 5.2.

2648 **Rationale:** There is insufficient evidence to suggest that non-food allergen avoidance has
2649 any effect on the natural history of FA.

2650 **Balance of benefits and harm:** It has been hypothesized that exposure to non-food
2651 allergens could increase the likelihood of developing a FA in patients at risk for atopic
2652 disease, but there are insufficient data to support this hypothesis.

2653 **Quality of evidence:** Low

2654 **Contribution of expert opinion to the recommendation:** Significant

2655 It should be noted that the definition of “at risk” used above differs from the definition of
2656 “high risk” used below in Section 5.2.3.

2657 **5.2.2 DIETARY AVOIDANCE OF FOODS WITH CROSS REACTIVITIES IN**
2658 **AT-RISK PATIENTS**

2659 **Guideline 35:** The EP suggests that patients at risk for developing FA do **not** need to
2660 limit exposure to foods that may be cross-reactive.

2661 **Rationale:** There is insufficient evidence to determine whether allergenic cross-
2662 reactivities of foods have clinical consequences.

2663 **Balance of benefits and harm:** It has been hypothesized that exposure to possible
2664 cross-reactive foods could result in an allergic response. However, unnecessary food
2665 avoidance can result in inadequate nutrient intake and growth deficits.

2666 **Quality of evidence:** Low

2667 **Contribution of expert opinion to the recommendation:** Significant

2668 Because allergenic food proteins may share structural or sequence similarity with other
2669 allergenic substances, sensitization to a particular food or even an aeroallergen can result
2670 in responses to other foods containing homologous proteins. Such cross-reactivity can be
2671 limited to IgE sensitization, or be associated with clinical reactivity. Although several
2672 reports have described cross-reactivity among food allergens (see Table 5.2), the EP
2673 identified only one small relevant RCT. Klemola et al.⁴¹ evaluated the incidence of
2674 adverse reactions or allergies to soy infant formulas in infants with cow’s milk allergy
2675 syndrome and found low rates of adverse events in both the soy formula and the placebo
2676 formula. Overall, the EP concludes that there is insufficient evidence to recommend a
2677 routine evaluation of the patient for allergenic cross-reactivities to other foods, or to limit
2678 exposure to foods that may be cross-reactive.

2679

2680 **Table 5.2: Food Allergen Cross-Reactivity**

Food group	Major allergens	Sensitization (%)	Clinical reactivity (%)	Comments	Key Refs (#)
Avian and mammalian proteins	Milk: cow vs other	20–100	4–92	<ul style="list-style-type: none"> High cross reactivity with goat, sheep and buffalo milk Low cross reactivity with mare, donkey and camel 	42–45
Avian and mammalian proteins	Milk vs beef/meat	-	10–20	<ul style="list-style-type: none"> Sensitization to bovine serum albumin is predictor 73–93% of beef allergic children reactive to cow milk 	46–48
Avian and mammalian proteins	Egg: hen vs other	Common	†	<ul style="list-style-type: none"> Cross reactivity varies among species, but common 	49
Avian and mammalian proteins	Egg vs chicken/meat	-	22–32	<ul style="list-style-type: none"> Bird-egg syndrome - sensitization to alpha-livetin 	50
Shellfish	Shrimp vs other crustacea	50–100	38 [†]	<ul style="list-style-type: none"> Tropomyosins are panallergens that are also responsible for cross reactions to crustaceans in those with dust mite and cockroach allergy 	51–54
Shellfish	Crustacea vs molluscs	47	14 [†]	<ul style="list-style-type: none"> Tropomyosins are panallergens that are also responsible for cross reactions to crustaceans in those with dust mite and cockroach allergy 	51–54
Shellfish	Molluscs vs molluscs	-	49 [†]	<ul style="list-style-type: none"> Tropomyosins are panallergens that are also responsible for cross reactions to crustaceans in those with dust mite and cockroach allergy 	51–54
Fish	Codfish vs other fish	5–100	30–75	<ul style="list-style-type: none"> Gad c 1 (codfish parvalbumin) is panallergen 	55–59
Tree nuts (TN)	TN vs other TN	92	12–(37) [†]	<ul style="list-style-type: none"> Higher serum IgE correlations between cashew and pistachio and between pecan and walnut. 	60–63
Tree nuts (TN)	TN vs peanut (legume)	59–86	33–34 [†]	<ul style="list-style-type: none"> Higher serum IgE correlations with almond and hazelnut 	61 and 62
Legumes	Peanut vs soy (other)	19–79	3–5; (28–30)*	<ul style="list-style-type: none"> Sensitization to lentils and chick peas may be associated with increased chance for multiple legume allergy 	64–68
Cereals	Wheat vs other	47–88	21	<ul style="list-style-type: none"> Most available data from patients with atopic dermatitis 	69–70

2681 † Percentage based on reported clinical reactions and not systematically evaluated by DBPCFC

2682 * Represents DBPCFC data for lupine challenge in peanut-sensitized patients

2683 Safety was reported for only one of four studies that examined specific immunotherapy
 2684 with cross-reactive allergens.³⁵ In this study, no local signs or gastrointestinal symptoms
 2685 were reported.

2686 **5.2.3 TESTING OF ALLERGENIC FOODS IN PATIENTS AT HIGH RISK**
2687 **PRIOR TO INTRODUCTION**

2688 **In Summary:** The EP concludes that there is insufficient evidence to recommend
2689 routine FA testing prior to the introduction of highly allergenic foods (e.g., milk,
2690 egg, and peanut) in children who are at high risk of reaction to introduction of such
2691 foods. The definition of children at high risk, in this specific situation, is of children
2692 with pre-existing severe allergic disease and/or a family history of FA. Nevertheless,
2693 there may be some value in FA evaluations that include a food challenge for a select
2694 group of patients with certain risk factors, such as having a sibling with peanut
2695 allergy¹⁰⁰ or evidence of another underlying FA (e.g., testing for tree nut allergy in a
2696 child with peanut allergy). It is possible that a FA evaluation prior to introduction of
2697 a food could potentially prevent allergic reactions. However, there is concern that
2698 widespread skin testing and sIgE testing is not needed and would lead to many false
2699 positive results as well as unnecessary dietary restrictions, especially if unconfirmed
2700 by oral food challenges. Overall, the risk/benefit of FA evaluation should be
2701 considered on an individual basis, especially for major food allergens (e.g., milk,
2702 egg, and peanut) in high-risk young children.

2703 **Guideline 36:** For the general population, with no high-risk factors of reaction to
2704 introduction of highly allergenic foods, the EP suggests that children **not** be tested for FA
2705 to highly allergenic foods prior to their introduction into the diet. These individuals in the
2706 general population are children who do not have pre-existing severe allergic disease and
2707 also do not have a family history of FA.

2708 **Rationale:** There is insufficient evidence to suggest whether, or which, foods should be
2709 tested prior to introduction.

2710 **Balance of benefits and harm:** Testing prior to introduction could potentially prevent
2711 allergic reactions, but there is currently no practical consensus on which (if any) foods
2712 should be tested.

2713 Quality of evidence: Low

2714 **Contribution of expert opinion to the recommendation:** Significant

2715 **5.2.4 TESTING IN INFANTS AND CHILDREN WITH PERSISTENT AD**

2716 **Guideline 37:** The EP suggests that children less than 5 years of age with moderate to
2717 severe AD be considered for FA evaluation for milk, egg, peanut, wheat, and soy, if **at**
2718 **least one** of the following conditions is met:

- 2719 ● The child has persistent AD in spite of optimized management and topical
2720 therapy.
- 2721 ● The child has a reliable history of an immediate reaction after ingestion of a
2722 specific food.

2723 **Rationale:** There is insufficient evidence to determine the appropriate age to test for
2724 response to foods known to commonly cause IgE-mediated FA in infants or young
2725 children with AD, or other risk factors. In spite of the lack of evidence, the opinion of the
2726 EP is that if a child is less than 5 years of age and has persistent AD there is benefit to
2727 finding out if the child is allergic to a food.

2728 **Balance of benefits and harm:** Early diagnosis can lead to better management of FA
2729 and reduce the risk of exposure to food antigens. However, testing is time-consuming and
2730 costly for patients and their families. Additionally, severely restrictive diets may be
2731 harmful.

2732 **Quality of evidence:** Low

2733 **Contribution of expert opinion to the recommendation:** Significant

2734 The question of when to evaluate a child, who is less than 5 years of age with moderate to
2735 severe AD, for FA has been somewhat controversial in the past 20 years. The EP
2736 identified the group of children thought to be most at risk for having FA and described
2737 them in Guideline 34 above. It should be noted that milk, egg, and peanut are most often
2738 found to be allergenic in this population. Many of these children also have sIgE to wheat
2739 and soy. Care should be taken to ensure these children are clinically allergic to a food
2740 prior to removing it completely from their diet.

2741 The question of what to recommend for children with delayed food reactions was also
2742 considered by the EP. While a history of a possible delayed reaction to a food is clinically
2743 important, it is not diagnostic of FA, and a proper evaluation (clinical history and
2744 diagnostic testing) should be completed.

2745 **5.3 PREVENTION OF FOOD ALLERGY**

2746 **5.3.1 MATERNAL DIET DURING PREGNANCY AND LACTATION**

2747 **Guideline 38** The EP does **not** recommend restricting maternal diet during pregnancy or
2748 lactation as a strategy for preventing the development or clinical course of FA.

2749 **Rationale:** There is insufficient evidence that maternal diet during pregnancy or lactation
2750 affects the development or clinical course of FA.

2751 **Balance of benefits and harms:** Restricting exposure to food antigens either during
2752 pregnancy or through breast milk has been hypothesized as a means of preventing the
2753 development of FA, but it has not been shown conclusively to prevent FA. Adequate
2754 nutritional status during pregnancy and lactation is essential for optimal infant health,
2755 growth, and development.

2756 **Quality of evidence:** Low

2757 **Contribution of expert opinion to the recommendation:** Significant

2758 Several authors have observed that maternal dietary antigens can pass into breast milk
2759 and have hypothesized a protective effect of a diet in which certain common allergens are
2760 reduced or avoided during pregnancy and lactation by women at risk of having infants
2761 likely to go on to develop atopic disease. However, the results of several studies are
2762 conflicting.

