1.03-3.5). This trial is published in abstract form only, with no details on the randomization being available.

Another recent systematic review by de Silva et al. found seven high-quality studies on maternal diets and also concluded that "overall, the evidence is not strong enough to recommend changing the diet or supplements of pregnant or breastfeeding women" to prevent food allergies in infants at normal or high risk of food allergies (de Silva et al., 2014).

The committee concludes that, to date, study findings provide limited evidence to support or discourage eliminating allergenic foods from the diet of pregnant or lactating women at high risk of having a child with allergies. Because the evidence about the benefits of consuming or eliminating allergenic foods during pregnancy and lactation is not clear, additional RCTs are warranted before providing advice in this regard. Studies exploring the effect on the development of food allergies in children of intake of allergens by the mother are in progress.

Breastfeeding

Breastfeeding is an important early life factor that determines an individual's gut microbiota and likely indirectly modulates immune responses. In addition, breastfeeding transfers bioactive compounds from the mother to the child that can also influence immune responses. However, the evidence assessing any potential link between breastfeeding and food allergies risk is not clear. Systematic analysis of observational studies on the protective effect of breastfeeding have shown conflicting results, and many of the studies included were conducted decades ago when food allergy was uncommon and methods of assessment were limited (Grimshaw et al., 2009). Most systematic reviews have failed to find a specific beneficial effect of breastfeeding on food allergy or food sensitization (de Silva et al., 2014; Kramer and Kakuma, 2012). Moreover, two cohort studies reviewed in de Silva et al. (2014) suggested that exclusive breastfeeding for 8 weeks did not reduce the risk of cow milk allergy (measured by parents report followed by SPT and oral food challenge) (Saarinen et al., 1999) and breastfeeding for 5 months or more may increase the likelihood of sensitization to egg in infants at high risk of atopy, although food allergy was not assessed (Wetzig et al., 2000). Importantly, the apparent negative effects of extensive breastfeeding may relate to the delayed introduction of first complementary foods rather than the effects of breast milk per se (see the section "Dual Allergen Exposure Hypotheses" in this chapter). Alternatively, these recent findings of increased risk of breastfeeding may simply be a misinterpretation of the data related to the reverse causation phenomenon (see the section "Methodological Limitations" in this chapter). One study found that the effects

of breastfeeding on food sensitization can be modified by genetic variants relevant to allergic diseases (Hong et al., 2011).

Lodge et al. undertook a systematic review to assess the role of breastfeeding in food allergy (Lodge et al., 2015). The review included nine cohort and four cross-sectional studies. The numbers of participants ranged from 163 to 21,766 (cohort studies) and from 1,278 to 13,110 (cross-sectional studies). No association with food allergy was found for more versus less[9] breastfeeding in the pooled estimate (6 cohort and 6 cross-sectional), although study heterogeneity was high. Various sub-analyses failed to find any protective association of breastfeeding for food allergy. The primary issue concerning the quality of these studies was the poor accuracy of outcome assessment. Only two studies used OFCs, the recognized gold standard for food allergy diagnosis; most studies relied on parental report of symptoms or on physician diagnosis.

The committee's review of the evidence found eight studies (seven cohort and one cross-sectional) that explored breastfeeding as a food allergy risk determinant. Although Ivakhnenko and Nyankovskyy showed that infants (N=240) who were breastfed had significant risk of developing an allergy to cow milk protein and had gastrointestinal symptoms of food allergy by age 18 months compared with those who were fed standard infant formula, the risk of bias of this trial was high due to unclear definitions and diagnoses of food allergy outcomes and high dropout rates (Ivakhnenko and Nyankovskyy, 2013). Two studies performed only unadjusted analyses so the results (mostly no significant associations) are likely to be confounded (Grimshaw et al., 2014; McGowan et al., 2015). The other four cohort studies showed associations between longer duration of breastfeeding (any or exclusive) and a lower risk of developing cow milk sensitization (Liao et al., 2014; N=258), food allergy (Stelmach et al., 2014; N=501; aOR: 0.88; 95% CI: 0.82-0.95), or multiple food allergy (predominantly egg) (Peters et al., 2015; N=5276; aOR: 1.17; 95% CI: 1.09-1.24) after adjusting for potential confounders. The single cross-sectional study did not find a significant association between exclusive breastfeeding (poorly defined) and food allergies among children (N=386) ages 0 to 18 years with atopic dermatitis. Luccioli et al. collected data from prospective cohort of children (N=1,363) who participated in the Infant Feeding Practices Study (IFPS) II and also found no significant relationship between breastfeeding for various periods and food allergies (Luccioli et al., 2014). Only some studies used OFC as an outcome measure (Grimshaw et al., 2014; Peters et al., 2015). The single