- 2763
- 2764 • Kramer et al.¹⁰ conducted a systematic review that evaluated the effect of
2765 maternal dietary avoidance on either treating or preventing atopic disease in
2766 children. The authors found no significant difference in the incidence of AD
2767 (relative risk (RR) 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-

2768 1.74) or milk (RR 0.86; 95% CI 0.16-4.59) during the first 18 months of life in
2769 infants whose mothers avoided dietary antigens during pregnancy. Avoidance of
2770 dietary antigens had no significant effect on the incidence of AD (RR 0.73; 95%
2771 CI 0.32-1.64).
2772 ● A non-randomized comparative study evaluated the effect of restricting maternal
2773 diet during lactation for the first 3 months after birth on the incidence of FA.
2774 Hattevig et al.⁷¹ reported study results at 18 months and Sigurs et al.⁷² reported
2775 results at 4 years of age. The authors found significantly reduced cumulative
2776 incidence and prevalence of AD at four years in children in the intervention group
2777 compared to the control group. This study was rated as low quality; however, the
2778 authors report that the two groups were comparable and matched through
2779 recruitment.

2780 5.3.2 BREASTFEEDING

2781 **Guideline 39:** The EP recommends that all infants be exclusively breastfed until 4 to
2782 6 months of age unless breastfeeding is contraindicated for medical reasons.

2783 **Rationale:** There is not strong evidence that breastfeeding has a protective role in
2784 preventing atopic disease. However, because of other benefits of breastfeeding, it is
2785 recommended that all infants, including those with a family history of atopic disease, be
2786 exclusively breastfed until 4 to 6 months of age, unless breastfeeding is contraindicated
2787 for medical reasons.

2788 **Balance of benefits and harms:** Whether exclusive breastfeeding has a beneficial role in
2789 preventing atopic disease is unclear.

2790 **Quality of evidence:** Low

2791 **Contribution of expert opinion to the recommendation:** Significant

2792 The protective role of breastfeeding in preventing atopic disease is uncertain, with some
2793 studies reporting favorable outcomes associated with breastfeeding^{73,74} and others
2794 reporting no effects.^{75,76} The effectiveness of combining exclusive breastfeeding with
2795 other interventions to prevent atopic disease is also unclear.

2796 In the German Nutritional Intervention Study (GINI), participants were randomly
2797 assigned to either exclusive breastfeeding or partial or complete cow's milk formula. The
2798 incidence of AD was compared.

2799 ● In a subgroup analysis, Schoetzau et al.⁷⁷ found a significantly lower risk of AD at
2800 one year of age in infants who were exclusively breastfed compared with infants
2801 who were not (9.5 percent versus 14.8 percent, respectively, p=0.015).
2802 ● Filipiak et al.⁷⁸ compared breastfeeding, use of hydrolyzed formulas, and delayed
2803 introduction of solid foods in intervention group infants with a separate control
2804 group of infants whose mothers did not receive these recommendations. They
2805 concluded that there was no evidence to support a protective effect of delayed
2806 introduction of solids for AD.

2807 The quality of evidence for whether breastfeeding reduces the likelihood of AD is low
2808 given that the EP found only one fair quality non-randomized comparative study
2809 addressing this question and conflicting evidence from that study.

2810 **5.3.3 SPECIAL DIETS IN INFANTS AND YOUNG CHILDREN**

2811 **5.3.3.1 Soy Infant Formula versus Cow's Milk Infant Formula**

2812 **Guideline 40:** The EP does **not** recommend using soy infant formula instead of cow's
2813 milk infant formula as a strategy for preventing the development of FA or modifying its
2814 clinical course in at-risk infants (as defined in Guidelines 34).

2815 **Rationale:** The literature reports little difference between soy infant formula and cow's
2816 milk infant formula for the prevention of FA in at-risk infants.

2817 **Balance of benefits and harms:** There appears to be neither long-term harm nor
2818 significant benefit in using soy infant formula.

2819 **Quality of evidence:** Moderate

2820 **Contribution of expert opinion to the recommendation:** Minimal

2821 **5.3.3.2 Hydrolyzed Infant Formulas versus Cow's Milk Infant Formula**

2822 **Guideline 41:** The EP suggests that exclusive use of extensively or partially hydrolyzed
2823 infant formulas be considered for infants who are not exclusively breastfed and are at risk
2824 for developing atopic disease. Cost or availability of extensively hydrolyzed infant
2825 formulas may be weighed as prohibitive factors.

2826 **Rationale:** The evidence indicates that extensively and partially hydrolyzed infant
2827 formulas reduce the development of FA in infants at risk for developing allergic disease.

2828 **Balance of benefits and harms:** There is some evidence that hydrolyzed infant formulas
2829 (particularly extensively and partially hydrolyzed infant formulas) may reduce infant and
2830 childhood allergy and cow's milk allergy in at-risk infants when compared with cow's
2831 milk infant formula. However, the cost of extensively hydrolyzed infant formulas is
2832 limiting to their practical use. There is no evidence to suggest exclusive feeding with a
2833 hydrolyzed formula is more likely to prevent atopic disease than exclusive breastfeeding.

2834 **Quality of evidence:** Moderate

2835 **Contribution of expert opinion to the recommendation:** Minimal

2836 **5.3.3.3 Soy Infant Formulas versus Hydrolyzed Infant Formulas versus Cow's Milk** 2837 **Infant Formulas**

2838 Osborn and Sinn⁷⁹ conducted a review to determine the effect of feeding adapted soy
2839 infant formula compared to human milk, hydrolyzed protein infant formulas, or cow's
2840 milk infant formula on infants who did not have a clinical FA in the first six months of
2841 life. They found three studies that compared soy infant formula to cow's milk infant
2842 formula. They reported no significant differences in incidence of childhood allergies,
2843 infant or childhood asthma, infant or childhood AD, or infant or childhood rhinitis.

2844 **5.3.3.4 Hydrolyzed Infant Formulas versus Cow’s Milk Infant Formula or**
2845 **Breastfeeding**

- 2846 ● Osborn and Sinn also conducted a Cochrane review comparing the effect of
2847 hydrolyzed infant formulas to cow’s milk infant formula or human milk in
2848 preventing FA.⁸⁰
- 2849 ○ Among four trials comparing short-term hydrolyzed infant formula feeding to
2850 human milk or cow’s milk infant formula, there were no significant
2851 differences in infant or childhood cow’s milk allergy.
 - 2852 ○ In a meta-analysis of seven studies comparing prolonged feeding with
2853 hydrolyzed infant formula or cow’s milk infant formula in infants at risk, the
2854 hydrolyzed infant formula resulted in a significant decrease in infant allergies
2855 (RR 0.79; 95 percent CI 0.66-0.94), but no difference in the incidence of
2856 childhood allergy (two studies, RR: 0.85, 95 percent CI 0.68-1.04). There
2857 were no significant differences in infant or childhood AD or infant or
2858 childhood asthma, rhinitis, and FA. The review provides limited evidence that
2859 prolonged feeding with hydrolyzed infant formulas in at-risk infants may
2860 reduce infant allergy and infant cow’s milk allergy when compared with
2861 cow’s milk infant formula.

- 2862 ● The review by Hays and Wood⁸¹ included controlled trials to assess the effect of
2863 hydrolyzed infant formulas in preventing allergies when compared with
2864 breastfeeding, cow’s milk infant formula, or soy infant formula, and the
2865 difference between extensively (eHF) and partially (pHF) hydrolyzed infant
2866 formulas. The authors included nine trials on eHFs (all were casein hydrolysate
2867 formulas) and 11 studies on pHFs (10 whey formulas and one casein formula).
2868 They concluded that, for both eHFs and pHFs, “the data support a protective
2869 effect...but the research falls short of meeting the American Academy of
2870 Pediatrics criteria⁸² for evidence of allergy prevention.”
- 2871 ● In the GINI study,^{83,84} 2,252 infants less than 2 weeks old with a parent or sibling
2872 with a history of atopy were randomly assigned to receive one of three hydrolyzed
2873 infant formulas or cow’s milk infant formula. Children were followed to 6 years.
2874 Children fed with partially hydrolyzed whey formula (pHF-W) and extensively
2875 hydrolyzed casein formula (eHF-C) were less likely to have “any allergy
2876 diagnosis from a physician” compared with children fed cow’s milk infant
2877 formula (47.1%, 46.1%, versus 56% respectively). However, there was no
2878 difference between extensively hydrolyzed whey infant formula (eHF-W) and
2879 cow’s milk infant formula.

2880 Lastly, the EP found no information in the literature on the effects of specialized diets on
2881 overall growth and development.

2882 Table 5.3 provides a summary of five randomized controlled trials that evaluated
2883 specialized infant formulas.

2884

2885 **Table 5.3: RCTs of Specialized Formulas for Infants and Young Children**

Ref #	Study Quality	Experimental Intervention Description	Control	Timing Info	Experimental Sample Size	Control Sample Size	Results
83 84	Good	Received one of the formulas: <ul style="list-style-type: none"> • pHF-W • eHF-W • eHF-C 	Cow's milk infant formula	6 years	<ul style="list-style-type: none"> • 557 pHF-W • 559 eHF-W • 580 eHF-C 	556	At 3 years of follow-up, there was no statistically significant effect on the incidence of asthma.
85	Fair	Lactating mothers and infants on elimination diets for cow's milk, egg, and fish, then assigned to either: <ul style="list-style-type: none"> • eHF-W • CMF* 	Continued breast milk for >9 months. Lactating mothers and infants were on elimination diets for cow's milk, egg, and fish	18 months	<ul style="list-style-type: none"> • 32 eHF-W • 39 CMF 	20	No statistical difference in the presence of atopic disease as judged by positive SPT or serum IgE
86	Good	Preterm infants were assigned either eHF, pHF or BMF** (with extensively hydrolyzed mixture) for 4–5 months	Infants received a standard infant formula for 4–5 months	Evaluated 4–5 months after intervention and again at 12 months	<ul style="list-style-type: none"> • 20 eHF • 22 pHF • 32 BMF 	26	No difference in the incidence of allergic diseases in preterm infants.
87	Fair	Formula made from chicken meat	Soy infant formula	14 days	20	18	12/18 children were intolerant to given soy formula compared with 4/ 20 children who received the chicken-meat based formula (p=0.009)
88	Good	Hypoallergenic formula supplemented with a mixture of short and long chain oligosaccharides	Hypoallergenic infant formula without the added supplement	2 years	66	68	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%, 7.6 vs 20.6%, 1.5 vs 10.3% respectively, p<0.05).

2886 * CMF cow's milk formula
 2887 ** BMF fortified breast milk

2888 **5.3.4 TIMING OF INTRODUCTION OF ALLERGENIC FOODS TO INFANTS**

2889 **Guideline 42:** The EP suggests that the introduction of solid foods should **not** be delayed
 2890 beyond 4 to 6 months of age. Potentially allergenic foods may be introduced at this time
 2891 as well.

2892 **Rationale:** There is insufficient evidence for delaying introduction of solid foods,
 2893 including potentially allergenic foods, beyond 4 to 6 months of age, even in infants at risk
 2894 of developing allergic disease.

2895 **Balance of benefits and harms:** Restricting exposure to food antigens during infancy
 2896 has been hypothesized as a means of preventing development of FA. However, restricting

2897 developmentally appropriate solid food variety beyond age 6 months can lead to
2898 inadequate nutrient intake, growth deficits, and feeding problems.

2899 **Quality of evidence:** Low

2900 **Contribution of expert opinion to the recommendation:** Significant

2901 Several guidelines by other organizations recommend delaying the introduction of solid
2902 foods to infants for 4 or 6 months after birth in an effort to prevent atopic disease.⁸⁹⁻⁹³
2903 However, there is no clear consensus regarding the risks and benefits of delaying the
2904 introduction of solid foods in infants beyond four to 6 months after birth.

2905 The EP identified two studies that evaluated the effect of breastfeeding in combination
2906 with delayed introduction of solid foods in infants at risk for all allergies.

- 2907
- 2908 ● Halmerbauer et al.⁹⁴ conducted a randomized controlled trial on environmental
2909 procedures to reduce house dust-mites as well as an educational intervention to
2910 delay introduction of solid foods. They found a significantly reduced risk of
2911 parent-reported food intolerance (vomiting, prolonged crying, diarrhea, and
2912 swollen lips after eating) in the intervention group. However, the study findings
2913 should be interpreted with caution because the study was only of fair quality and
2914 the intervention included both breastfeeding and education on delayed
introduction of solid foods.
 - 2915 ● Kajosaari⁹⁵ reported results from a comparative study that evaluated the effect of
2916 exclusive breastfeeding and delayed introduction of solid foods until 6 months in
2917 at-risk infants. They found a possible protective effect of exclusive breastfeeding
2918 for 6 months. This study was rated as poor quality because it was not randomized,
2919 and no information was provided on the comparability of the two groups.

2920 In a comparative study of more than 900 families by Venter et al.,⁹⁶ introduction of solid
2921 foods after weaning or after 16 weeks increased the likelihood of FA at 1 and 3 years
2922 ($p=0.02$ for both ages).

2923 The quality of evidence for this key question is low given that only two controlled trials
2924 of relatively low quality address this question. No controlled studies have addressed
2925 delayed introduction of solid foods in children who are not at risk for atopic disease.

2926 **5.4 KNOWLEDGE GAPS**

2927 With the lack of large numbers of well-controlled studies in managing and preventing
2928 FA, there are several areas where expert opinion was important in making either
2929 recommendations or suggestions. These areas include

- 2930
- 2931 ● Food avoidance and the rate of remission of a specific FA
 - 2932 ● The possibility of avoiding potentially allergenic foods as a means of managing
AD, EoE, or asthma in patients without documented or proven FA
 - 2933 ● Determining the timing of follow-up testing for individuals with FA on the basis
2934 of the specific allergenic food

- 2935 ● The use of allergen-specific immunotherapy as primary treatment for FA in
- 2936 clinical practice settings
- 2937 ● The practice of restricting maternal diet during pregnancy or lactation as a
- 2938 strategy to prevent the development or clinical course of FA
- 2939 ● The exclusive use of extensively or partially hydrolyzed infant formulas in infants
- 2940 who are not exclusively breastfed and are at risk for developing atopic disease.

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3252 **SECTION 6 DIAGNOSIS AND MANAGEMENT OF**
3253 **FOOD-INDUCED ANAPHYLAXIS AND OTHER ACUTE**
3254 **ALLERGIC REACTIONS TO FOODS**

3255 Food-induced anaphylaxis is a potentially fatal disorder and, like other forms of
3256 anaphylaxis, is increasing in incidence in industrialized countries.¹⁻⁶ Although food-
3257 induced anaphylaxis is not always easily recognized, the early recognition of certain
3258 signs and symptoms associated with a reaction, the timing of the reaction, and the
3259 existence of concomitant factors and disease processes help make the diagnosis. Prompt
3260 recognition and management is essential to ensure a good outcome.⁷ Anaphylaxis is
3261 significantly under-recognized and under-treated,^{1,2,4,8} possibly due in part to failure to
3262 appreciate anaphylaxis presenting without obvious cutaneous symptoms (10 to 20 percent
3263 of cases) or overt shock. This section of the Guidelines focuses on the diagnosis and
3264 management of food-induced anaphylaxis mediated through immune mechanisms
3265 associated with IgE antibody.

3266 RAND Corporation conducted a systematic literature review of the topic area of food-
3267 induced anaphylaxis and found a paucity of studies meeting standards for inclusion in
3268 these Guidelines. Thus, the evidence base for the recognition, diagnosis, and especially
3269 the management of food-induced anaphylaxis, is significantly limited. Consequently,
3270 much of this section's information and cited literature are provided by the Expert Panel
3271 (EP) based on individual citations deemed to be relevant and their own experience and
3272 opinion. Much of this information is gleaned from the available literature related to
3273 anaphylaxis in general and applied specifically to food allergy.

3274 **6.1 DIAGNOSIS OF ACUTE, LIFE-THREATENING, IgE-**
3275 **MEDIATED FOOD ALLERGIC REACTIONS**

3276 **Guideline 43:** The EP recommends that the clinician considering a diagnosis of
3277 food-induced anaphylaxis should understand

- 3278 ● The signs and symptoms characteristic of anaphylaxis
- 3279 ● The timing of symptoms in association with food ingestion/exposure
- 3280 ● Co-morbid conditions, such as asthma, which may affect treatment and outcome
- 3281 ● Laboratory parameters are of limited utility in the acute care setting

3282 **Rationale:** The evidence and expert opinion support prompt recognition and diagnosis of
3283 food-induced anaphylaxis.

3284 **Balance of benefits and harms:** Prompt recognition and diagnosis of food-induced
3285 anaphylaxis is essential and necessary to ensure appropriate health outcomes and to
3286 prevent progression to life-threatening reactions. Potential harm, including the possibility
3287 of death, exists if the diagnosis is delayed or not recognized.

3288 **Quality of evidence:** Low

3289 **Contribution of expert opinion to the recommendation:** Significant

3290 **6.1.1 DEFINITION OF ANAPHYLAXIS**

3291 Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause
3292 death.^{2,9} Typically IgE-mediated food-induced anaphylaxis is believed to involve
3293 systemic mediator release from sensitized mast cells and basophils.¹⁰ The term
3294 “anaphylactoid” has been used in the past to indicate adverse reactions that are not
3295 IgE-mediated and typically are not life threatening. This term is imprecise and will not be
3296 used here.

3297 **6.1.2 DIAGNOSIS OF ANAPHYLAXIS**

3298 The diagnosis of anaphylaxis, either in general or specifically food-induced, is based on
3299 clinical findings and a detailed description of the acute episode, in association with
3300 known or suspected food exposure. The contribution of laboratory testing for the
3301 diagnosis of anaphylaxis is minimal, except where it may be important to diagnose the
3302 condition of food allergy. The most common food triggers for anaphylaxis are peanut,
3303 tree nuts, milk, egg, fish, and crustacean shellfish. The incidence is variable depending on
3304 age, regional diets, food preparation, amount of exposure, and timing of first
3305 exposure.^{11,12} Association with a specific food is reported in up to 80 percent of
3306 anaphylaxis cases when reviewed from administrative databases or acute care
3307 settings.^{3,13–21}

3308 The medical history is an essential aspect in establishing a diagnosis of food-induced
3309 anaphylaxis. A history of prior food allergic reactions or prior diagnosis of food allergy
3310 (as defined in Section 4) in association with known ingestion of a food protein is
3311 beneficial. However, anaphylaxis in association with first-time food ingestion can occur
3312 at any age and is more common in young children. Studies have shown that anaphylaxis
3313 in the school setting occurs in as many as 20 percent of children with first-time food
3314 exposure.²²

3315 **6.1.2.1 Diagnostic criteria for anaphylaxis**

3316 New diagnostic criteria for anaphylaxis were published in 2006⁷ with the intent to help
3317 clinicians both recognize the spectrum of signs and symptoms that comprise anaphylaxis
3318 and establish a more systematic approach to its diagnosis and management. The
3319 following three criteria were established, and the presence of **any one** of these criteria
3320 indicates that anaphylaxis is highly likely:

- 3321
- 3322 ● Acute onset of an illness (over minutes to several hours) involving skin, mucosal
3323 tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-
3324 uvula), and at least one of the following:
 - 3325 ○ Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor,
3326 reduced peak expiratory flow, hypoxemia)
 - 3327 ○ Reduced blood pressure (BP) or associated symptoms of end-organ
3328 dysfunction (e.g., hypotonia (collapse), syncope, incontinence)
 - 3329 ● Two or more of the following that occur rapidly after exposure to a likely allergen
for that patient (minutes to several hours):