[9] More or Less: The authors included all studies. When multiple odds ratios were available for a single study, the authors preferentially selected estimates for exclusive breastfeeding, then longest duration versus shortest. When multiple ages of outcome were available, the authors chose the oldest up to 18 years.

cross-sectional study did not find a significant association between exclusive breastfeeding (poorly defined) and food allergies among children, ages 0 to 18 years, with atopic dermatitis (Mailhol et al., 2014).

As mentioned above, investigation of the role of breastfeeding in allergic disease is particularly prone to confounder bias because families who are at high risk of allergy are more likely to breastfeed, as recommended by some guidelines. In addition, the composition of human milk changes from colostrum to late lactation and throughout the day, and differs from mother to mother (Ballard and Morrow, 2013) and could therefore affect health outcomes of the child. Compounding the difficulties in this area is the inability to randomize to a nonbreastfeeding arm, as this would be unethical given the many well-established benefits of breastfeeding, such as protection against some chronic diseases, obesity, and infections.

The committee concludes that due to inconsistencies in results from prospective studies, the evidence that breastfeeding is protective against food allergies is limited. Strong evidence is unlikely to be forthcoming because of the ethical inability to randomize a population to breastfeeding alternatives. However, additional well-designed prospective research studies in infants at low and high risk for food allergy are needed.

Types of Infant Formula

Significant interest has been expressed in the use of modified infant formulas—especially partially hydrolyzed formulas (PHF), which include longer cow milk peptides, and extensively hydrolyzed cow's milk formulas (EHF), which include di- and tri-peptides derived from cow milk protein—as a way to avoid allergen exposure and prevent early childhood allergic disease. As a result of demand from families with a history of allergy seeking readily available primary prevention interventions, industry has responded with the development of a variety of "allergy prevention" formulae, and expert bodies have provided recommendations regarding their use for preventing allergies. Some infant feeding guidelines have recommended that hydrolyzed formula can be considered as primary prevention therapy for some allergic diseases. In the United States, a policy statement from the American Academy of Pediatrics indicated that in studies of infants at high risk of atopy, modest evidence supports the delay or prevention of onset atopic dermatitis by the use of hydrolyzed, and particularly extensively hydrolyzed, formulas (Greer et al., 2008). In Australia, the Australasian Society of Clinical Immunology and Allergy *Guidelines: Infant Feeding and Allergy Prevention* no longer recommends hydrolyzed formulas as primary prevention therapy for allergic diseases. The guidelines now state, "Based on a recently published review of studies (Boyle et al., 2016), no consistent convincing evidence supports a protective role for partially hydrolyzed for-

mulas (usually labelled 'HA' or Hypoallergenic) or extensively hydrolyzed formulas for the prevention of eczema, food allergy, asthma or allergic rhinitis in infants or children" (ASCIA, 2016b).

A Cochrane review supports the use of hydrolyzed formula to prevent allergy in high-risk infants who are unable to be completely breastfed but not for those infants who can breastfed (Osborn and Sinn, 2006, 2009). Critics of this Cochrane review have pointed out that it suffers from small-study publication bias (i.e., scarcity of small negative studies) (Lowe et al., 2013) and thus the beneficial effect of PHF was likely overestimated. Due to the methodological concerns and inconsistency of the findings of the studies included in the review, the authors themselves recommend that further larger trials be conducted. Subsequently, new evidence from a large intervention trial of 620 high-risk infants (the Melbourne Atopic Cohort Study) has emerged. Findings from this trial challenge the effectiveness of PHF (Lowe et al., 2011).