- 3330 ○ Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush,
- 3331 swollen lips-tongue-uvula)
- 3332 ○ Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor,
- 3333 reduced peak expiratory flow, hypoxemia)
- 3334 ○ Reduced BP or associated symptoms of end-organ dysfunction (e.g.,
- 3335 hypotonia, syncope, incontinence)
- 3336 ○ Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
- 3337 ● Reduced BP after exposure to a known allergen for that patient (minutes to
- 3338 several hours). Reduced BP is defined
- 3339 ○ In adults, as a systolic BP of less than 90 mm Hg or greater than 30 percent
- 3340 decrease from that person's baseline
- 3341 ○ In infants and children, as a low systolic BP (age-specific) or greater than
- 3342 30 percent decrease in systolic BP. Low systolic BP is defined as
- 3343 – Less than 70 mm Hg for 1 month to 1 year of age
- 3344 – Less than (70 mm Hg plus twice the age) for 1 to 10 years
- 3345 – Less than 90 mm Hg for 11 to 17 years of age
- 3346 **Note:** In infants and young children, hypotension may be a late manifestation of
- 3347 hypovolemic shock. Tachycardia, in the absence of hypotension, may also
- 3348 indicate shock.²³

3349 **6.1.3 SIGNS AND SYMPTOMS OF FOOD-INDUCED ANAPHYLAXIS**

3350 Usually, anaphylaxis involves more than one organ system, which helps to distinguish it
 3351 from other acute reactions such as asthma exacerbations, respiratory symptoms,
 3352 urticaria/angioedema, or gastrointestinal symptoms. The signs and symptoms for
 3353 anaphylaxis in general are the same for food-induced anaphylaxis,^{6,7,11,24-26} and include

- 3354 ● Cutaneous symptoms, which occur in the majority of patients, and include
- 3355 flushing, pruritus, urticaria, and angioedema. However, 10 to 20 percent of cases
- 3356 have no cutaneous manifestations.
- 3357 ● Respiratory symptoms, which occur in up to 70 percent of cases, and include
- 3358 nasal congestion and rhinorrhea, throat pruritus and laryngeal edema, choking,
- 3359 wheeze, cough and dyspnea.
- 3360 ● Gastrointestinal symptoms, which occur in up to 40 percent of cases, and include
- 3361 cramping, abdominal pain, nausea, emesis, and diarrhea.
- 3362 ● Cardiovascular symptoms, which occur in up to 35 percent of cases, and include
- 3363 dizziness, tachycardia, hypotension and collapse.
- 3364 ● Other symptoms, which may include anxiety, mental confusion, lethargy, and
- 3365 seizures.

3366 Any of these symptoms may culminate in death.

3367 **6.1.4 TIME COURSE**

3368 Food-induced anaphylaxis is typically characterized by a defined exposure to a food
 3369 allergen that is followed by a rapid onset and evolution of symptoms over minutes to
 3370 several hours. Deaths from food-induced anaphylaxis have been reported within

3371 30 minutes to 2 hours of exposure²⁷⁻²⁹ and usually result from respiratory compromise.¹¹
3372 Food-induced anaphylaxis can also have a milder course and resolve spontaneously, most
3373 likely due to endogenous production of vasoconstrictors (e.g., epinephrine, endothelin,
3374 angiotensin II and others).^{25,30,31}

3375 The time course of anaphylaxis may fall into three potential reaction courses: uniphasic,
3376 biphasic, and protracted.

- 3377 ● Uniphasic reactions occur immediately after exposure and resolve with or without
3378 treatment within the first minutes to hours, and then do not recur during that
3379 anaphylaxis episode.
- 3380 ● Biphasic reactions are defined as a recurrence of symptoms that develops after
3381 apparent resolution of the initial reaction. Biphasic reactions have been reported
3382 to occur in 1 to 20 percent of anaphylaxis episodes and typically occur about
3383 8 hours after the first reaction, although recurrences have been reported up to
3384 72 hours later.^{29,32,33}
- 3385 ● Protracted reactions are defined as any anaphylaxis episode that lasts for hours or
3386 days following the initial reaction.²⁹

3387 Fatalities associated with food-induced anaphylaxis occur and are most commonly
3388 associated with peanut or tree nut ingestion.²⁷⁻²⁹ Such fatalities are associated with
3389 delayed use or lack of proper epinephrine dosing. The highest risk groups for fatal
3390 anaphylaxis associated with food ingestion are

- 3391 ● Adolescents and young adults
- 3392 ● Individuals with known food allergy and with a prior history of anaphylaxis
- 3393 ● Individuals with asthma, especially those with poor control (although fatal
3394 reactions may occur even in individuals with mild asthma)
- 3395 ● Individuals without ready access to epinephrine²⁷⁻²⁹

3396 **6.1.5 CO-MORBID DISEASES AND FACTORS THAT INCREASE THE RISK** 3397 **OF ANAPHYLAXIS TO FOODS**

3398 Co-morbidities may affect symptom severity and treatment response in patients with
3399 food-induced anaphylaxis.^{25,26,30,34}

- 3400 ● Asthma is the most important risk factors for a poor outcome. Persistent asthma,
3401 especially if not optimally controlled, is an important risk factor for death from
3402 anaphylaxis, especially in adolescents and young adults.^{27-29,35,36}
- 3403 ● Cardiovascular disease is also an important risk factor for death from anaphylaxis,
3404 especially in middle-aged and older individuals.³⁷
- 3405 ● Other disorders, such as mastocytosis, chronic lung disease (chronic obstructive
3406 pulmonary disease and recurrent pneumonia), and anatomic airway obstruction
3407 (e.g., airway hemangiomas, laryngotracheomalacia), may also increase risk.

3408 Certain medications may also affect symptom severity and treatment response in patients
3409 with food-induced anaphylaxis.

- 3410 • Beta-adrenergic antagonists may decrease the response to epinephrine therapy in
3411 patients undergoing anaphylaxis.
3412 • Angiotensin-converting enzyme inhibitors and, to a lesser extent, angiotensin II
3413 receptor blockers, may interfere with endogenous compensatory mechanisms,
3414 resulting in more severe or prolonged symptoms.³⁸
3415 • Alpha-adrenergic blockers may decrease the effects of endogenous or exogenous
3416 epinephrine at alpha-adrenergic receptors, rendering patients less responsive to
3417 epinephrine.³⁹

3418 **6.1.6 OTHER DISEASES ASSOCIATED WITH ACUTE REACTIONS TO**
3419 **FOOD**

3420 Several other food allergy disorders, described in detail in Sections 2, 3, and 4, may have
3421 acute symptoms after food ingestion.

- 3422 • Some disorders share IgE-mediated mechanisms such as localized urticaria or
3423 angioedema, generalized flushing, oral allergy syndrome, and food-dependent,
3424 exercise-induced anaphylaxis and may progress to life-threatening anaphylaxis.
3425 • Others are non-IgE-mediated disorders such as food protein-induced enterocolitis
3426 syndrome (FPIES) and allergic proctocolitis that may present with acute,
3427 repetitive gastrointestinal symptoms. In particular, FPIES may be confused with
3428 anaphylaxis because patients, minutes to hours after food or formula ingestion,
3429 often develop repetitive emesis in association with pallor, diarrhea, lethargy, and
3430 hypotension due to massive intravascular fluid shifts. Patients with FPIES require
3431 treatment via aggressive fluid resuscitation and typically do not respond to
3432 epinephrine, in contrast to patients with acute reactions due to IgE-mediated
3433 disease.

3434 **6.1.7 LABORATORY TESTING**

3435 Testing is of limited value in the acute setting. The diagnosis of food-induced
3436 anaphylaxis may be supported by tests that assess for sensitization to the suspect food
3437 allergen. However, the diagnosis is rarely supported by tests that document elevated mast
3438 cell and basophil mediators, including plasma histamine and serum or plasma total
3439 tryptase.⁴⁰⁻⁴⁴ The use of these assays to diagnose food-induced anaphylaxis is
3440 unrealistic^{42,43,45,46} because histamine is very labile and requires special handling of
3441 samples for processing. Tryptase lacks specificity and is not elevated in food-induced
3442 anaphylaxis. However, in the case of suspected anaphylaxis, elevated serum tryptase or
3443 urinary histamine levels may be very useful to confirm the diagnosis of anaphylaxis (or
3444 possibly systemic mastocytosis), but may not be indicative of a food-induced reaction.
3445 A negative tryptase finding also does not rule out food-induced anaphylaxis.

3446 Epicutaneous prick skin testing and serum allergen-specific IgE testing (e.g.,
3447 ImmunoCAP) may provide information regarding a specific food allergy (see Section 4,
3448 but do not yield information about the cause of or risk for anaphylaxis. Rather, these tests
3449 may be used as adjuncts to evaluate for allergen sensitization, while other tests (such as
3450 double-blind placebo-controlled food challenge) are useful to determine clinical allergy

3451 (see Section 4). Correlation of testing with timing of ingestion and associated reaction,
 3452 symptom profile, and response to therapy are important to make the definitive diagnosis.
 3453 Additionally, there are no tests available to predict severity of IgE-mediated reactions.

3454 **6.2 TREATMENT OF ACUTE, LIFE-THREATENING, IGE-**
 3455 **MEDIATED FOOD ALLERGIC REACTIONS**

3456 **Guideline 44:** The EP recommends that treatment for food-induced anaphylaxis should
 3457 focus on the following:

- 3458 • Prompt and rapid treatment after onset of symptoms (see Table 6.1 for
- 3459 pharmacologic treatment in an outpatient or hospital setting)
- 3460 • Intramuscular (IM) epinephrine as first-line therapy
- 3461 • Other treatments, which are adjunctive to epinephrine dosing

3462 **Rationale:** Evidence supports the implementation of rapid response and treatment for
 3463 food-induced anaphylaxis and the use of IM epinephrine as first-line therapy.

3464 **Balance of benefits and harms:** The benefits of appropriate treatment for anaphylaxis
 3465 begin with IM epinephrine injection. Benefits of epinephrine treatment far outweigh the
 3466 risks of unnecessary dosing. Delays in instituting therapy with epinephrine are associated
 3467 with risks of death and morbidity.

3468 **Quality of evidence:** Moderate

3469 **Contribution of expert opinion to the recommendation:** Significant

3470 **Table 6.1: Summary of Pharmacological Management of Food-induced Anaphylaxis**
 3471 **in Outpatient and Hospital Settings**

Drug (route)	Dose	Maximum dose	Outpatient, first line	Outpatient, adjunctive	Hospital, first line	Hospital, adjunctive
Epinephrine autoinjector (IM)	0.15 mg (For individuals 10–25kg)	-	√	-	√	-
Epinephrine autoinjector (IM)	0.3 mg (For individuals > 25kg)	-	√	-	√	-
Epinephrine IM (1:1000)	0.01 mg/kg	0.3 mg	√	-	√	-
Albuterol (Inhaler or nebulizer)	Metered-dose, every 20 minutes	-	-	√	-	√
Diphenhydramine (IV or oral)	1–2 mg/kg	50 mg	-	√	-	√
Vasopressors	Titrate to effect	-	-	-	-	√
Glucagon	5–15 µg/minute	-	-	-	-	√
Ranitidine (IV or oral)	1–2 mg/kg	75–150 mg	-	-	-	√
Prednisone (oral) or methylprednisolone (IV)	1 mg/kg	60–80 mg	-	-	-	√

3472 As in all anaphylaxis, prompt assessment and treatment are critical for food-induced
 3473 anaphylaxis events. Failure to respond promptly can result in rapid demise and death
 3474 within 30–60 minutes.^{21,28,29,35–37,47}

3475 The cornerstones of initial management should begin with the following **concurrent**
3476 steps⁴⁸

- 3477 ● Elimination of additional allergen exposure
- 3478 ● Call for help (summon a resuscitation team in the hospital setting, call 911 or an
3479 equivalent service in the community setting) although attempts to summons help
3480 should not delay use of epinephrine
- 3481 ● IM injection of epinephrine

3482 These actions should be quickly followed by these additional steps⁴⁹⁻⁵²

- 3483 ● Place the patient in the supine position, with the lower extremities elevated (if
3484 tolerated)
- 3485 ● Provide supplemental oxygen
- 3486 ● Administer intravenous (IV) fluid (volume resuscitation)
- 3487 ● Administer epinephrine as soon as possible once anaphylaxis is recognized, and
3488 transport the patient to the nearest emergency facility. Delayed administration of
3489 epinephrine has been implicated in contributing to fatalities^{27-29,46}

3490 In a study of 13 fatal or near-fatal food-induced anaphylactic reactions in children, six of
3491 the seven children who survived received epinephrine within 30 minutes of ingesting the
3492 food, whereas only two of the six children who died received epinephrine within the first
3493 hour.²⁹ Similar findings have continued in ongoing reports of fatal anaphylaxis using the
3494 food allergy anaphylaxis registry.^{27,28} Epinephrine, therefore, should be available at all
3495 times to patients at risk. A recent study in schools also highlights the fact that children
3496 with food allergy often do not have ready access to epinephrine at school, further placing
3497 them at increased risk.⁵³

3498 **6.2.1 PHARMACOLOGIC TREATMENT**

3499 Pharmacologic treatment of food-induced anaphylaxis is based on extrapolation from
3500 therapies used in cardiac arrest and asthma, from uncontrolled human trials of
3501 anaphylaxis during insect sting challenges, and from studies of anaphylaxis in animal
3502 models.² Randomized, controlled studies that meet current standards have not been
3503 performed for any therapeutic interventions during actual anaphylaxis in humans.
3504 Placebo-controlled trials for epinephrine use have not been performed during anaphylaxis
3505 and will likely never be performed due to ethical considerations in a disease that can kill
3506 within minutes and requires prompt intervention.⁵⁴

3507 The evidence base for the pharmacologic management of an acute anaphylaxis episode
3508 has been extensively studied in three Cochrane collaborative reviews.⁵⁵⁻⁵⁷ From the
3509 literature reviewed, the EP did not identify any randomized controlled trials (RCTs) that
3510 met current standards. However, these reviews highlight that epinephrine has been
3511 relatively well-investigated in terms of

- 3512 ● Observational studies
- 3513 ● RCTs in patients not experiencing anaphylaxis at the time of administration
- 3514 ● Epidemiologic studies

- 3515 ● Fatality studies
- 3516 ● *In vitro* studies and studies in animal models

3517 Experts in the field agree that epinephrine is the only first-line treatment for anaphylaxis.
 3518 There is no substitute for epinephrine, thus all other treatments are adjunctive.
 3519 Antihistamines (both H1 and H2 blockers), corticosteroids, or both are commonly used in
 3520 the treatment of anaphylaxis, but there are little or no data demonstrating their functional
 3521 role or effectiveness.

3522 **In summary: The use of antihistamines is the most common reason reported for not**
 3523 **using epinephrine³¹ and may place the patient at significantly increased risk for**
 3524 **progression toward a life-threatening reaction.**

3525 Table 6.2 briefly summarizes the pharmacologic management of anaphylaxis in
 3526 outpatient and hospital settings. A more complete summary of the pharmacologic
 3527 management of anaphylaxis is given below.

3528 **Table 6.2: Summary of the Pharmacologic Management of Anaphylaxis (adapted⁴⁹)**

3529

3530 **In the outpatient setting**

- 3531 ● First line treatment
 - 3532 ○ Epinephrine Autoinjector
 - 3533 – 10 to 25 kg: 0.15 mg epinephrine IM (anterior-lateral thigh)
 - 3534 – >25 kg: 0.3 mg epinephrine IM (anterior-lateral thigh)
 - 3535 ○ Epinephrine (1:1000), 0.01 mg/kg per dose; maximum dose, 0.3 mg per dose
 3536 IM (anterior-lateral thigh)
- 3537 ● Adjunctive treatment
 - 3538 ○ Albuterol (β_2 -agonist) metered-dose inhaler or nebulized solution every
 3539 20 min or continuously as needed
 - 3540 ○ Diphenhydramine (H_1 antagonist), 1 to 2 mg/kg per dose; maximum dose,
 3541 50 mg IV or oral (oral liquid is more readily absorbed than tablets)
 - 3542 ○ Oxygen therapy
 - 3543 ○ Intravenous fluids in large volumes if patients present with orthostasis,
 3544 hypotension or incomplete response to IM epinephrine
 - 3545 ○ Patient positioning, recumbent position with lower extremities elevated

3546 **Hospital-based**

- 3547 ● First line treatment
 - 3548 ○ Epinephrine IM as above, consider intermittent IV epinephrine boluses vs.
 3549 continuous epinephrine infusion for persistent hypotension; alternative is
 3550 endotracheal epinephrine
- 3551 ● Adjunctive treatment
 - 3552 ○ Vasopressors for refractory hypotension, titrate to effect
 - 3553 ○ Glucagon for refractory hypotension 5 to 15 μ g/min, titrate to effect
 - 3554 ○ Albuterol (β_2 -agonist) nebulized solution or metered dose inhaler every
 3555 20 min or continuous as needed

- 3556 ○ Diphenhydramine (H₁ antagonist), 1 to 2 mg/kg per dose; maximum dose,
- 3557 50 mg oral, IV, and IM (if not already given)
- 3558 ○ Ranitidine (H₂ antagonist), 1 to 2 mg/kg per dose; maximum dose, 75 to
- 3559 150 mg oral and IV
- 3560 ○ Corticosteroids: prednisone at 1 mg/kg with a maximum dose of 60 to 80 mg
- 3561 oral or methylprednisolone at 1 mg/kg with a maximum dose of 60 to 80 mg
- 3562 IV
- 3563 ○ Oxygen therapy
- 3564 ○ Intravenous fluids in large volumes if patients present with orthostasis,
- 3565 hypotension or incomplete response to IM epinephrine
- 3566 ○ Patient positioning, recumbent position with lower extremities elevated

3567 **Discharge therapy**

- 3568 ● First line treatment:
 - 3569 ○ Epinephrine autoinjector prescription and instructions
 - 3570 ○ Education on avoidance of allergen
 - 3571 ○ Follow-up with primary care physician
 - 3572 ○ Consider referral to an allergist
 - 3573 ● Adjunctive treatment:
 - 3574 ○ Diphenhydramine (H₁ antagonist) every 6 h for 48 to 72 hr
 - 3575 ○ Ranitidine (H₂ antagonist), twice daily for 48 to 72 hr
 - 3576 ○ Prednisone (corticosteroid) twice daily for 48 to 72 hr
-

3578 **6.2.1.1 Epinephrine—First Line Treatment**

3579 Epinephrine is the drug of choice for anaphylaxis and should be administered as **first-line**
 3580 **therapy**. The pharmacologic actions of this agent address the pathophysiologic changes
 3581 that occur in anaphylaxis better than any other single drug. Failure to administer
 3582 epinephrine early in the course of treatment has been repeatedly implicated in
 3583 anaphylaxis fatalities.^{1,6,8,27–29,58} Despite this fact, physicians often fail to prescribe
 3584 epinephrine, and emergency responses can vary by region.^{2,15,31,59,60}

3585 The therapeutic actions of epinephrine, which encompass a broad range of effects
 3586 germane to the mechanisms of anaphylaxis, include the following⁵²

- 3587 ● Increased vasoconstriction, increased peripheral vascular resistance, and
- 3588 decreased mucosal edema via alpha-1 adrenergic agonist receptor effects
- 3589 ● Increased inotropy and increased chronotropy via beta-1 adrenergic receptor
- 3590 agonist effects
- 3591 ● Bronchodilation and decreased release of mediators of inflammation from mast
- 3592 cells and basophils via beta-2 adrenergic receptor agonist effects.

3593 Epinephrine has a narrow toxic-therapeutic index (risk-to-benefit ratio). In therapeutic
 3594 doses and by any route, epinephrine frequently causes transient adverse effects in
 3595 individuals of all ages. These include anxiety, fear, restlessness, headache, dizziness,
 3596 palpitations, pallor, and tremor.⁵² Rarely, and especially after overdose, it may lead to

3597 ventricular arrhythmias, angina, myocardial infarction, pulmonary edema, sudden sharp
3598 increase in BP, and intracranial hemorrhage.⁵²

3599 Epinephrine has an onset of action within minutes but is rapidly metabolized. Therefore,
3600 the effect is often short-lived and repeated doses may be necessary.^{31,61,62} Epinephrine
3601 can be delivered through a variety of routes including IM, IV, and endotracheal.
3602 Subcutaneous injection is of limited benefit when compared to IM dosing⁵¹ and should
3603 not be used.