The German Infant Nutritional Intervention (GINI) study was a trial aimed at exploring the effect of hydrolyzed formulas (compared to cow milk formula) in preventing allergic diseases in infants at high risk of atopy. Infants (N=2,252) were randomly assigned at birth to receive partially or extensively hydrolyzed whey formula, extensively hydrolyzed casein formula, or cow milk formula as milk substitute for the first 4 months when breastfeeding was insufficient. In a follow up until the children were age 6 years, hydrolyzed infant formulas prevented eczema and allergic manifestation (atopic dermatitis, food allergy, allergic urticaria, asthma, and hay fever/allergic rhinitis) (von Berg et. al., 2008). However, subsequent results showed little evidence of an ongoing preventive effect between the ages of 7 and 10 years (von Berg et al., 2013a). These more recent findings have not yet been incorporated into the Cochrane review. Likewise, the European Academy of Allergy & Clinical Immunology (EAACI) systematic review included both the Cochrane review and the Melbourne Atopic Cohort Study as well as the preliminary GINI results but did not include the latest results from the GINI study. Therefore, their conclusion supported the protective effect for PHF. Interestingly, the most recent findings from the GINI study suggest that casein-predominant EHF might be expected to have a greater biological effect than PHF because the formula is more extensively modified (von Berg et al., 2013a,b). However, most infant feeding guideline recommendations are based on the reality that PHF is both cheaper and more palatable than EHF and therefore should be considered instead of EHF. Additionally, in some countries EHF is only available with a prescription, which significantly increases costs to the health care system.

Most recently, Boyle et al. conducted a systematic review and meta-analysis of studies to determine whether feeding infants with hydrolyzed formulas reduces their risk of allergic disease (Boyle et al., 2016). Their

search yielded 37 intervention trials of more than 19,000 participants, although few studies included in the meta-analysis were published in the past 10 years. For the majority of studies, infants were considered to be at high risk of allergy because a first degree relative had a history of allergic disease. Overall, the pooled data showed no significant reduction in risk of any food allergy in infants ages 0 to 4 years when they were fed EHF or PHF compared to standard cow milk formula. On concluding the review, the authors found that previous studies suffered from unclear or high risk of bias. The review also showed evidence of conflict of interest and had inadequate methods of randomization and treatment allocation (selection bias). The authors recommended that international infant guidelines should be revised to remove the recommendation that hydrolyzed formula protects against allergic disease. In addition, a review of systematic reviews also stated that evidence is insufficient to conclude that the use of hydrolyzed formulas may reduce food allergy or sensitization when compared with standard formula in children with high atopy risk, and no evidence supports hydrolyzed formulas over breast milk for prevention of food sensitization or food allergy (Lodge et al., 2013).

The committee concludes that the studies on the effects of PHF or EHF for preventing food allergies have methodological flaws and their findings are inconsistent. Therefore, evidence on the effect of PHF or EHF for the prevention of food allergies is limited. If this area were to be investigated, high-quality RCT studies on the effects of PHF and EHF to determine whether hydrolyzed infant formulas influence the onset of food allergies would be needed before the use of these formulas could be recommended for prevention.

Dual Allergen Exposure Hypothesis

The "Dual Allergen Exposure" hypothesis proposes that allergic sensitization to foods may occur through exposure to low doses of allergen through the skin due to food allergens in the environment being absorbed through a damaged skin barrier (such as in eczema or presence of filaggrin loss-of-function mutations). This hypothesis also proposes that oral exposure to these allergens through consumption of allergenic foods early in infancy, before skin sensitization, leads to lasting oral tolerance and prevents the development of sensitization and allergy even with subsequent skin exposure (Du Toit et al., 2016; Lack, 2012; Lack et al., 2003) (see Figure 5-4).

Mechanistic evidence supporting this hypothesis comes from mouse models (Strid et al., 2005). Recent studies suggest that the activation of innate immune pathways in the skin through thymic stromal lymphopoietin, an interleukin (IL)-7-like cytokine associated with atopic dermatitis