- 3604 • **IM epinephrine** is recommended over subcutaneous injection because it provides
3605 more rapid plasma and tissue concentrations of epinephrine.^{7,35,51} The dose should
3606 be given intramuscularly into the anterolateral thigh in the vastus lateralis muscle.
3607 When using an epinephrine autoinjector (e.g., EpiPen® or Twinject®), children
3608 weighing less than 25 kg should receive the 0.15 mg pediatric dose.⁶³ Children
3609 over 25 kg through adults should use the 0.3 mg dose. The needle used in
3610 autoinjectors in adults should be of adequate length to reach the muscle beneath
3611 the subcutaneous adipose tissue over the vastus lateralis muscle (e.g., 1.5 inches
3612 in a normal adult). IM injection into the thigh may be impossible in overweight or
3613 obese individuals, especially women who have higher subcutaneous fat tissue.^{64,65}
3614 In the circumstance of inadequate IM dosing, subcutaneous dosing will provide
3615 some benefit but will be less effective than IM dosing; therefore, alternatives may
3616 need to be considered, such as deltoid site delivery or needle/syringe dosing of
3617 aqueous epinephrine.
- 3618 • **IV epinephrine** is recommended for patients who do not respond to an initial (or
3619 repeated) IM injection of epinephrine and whose fluid resuscitation may not be
3620 adequately perfusing muscle tissues.²⁵
- 3621 • **Endotracheal epinephrine** can be delivered if IV access cannot be obtained
3622 immediately. The efficacy of this delivery method is based upon small series of
3623 patients experiencing cardiac arrest.²⁶ Sublingual epinephrine is in early
3624 development stages and not yet available for clinical use.⁶⁶
- 3625 • **Repeated dosing of epinephrine** may be required if a patient responds poorly to
3626 the initial dose or has ongoing or progressive symptoms despite initial dosing.
3627 Several reports of patients receiving epinephrine for food and other allergen
3628 anaphylaxis or food-induced anaphylaxis^{61,62} note that approximately 10 to
3629 20 percent of individuals who receive epinephrine will require more than one dose
3630 before recovery of symptoms. In many of the cases, the subsequent doses of
3631 epinephrine were given less than 15 minutes from the first dose (some more than
3632 1 hour) despite recommendations to repeat dosing as frequently as every 5 to
3633 15 minutes. Optimal dosing interval for repeated dosing has not been studied
3634 prospectively.

3635 6.2.1.2 Adjunctive Treatment

- 3636 • **H1 Antihistamines.** In contrast to epinephrine, there is very limited scientific
3637 evidence to support the use of H1 antihistamines in the emergency treatment of
3638 anaphylaxis.⁴ H1 antihistamines are useful only for relieving itching and urticaria.
3639 They do not relieve stridor, shortness of breath, wheezing, gastrointestinal

3640 symptoms, or shock. Therefore, they should be considered adjunctive therapy and
3641 should not be substituted for epinephrine.^{17,27-29,47,55,67}

3642

3643 The first-generation H1 antihistamines are most commonly administered due to
3644 their availability for IV and oral dosing when compared to second-generation
3645 antihistamines. Both have onset of action within 20 to 60 minutes, but first-
3646 generation antihistamines have a shorter duration of action, lasting 4 to 7 hours
3647 compared to 12 to 24 hours for second-generation antihistamines. Additionally,
3648 sedation and psychomotor impairment must be recognized as side effects of the
3649 first-generation antihistamine medications that may decrease cognitive awareness
3650 of symptoms.^{55,67}

3651 ● **Corticosteroids.** Very little information is available to support or refute the use of
3652 corticosteroids for the treatment of acute anaphylaxis. However, their empiric use
3653 is prevalent and supported by many clinicians. Corticosteroids are not helpful in
3654 the treatment of acute anaphylaxis due to their slow onset of action (4 to 6 hr).

3655 These agents are often given because of their anti-inflammatory properties that
3656 benefit allergic and inflammatory disease and also because they may help to
3657 prevent the biphasic or protracted reactions, which occur in up to 20 percent of
3658 individuals.^{1,33} Treatment should be stopped within 2 to 3 days, since all biphasic
3659 reactions reported to date have occurred within 3 days.³³

3660 ● **H2 Antihistamines.** There is minimal evidence to support the use of H2
3661 antihistamines in the emergency treatment of anaphylaxis.⁶⁹ Some clinicians use
3662 these medications as empiric therapy under the premise that they further bind
3663 histamine receptor isoforms. However, studies to support this idea are lacking.

3664 ● **Bronchodilator medications.** For the treatment of bronchospasm not responsive
3665 to IM epinephrine, inhaled bronchodilators, such as albuterol, should be used as
3666 needed and should be considered to be adjunctive therapy to epinephrine
3667 administration. Albuterol does not relieve airway edema and should not be
3668 substituted for IM epinephrine dosing in the treatment of anaphylaxis. In most
3669 emergency care settings, nebulized therapy may be more practical than metered-
3670 dose inhalers (with spacers) for patients with respiratory distress, but metered-
3671 dose inhalers can also be helpful when the respiratory distress is mild or when
3672 nebulized therapy is not available. Moreover, the effectiveness of albuterol
3673 delivery via nebulizer versus metered-dose inhaler (with spacer) remains
3674 uncertain for patients with severe respiratory distress. Therefore, the EP
3675 recommends albuterol administration via nebulizer (if available) in this setting.

3676 ● **Oxygen therapy.** Oxygen should be administered initially to all patients
3677 experiencing anaphylaxis, especially those with evidence of hypoxia or
3678 respiratory distress. Not only does supplemental oxygen help with optimization of
3679 oxygen delivery and organ perfusion, but it also serves to help with
3680 bronchodilation.²⁴

3681 ● **Intravenous Fluids.** Many patients with anaphylaxis require IV fluids. Massive
3682 fluid shifts can occur rapidly in anaphylaxis due to increased vascular
3683 permeability, with transfer of up to 35 percent of the intravascular volume into the
3684 extravascular space within minutes.⁴⁰ Any patient who does not respond promptly
3685 and completely to injected epinephrine should be assumed to have **intravascular**

3686 **volume depletion** causing persistent hypotension despite maximum
3687 vasoconstriction. These patients should receive large volume fluid resuscitation,
3688 with normal saline being the preferred treatment. Larger volume fluid
3689 resuscitation should be initiated immediately in patients who present with
3690 orthostasis, hypotension, or incomplete response to IM epinephrine.²⁴
3691 ● **Vasopressors.** Patients who have persistent hypotension despite the
3692 administration of epinephrine and IV fluids should receive vasopressor
3693 medications titrated to the desired effect of restoring blood pressure. Due to the
3694 narrow benefit-to-risk ratio of these medications,⁷⁰ patients requiring vasopressors
3695 should be transferred to a hospital setting for acute care. There is no compelling
3696 evidence to support one vasopressor over another in this clinical scenario.
3697 ● **Patient positioning.** The patient should be placed in the recumbent position with
3698 the lower extremities elevated to maximize perfusion of vital organs. This also
3699 helps prevent "empty ventricle syndrome," in which severe hypotension leads to
3700 inadequate cardiac filling and electrical cardiac activity without a pulse.⁷¹
3701 Individuals with respiratory distress or vomiting may not tolerate the recumbent
3702 position.
3703 ● **Medications and confounding factors that may affect treatment response.**
3704 Concurrent administration of certain medications may affect the patient's ability
3705 to respond to both treatment and compensatory physiologic responses.
3706 Beta-adrenergic antagonists, administered orally, parenterally, or topically (e.g.,
3707 eye drops) may decrease the effects of endogenous or exogenous epinephrine at
3708 beta-adrenergic receptors and render patients less responsive to epinephrine.⁷²
3709 Patients receiving beta-blockers may be resistant to treatment with epinephrine
3710 and can develop refractory hypotension and bradycardia. Glucagon should be
3711 administered in this setting because it has inotropic and chronotropic effects that
3712 are not mediated through beta-receptors.⁶⁰ A dose of 1 to 5 mg in adults (in
3713 children, 20 to 30 µg/kg, to a maximum of 1 mg) administered intravenously over
3714 5 minutes is recommended, which may be repeated or followed by an infusion of
3715 5 to 15 µg/minute.²⁶ Rapid administration of glucagon can induce vomiting.
3716 ● **Refractory anaphylaxis: patients without effective epinephrine response.**
3717 There are no published prospective studies on the optimal management of
3718 refractory anaphylactic shock. Repeated use of epinephrine, as well as intravenous
3719 fluids, corticosteroids, and vasopressor agents may be needed.²⁴ Prompt transfer
3720 to an acute-care facility and intensive-care unit for treatment and monitoring is
3721 essential.
3722 ● **Possible risks of acute therapy for anaphylaxis.** There are no absolute
3723 contraindications to epinephrine use in anaphylaxis.^{24,43} However, there are
3724 subgroups of patients who might theoretically be at higher risk for adverse effects
3725 during epinephrine therapy. Because the risk of death or serious disability from
3726 anaphylaxis itself usually outweighs other concerns,^{24,43} existing evidence clearly
3727 favors the benefit of epinephrine administration in most situations. Some level of
3728 decision-making regarding the risk/benefit ratio for the patient may be warranted,
3729 and especially for patients
3730 ○ With cardiovascular diseases, and who are reluctant to receive epinephrine
3731 due to fear of adverse cardiac effects. These patients should be made aware

3732 that myocardial ischemia and dysrhythmias can occur in untreated
3733 anaphylaxis.⁴⁰
3734 ○ Receiving monoamine oxidase inhibitors (which block epinephrine
3735 metabolism), or tricyclic antidepressants (which prolong epinephrine duration
3736 of action)
3737 ○ Receiving stimulant medications (e.g., amphetamines or methylphenidate used
3738 in the treatment of attention-deficit-hyperactivity disorder) or abusing cocaine
3739 ○ With certain preexisting conditions, such as recent intracranial surgery, aortic
3740 aneurysm, uncontrolled hyperthyroidism or hypertension; and
3741 ○ Who are pregnant, due to possible risks of ischemic effects on the unborn
3742 fetus.