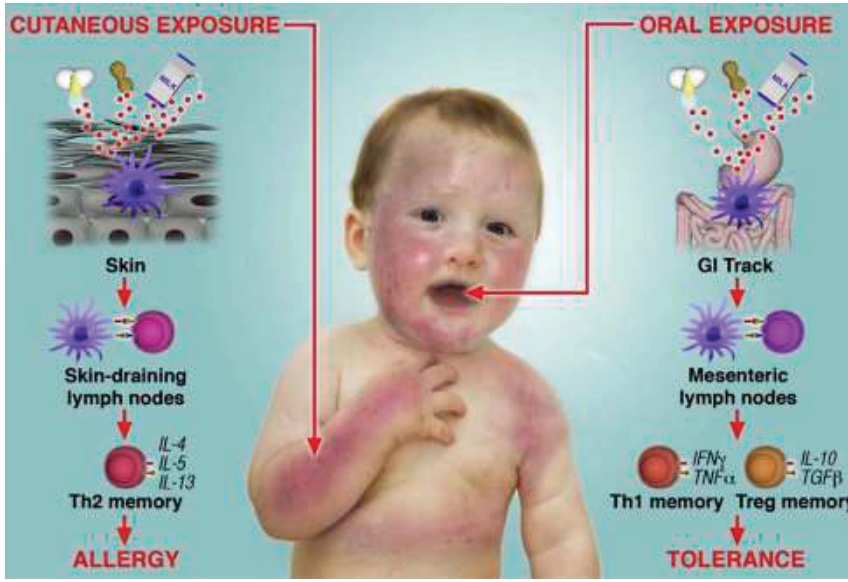

FIGURE 5-4 Dual-allergen exposure hypothesis for the pathogenesis of food allergy. Allergic sensitization can result from cutaneous exposure and tolerance is favored as a result of oral exposure to food.
NOTE: GI = gastrointestinal, Treg = T regulatory.
SOURCE: Lack, 2012. Reprinted with permission from Elsevier.

and asthma, and basophil activation may play a key role in development of food allergy secondary to cutaneous sensitization in animal models (Muto et al., 2014; Noti et al., 2014).

Studies of human populations to date have primarily focused on peanut allergy. One human study demonstrated that peanut allergens can be found in the household environment and that higher exposure to environmental peanut antigens appears to increase the risk of peanut allergy in children with either filaggrin loss-of-function mutations or atopic dermatitis (Brough et al., 2014).

Other contextual factors support this hypothesis. Weaning practices in developed countries, coupled with high eczema rates may contribute to the high prevalence of food allergy. In the Western world, eczema prevalence is as high as 25 percent by age 1 year (Martin et al., 2013). (As noted previously, eczema frequently co-associates with food allergy, with 50 percent of those with early onset, moderately severe eczema developing food allergy by age 1 year [Martin et al., 2015].) This, coupled with recommendations

in the late 1990s and early 2000s to delay allergenic solids (e.g., egg until age 24 months and peanut until age 3 years) provide the correct temporal framework for this practice to have had a potential effect on the epidemic (Koplin and Allen, 2013). The following section presents the evidence on the main factors related to this hypothesis, namely skin barrier function and timing of introduction of foods. The section also includes the results from recent studies on introduction of diet diversity in early life.

Adequate Early Life Skin Barrier Function

It is important to note that mutations leading to filaggrin loss-of-function appear to be equally common among individuals with asymptomatic food sensitization and those with true food allergy (Tan et al., 2012a), suggesting that filaggrin confers a risk for food sensitization—the first step to food allergy—but not for food allergy itself. Previous studies reporting an association with food allergy were not designed to untangle any differential effect between sensitized tolerant and sensitized allergic individuals (Brown et al., 2011). Recent data from the Isle of Wight birth cohort used path analysis to demonstrate that the effect of filaggrin loss-of-function mutations on food allergy at age 10 years occurred indirectly through an effect on eczema and food sensitization in early childhood (Venkataraman et al., 2014). Together, these findings suggest that skin barrier function plays a role in sensitization status but not in food allergy or tolerance.

Two recent RCTs have investigated the application of daily moisturizer from birth in an attempt to reduce infantile eczema. Although the studies are small in size, the results support the idea that the integrity of the skin barrier is related to preventing food allergy. One RCT in the United States and the United Kingdom (N=124) examined the effects of an intervention that consisted of the use of an emollient at least once per day on neonates at risk of atopic dermatitis (Simpson et al., 2014). Atopic dermatitis was measured at 6 months. The results demonstrated a significant protective effect against atopic dermatitis (relative risk [RR]: 0.50; 95% CI: 0.28-0.9; P=0.017). The second trial examined the effect of using a moisturizer from the first week of life on eczema as a primary outcome and egg sensitization (but not allergy) as a secondary outcome in a group of 118 neonates at high risk of atopic dermatitis (Horimukai et al., 2014). At 32 weeks postnatal age, application of moisturizer to neonates was effective at preventing atopic dermatitis after 32 weeks, but unfortunately the trial showed no evidence of a reduction in sensitization to egg white in this relatively small study of 118 infants. However, a higher proportion of infants with atopic dermatitis showed egg sensitization compared with infants without atopic dermatitis.