3743 ● **Treatment to prevent biphasic or protracted food allergic reactions.** Very
3744 little information exists that defines the mechanism of biphasic or protracted
3745 allergic reactions. Similarly, little information exists to support specific therapy to
3746 prevent biphasic or protracted food-induced allergic reactions. In general,
3747 induction and recruitment of inflammatory cells and release of preformed, long-
3748 acting mediators from mast cells have been implicated as mechanisms.³³
3749 Although little data supports their use, systemic corticosteroids often are
3750 recommended medications to prevent biphasic or protracted food allergic
3751 reactions due to their anti-inflammatory properties.
3752 ● **Management of milder, acute food allergic reactions in healthcare settings.**
3753 Milder forms of allergic reactions, such as flushing, urticaria or isolated, mild
3754 angioedema, or symptoms of oral allergy syndrome can be treated with H1 and
3755 H2 antihistamine medications.^{12,69} When antihistamines alone are given, ongoing
3756 observation and monitoring is warranted to ensure a lack of progression to more
3757 significant symptoms of anaphylaxis. If progression or increased severity is noted,
3758 epinephrine should be administered immediately. Additionally, if there is a
3759 history of a prior severe allergic reaction, epinephrine should be administered
3760 promptly and earlier in the course (e.g., at the onset of even mild symptoms).

3761 **6.3 MANAGEMENT FOLLOWING FOOD-INDUCED** 3762 **ANAPHYLAXIS**

3763 **Guideline 45:** The EP recommends that the management of food-induced anaphylaxis
3764 should focus on the following

- 3765 ● Dosing with IM epinephrine followed by transfer to an emergency facility for
3766 observation and possible further treatment
- 3767 ● Observation for 4 to 6 hours or longer based on severity of the reaction
- 3768 ● Education for patient and family for
 - 3769 ○ Trigger avoidance
 - 3770 ○ Early recognition of signs and symptoms
 - 3771 ○ Anaphylaxis Emergency Action Plan implementation
 - 3772 ○ Appropriate IM epinephrine administration
 - 3773 ○ Education on medical identification jewelry or an Anaphylaxis Wallet Card
- 3774 ● Epinephrine autoinjector prescription and training provided at the time of
3775 discharge

- 3776 • Follow-up appointment with primary healthcare provider, (after the food-induced
- 3777 anaphylactic reaction) with consideration for additional follow-up with an
- 3778 allergist
- 3779 **Rationale:** Despite the lack of evidence, the EP recommends close monitoring, scheduled
- 3780 follow-up, and patient education for effective management following anaphylaxis.
- 3781 **Balance of benefits and harms:** The benefits of appropriate management following
- 3782 food-induced anaphylaxis should serve to further protect the patient through long-term
- 3783 follow-up, care and education with the benefit of preventing subsequent events. The
- 3784 potential harm is minimal if appropriate education is employed.
- 3785 **Quality of evidence:** Low
- 3786 **Contribution of expert opinion to the recommendation:** Significant

3787 **6.3.1 OBSERVATION PERIOD**

3788 There is no consensus in the literature regarding the optimal amount of time that a
 3789 patient, who has been successfully treated for anaphylaxis, should be observed prior to
 3790 discharge. All patients that receive epinephrine for food-induced anaphylaxis should
 3791 proceed to an emergency facility for observation and possibly additional treatment. A
 3792 reasonable length of time to consider for observation is 4 to 6 hours in most patients who
 3793 have experienced anaphylaxis, with prolonged observation times or hospital admission
 3794 for patients with severe or refractory symptoms.^{9,26}

3795 **6.3.2 DISCHARGE PLAN FOLLOWING TREATMENT FOR FOOD-INDUCED** 3796 **ANAPHYLAXIS**

3797 All patients who have experienced anaphylaxis should be sent home with the following:

- 3798 • Anaphylaxis Emergency Action Plan
- 3799 • Epinephrine auto-injector(s) (or two-pack prescription)
- 3800 • Plan for monitoring auto-injector expiration dates
- 3801 • Plan for arranging further evaluation, and
- 3802 • Printed information about anaphylaxis and its treatment³¹

3803 **6.3.2.1 Anaphylaxis Emergency Action Plan**

3804 Patients should be given a written Anaphylaxis Emergency Action Plan that contains
 3805 information about self-injection of epinephrine prior to discharge^{25,73} (see Sample Action
 3806 Plan in Appendix C). Patients should be instructed on the value of medic-alert jewelry to
 3807 easily identify themselves as a patient with anaphylaxis potential and their food allergen
 3808 triggers.

3809 **6.3.2.2 Epinephrine auto-injector (or two-pack prescription)**

3810 All patients experiencing anaphylaxis should be provided directly with an epinephrine
 3811 auto-injector or, if this is not possible, with a prescription (recommend prescription is for
 3812 an epinephrine two-pack), and advised to fill it immediately.

3813

3814 Other patients that should be given an epinephrine autoinjector include

- 3815 ● Patients with a history of a prior systemic allergic reaction
- 3816 ● Patients with food allergy and asthma
- 3817 ● Patients with a known food allergy to peanut, tree nut, fish, and crustacean
- 3818 shellfish (i.e., allergens known to be associated with more fatal and near-fatal
- 3819 allergic reactions)

3820 In addition, consideration should be given to prescribing an epinephrine autoinjector to
3821 all food allergic patients having IgE-mediated reactions because of the inability of the
3822 patient to predict the severity of any subsequent reactions.

3823 Instructions in the proper use of epinephrine autoinjectors should be reviewed verbally
3824 and accompanied by a written Anaphylaxis Emergency Action Plan. Special care should
3825 be taken to explain the importance of carrying epinephrine at all times and on advising
3826 the patient to make sure that family and friends are aware of the risks of anaphylaxis, the
3827 patient's triggers, and how to administer epinephrine. Where allowed by state law,
3828 students should be advised to carry their epinephrine auto-injector to and from school.

3829 **6.3.2.3 Plan for monitoring auto-injector expiration dates**

3830 Patients and family members should be advised to regularly check the epinephrine auto-
3831 injector expiration dates. Ideally, the prescribing physician's office should notify patients
3832 (or the family members of patients who are minors) by telephone and/or mail that their
3833 auto-injector will soon reach its expiration date and that the prescription should be
3834 renewed.

3835 **6.3.2.4 Plan for arranging further evaluation**

3836 Advice should be provided to the patient regarding follow-up with his or her primary care
3837 provider within 1 to 2 weeks after a food-induced anaphylaxis event. Additional
3838 information may be needed about obtaining a referral to an allergist or about how to seek
3839 consultation directly with an allergist for testing, diagnosis, and ongoing management of
3840 the allergy. Direct communication between the treating clinician and the primary care
3841 provider is recommended in order to ensure that appropriate follow-up is attained.

3842 **6.3.2.5 Printed information about anaphylaxis and its treatment**

3843 The emergency doctor, treating physician, or healthcare provider should provide the
3844 patient who has been treated for anaphylaxis and is subsequently leaving the emergency
3845 department or hospital with printed information about anaphylaxis and its treatment.⁷⁴
3846 The mnemonic "SAFE" has been developed to remind clinicians of the four basic action
3847 steps suggested for these patients.⁷⁴ The SAFE (Seek support, Allergen identification and
3848 avoidance, Follow-up with specialty care; Epinephrine for emergencies) counseling is
3849 outlined below and has been incorporated into printable patient information materials.

- 3850 ● **Seek support** – the healthcare provider should advise patients that
- 3851 ○ They have experienced anaphylaxis, which is a life-threatening condition.

- 3852 ○ Symptoms of the current episode may recur up to three days after the initial
- 3853 onset of symptoms.
- 3854 ○ They are at risk for repeat episodes of anaphylaxis in the future.
- 3855 ○ At the first sign of recurrence of symptoms, the patient should give
- 3856 himself/herself epinephrine and then immediately call an ambulance or get to
- 3857 the nearest emergency facility.
- 3858 ● **Allergen identification and avoidance** – the healthcare provider should
- 3859 ○ Make efforts to identify the patient's trigger (through history and with follow-
- 3860 up for further testing) before the patient is discharged.
- 3861 ○ Emphasize the importance of subsequent testing to determine and verify the
- 3862 trigger, so that it can be successfully avoided in the future.
- 3863 ● **Follow-up with specialty care** – the healthcare provider should
- 3864 ○ Advise the patient to follow-up with their primary care provider and that they
- 3865 may benefit from subspecialty allergy evaluation.
- 3866 ● **Epinephrine for emergencies** – the healthcare provider should
- 3867 ○ Provide the patient with self-injectable epinephrine or a prescription, and
- 3868 educate the patient about its use prior to discharge.
- 3869 ○ Advise the patient and/or family members to routinely check the expiration
- 3870 date of the auto-injector.

3871 Other sources of accurate patient information, accessible through the Internet, include the
 3872 American Academy of Allergy, Asthma and Immunology (www.aaaai.org) and the
 3873 American College of Allergy, Asthma and Immunology (www.acaai.org).

3874 **6.4 KNOWLEDGE GAPS**

3875 Due to a lack of controlled studies in the area of food-induced anaphylaxis management,
 3876 significant knowledge gaps exist in several areas including

- 3877 ● The role of a variety of medications (e.g., corticosteroids, antihistamines, others)
- 3878 in acute management and prevention of follow-up reactions.
- 3879 ● The true incidence of biphasic and protracted reactions related to food-induced
- 3880 anaphylaxis and appropriate medical management to prevent or effectively treat
- 3881 these reactions.
- 3882 ● The relative benefits of certain alternative routes of epinephrine administration
- 3883 (e.g., sublingual).
- 3884 ● The most effective methods for appropriate education of patients, families,
- 3885 healthcare providers and others to most effectively protect patients at risk for
- 3886 anaphylaxis related to food proteins.

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~~4058~~ * Supplementary document identified by the EP
4060

4061 **APPENDIX A: COORDINATING COMMITTEE MEMBER**
4062 **ORGANIZATIONS**

- 4063 **Agency for Healthcare Research and Quality (AHRQ)**
- 4064 **Allergy and Asthma Network Mothers of Asthmatics (AANMA)**
- 4065 **American Academy of Allergy, Asthma and Immunology (AAAAI)**
- 4066 **American Academy of Dermatology (AAD)**
- 4067 **American Academy of Emergency Medicine (AAEM)**
- 4068 **American Academy of Pediatrics (AAP)**
- 4069 **American Academy of Physician Assistants (AAPA)**
- 4070 **American College of Allergy, Asthma and Immunology (ACAAI)**
- 4071 **American College of Emergency Physicians (ACEP)**
- 4072 **American College of Gastroenterology (ACG)**
- 4073 **American College of Physicians (ACP)**
- 4074 **American Dietetic Association (ADA)**
- 4075 **American Nurses Association (ANA)**
- 4076 **American Partnership for Eosinophilic Disorders (APFED)**
- 4077 **American Society for Nutrition (ASN)**
- 4078 **American Thoracic Society (ATS)**
- 4079 **Asthma and Allergy Foundation of America (AAFA)**
- 4080 **Centers for Disease Control and Prevention (CDC)**
- 4081 **European Academy of Allergy and Clinical Immunology (EAACI)**
- 4082 **Food Allergy and Anaphylaxis Network (FAAN)**
- 4083 **Food Allergy Initiative (FAI)**
- 4084 **Inflammatory Skin Disease Institute (ISDI)**
- 4085 **National Association of School Nurses (NASN)**
- 4086 **National Heart, Lung and Blood Institute (NHLBI)**
- 4087 **National Institute of Allergy and Infectious Disease (NIAID)**
- 4088 **National Institute of Child Health and Human Development (NICHD)**
- 4089 **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**
- 4090 **National Institute of Nursing Research (NINR)**
- 4091 **North American Society for Pediatric Gastroenterology, Hepatology and Nutrition**
- 4092 **(NASPGHAN)**
- 4093 **Society for Pediatric Dermatology (SPD)**
- 4094 **Society of Pediatric Nurses (SPN)**
- 4095 **United States Department of Agriculture (USDA)**
- 4096 **United States Environmental Protection Agency (EPA)**

4098 **APPENDIX B: EXPERT PANEL MEMBERS**

4099 **Chair:**

4100 **Joshua A. Boyce, MD**

4101 Associate Professor of Medicine

4102 Harvard Medical School

4103 Specialty: Allergy, Pediatric Pulmonology

4104 **Panelists:**

4105 **S. Hasan Arshad, MBBS, MRCP, DM, FRCP**

4106 Reader in Allergy, Infection, Inflammation and Repair

4107 University of Southampton

4108 Specialty: Allergy/Epidemiology

4109 **Amal Assa'ad, MD**

4110 Professor, Director, Allergy & Immunology fellowship

4111 Associate Director, Division of Allergy & Immunology

4112 Cincinnati Children's Hospital Medical Center

4113 Specialty: Allergy/Pediatrics

4114 **Sami L. Bahna, MD, DrPH**

4115 Professor of Pediatrics & Medicine, Chief of Allergy & Immunology Section, Director of

4116 Allergy & Immunology Training Program

4117 Louisiana State University Health Sciences Center

4118 Specialty: Allergy

4119 **Lisa A. Beck, MD**

4120 Associate Professor of Dermatology, Director of Translational Research

4121 University of Rochester Medical Center

4122 Specialty: Dermatology

4123 **A. Wesley Burks, MD**

4124 Professor, Department of Pediatrics

4125 Duke University

4126 Specialty: Allergy/Pediatrics

4127 **Carol Byrd-Bredbenner PhD, RD, FADA**

4128 Professor of Nutrition/Extension Specialist

4129 Rutgers, The State University of New Jersey

4130 Specialty: Nutrition/Education

4131

- 4132 **Carlos A. Camargo, MD, DrPH**
4133 Director, EMNet Coordinating Center
4134 Massachusetts General Hospital
4135 Harvard Medical School
4136 Specialty: Epidemiology/Emergency Medicine
- 4137 **Lawrence Eichenfield, MD**
4138 Professor, Department of Pediatrics and Medicine (Dermatology)
4139 University of California, San Diego School of Medicine
4140 Director, Children's Specialists of San Diego
4141 Rady Children's Hospital, San Diego
4142 Specialty: Dermatology/Pediatrics
- 4143 **Glenn T. Furuta, MD**
4144 Associate Professor
4145 University of Colorado Denver, School of Medicine
4146 Specialty: Gastroenterology/ Pediatrics
- 4147 **Jon M. Hanifin, MD**
4148 Professor of Dermatology
4149 Oregon Health and Science University
4150 Specialty: Dermatology
- 4151 **Carol Jones, RN, AE-C**
4152 Certified Asthma Nurse Educator & Consultant
4153 Specialty: Nursing, Education
- 4154 **Stacie M. Jones, MD**
4155 Professor of Pediatrics, Chief of Allergy/Immunology
4156 University of Arkansas for Medical Sciences and Arkansas Children's Hospital
4157 Specialty: Allergy/Pediatrics
- 4158 **Monica Kraft, MD**
4159 Professor of Medicine
4160 Director, Duke University Asthma Allergy and Airway Center
4161 Duke University Medical Center
4162 Specialty: Pulmonology/Internal Medicine/Critical Care
- 4163 **Bruce D. Levy, MD**
4164 Pulmonary and Critical Care Medicine
4165 Brigham and Women's Hospital
4166 Specialty: Pulmonology
- 4167

- 4168 **Phil Lieberman, MD**
4169 Clinical Professor of Medicine, Division of Allergy and Immunology
4170 Clinical Professor of Pediatrics
4171 University of Tennessee
4172 Specialty: Allergy
- 4173 **Stefano Luccioli, MD**
4174 Senior Medical Advisor
4175 Office of Food Additive Safety, CFSAN, FDA
4176 Specialty: Allergy/Internal Medicine
- 4177 **Kathleen M. McCall, BSN, RN**
4178 Case Manager, Primary Care
4179 Children's Hospital of Orange County
4180 Specialty: Nursing
- 4181 **Hugh A. Sampson, MD**
4182 Professor of Pediatrics
4183 Mount Sinai School of Medicine
4184 Specialty: Allergy/Pediatrics
- 4185 **Lynda C. Schneider, MD**
4186 Director, Allergy Program, Director, Atopic Dermatitis Center
4187 Children's Hospital, Boston
4188 Associate Professor of Pediatrics
4189 Harvard Medical School
4190 Specialty: Allergy/Pediatrics
- 4191 **Ronald A. Simon, MD**
4192 Head, Division of Allergy, Asthma and Immunology, Adjunct Professor, Dept. Of
4193 Molecular & Experimental Medicine
4194 The Scripps Research Institute
4195 Specialty: Allergy/Internal Medicine
- 4196 **F. Estelle R. Simons, MD**
4197 Professor, Department of Pediatrics & Child Health
4198 Professor, Department of Immunology
4199 University of Manitoba
4200 Specialty: Allergy/Pediatrics
- 4201 **Stephen J. Teach, MD, MPH**
4202 Associate Chief, Division of Emergency Medicine
4203 Children's National Medical Center
4204 Specialty: Pediatrics/Emergency Medicine

4205 **Robert A. Wood, MD**
4206 Professor of Pediatrics
4207 Johns Hopkins School of Medicine
4208 Specialty: Allergy/Pediatrics

4209 **Barbara P. Yawn, MD, MPH, MSc**
4210 Director, Department of Research
4211 Olmstead Medical Center
4212 Specialty: Family Medicine

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4214 **APPENDIX C: SAMPLE OF AN ANAPHYLAXIS**
4215 **EMERGENCY ACTION PLAN**

4216
4217 **NAME:** _____ **AGE:** _____

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4219 **ALLERGY TO:** _____

4220
4221 **Asthma: Yes (high risk for severe reaction) No**

4222
4223 **Other health problems besides anaphylaxis:**
4224 _____
4225 _____

4226
4227
4228 **Concurrent medications, if any:**
4229 _____
4230 _____

4231 **SYMPTOMS OF ANAPHYLAXIS INCLUDE:**

- 4232
- 4233 • MOUTH itching, swelling of lips and/or tongue
 - 4234 • THROAT* itching, tightness/closure, hoarseness
 - 4235 • SKIN itching, hives, redness, swelling
 - 4236 • GUT vomiting, diarrhea, cramps
 - 4237 • LUNG* shortness of breath, cough, wheeze
 - 4238 • HEART* weak pulse, dizziness, passing out
- 4239

4240 Only a few symptoms may be present. Severity of symptoms can change quickly.
4241 *Some symptoms can be life-threatening! **ACT FAST!**

4242 **WHAT TO DO:**

4243
4244 **1. INJECT EPINEPHRINE IN THIGH USING (check one):**

- 4245
- 4246 EpiPen Jr (0.15 mg) Twinject 0.15 mg
 - 4247 EpiPen (0.3 mg) Twinject 0.3 mg
- 4248

4249
4250 Other medication/dose/route:

4251 _____
4252 **IMPORTANT: ASTHMA PUFFERS AND/OR ANTIHISTAMINES CAN'T BE DEPENDED ON**
4253 **IN ANAPHYLAXIS!**

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2. CALL 911 or RESCUE SQUAD (BEFORE CALLING CONTACTS)!

3. EMERGENCY CONTACTS

#1: home _____ work _____ cell _____
#2: home _____ work _____ cell _____
#3: home _____ work _____ cell _____

DO NOT HESITATE TO GIVE EPINEPHRINE!

COMMENTS:

Doctor's Signature/Date Parent's Signature (for individuals under age 18 yrs)/Date

Adapted from J Allergy Clin Immunol 1998;102:173–176 and J Allergy Clin Immunol 2006;117:367–377