The committee concludes that limited but consistent evidence on mutations on the filaggrin gene and on preventing eczema at early age suggests that impairment of skin barrier function plays a role in sensitization status as the first step on the path to food allergy.

Timing of Introduction of Solids and Infant Feeding

The dual antigen exposure hypothesis states that the second factor in the two steps to food allergy is the delay in oral allergen exposure. Until recently, delayed introduction of solids and particularly allergenic solids into the infant's diet was a strategy adopted in many countries with the aim of reducing or preventing food allergies. Although exclusive breastfeeding for the first 6 months of life has been universally recommended in all countries to promote its health benefits (WHO, 2016), as described above, no evidence indicates that exclusive breastfeeding prevents the development of food allergies.

In 2008 and 2009, specific dietary advice to avoid peanuts in the United Kingdom and the United States, respectively, was rescinded (Greer et al., 2008; NHS, 2015a) based largely on the premise that evidence was insufficient to promote avoidance as a strategy to prevent food allergies. More recent advice does not state whether infants should actively receive allergenic foods, and if so at what age. Indeed, a recent nationwide UK dietary survey showed that only 8 percent of children younger than age 1 year had consumed any foods containing peanut (McAndrew et al., 2012).

The EAACI systematic review includes three cohort studies that found that the concept of delaying solid foods or cow milk consumption until 4 months of age does not appear to confer any benefit in terms of food allergies (de Silva et al., 2014). Most recently, evidence has been accumulating about the benefits of introducing allergens early. This section will focus on the most recent RCTs that evaluate the benefits of introducing allergens early in life.

In 2008, Du Toit et al. found that the level of peanut allergy in Jewish children in the United Kingdom was 10-fold higher than that of Jewish children in Israel and that median consumption of peanut protein was 0 g per month in the United Kingdom versus 7.1 g per month in Israel[10] (Du Toit et al., 2008). Based on these results, Du Toit et al. conducted a large RCT to formally assess whether early introduction of peanut prevented the development of peanut allergy at age 5 years (Du Toit et al., 2015). The LEAP (Learning Early about Peanut Allergy) study randomized 640 highly

[10] At the time, it was common practice in Israel to introduce a peanut snack (Bamba) as a weaning food into the diet of infants around the age of 4 to 6 months. In contrast, UK guidelines at the time recommended that children avoid peanut until after age 3 years.

atopic children with severe eczema and/or egg allergy to either consumption or avoidance of peanut at ages 4 to 11 months and the intervention continued until the children were age 5 years. The results showed that early consumption of peanut reduced the prevalence of peanut allergy (diagnosed by DBPCOFC) at age 5 years by more than 80 percent. The reduction was effective in children who were either SPT negative or SPT positive to peanut (wheals of 1, 2, 3, or 4 mm). As 17 percent of the LEAP cohort had peanut-specific IgE ≥0.35 at entry into the study and 27 percent had detectable IgE (≥0.1 kU_A/L), prevention of peanut allergy was occurring for the majority of children after IgE sensitization had occurred; this represents secondary prevention (Du Toit et al., 2013). However, for infants in the group who were SPT negative at enrollment and who had no detectable IgE, early consumption of peanut also reduced the prevalence of peanut allergy (6 percent and 1 percent in the peanut avoidance group and in the peanut consuming group, respectively). This primary prevention strategy also was effective in a secondary analysis in children of different races.

As reviewed in Chapter 4, at the moment, we do not have definitive biomarkers to define tolerance. It is of interest that during the LEAP study, an early rise in peanut-specific IgG4 and peanut-specific IgG4/IgE ratio occurred in the peanut-consuming group (Du Toit et al., 2015). A high peanut-specific IgG4/IgE ratio was associated with protection against peanut allergy. Although the peanut-specific IgG4/IgE ratio decreased in the original peanut-consuming group during the period of peanut avoidance in the follow-up LEAP-On Study (Du Toit et al., 2016), it remained significantly higher than in the original peanut avoidance group. Interestingly in LEAP, peanut-specific IgE was not significantly different between the original peanut consuming and peanut avoidance groups throughout the study. However, peanut-specific IgE to Ara h 2 started to decline in the original peanut consuming group after 2.5 years of consumption, and continued to decline despite 1 year of peanut avoidance in that group between ages 5 and 6 years (Du Toit et al., 2016). This suggests potentially that high production of allergen-specific IgG4 may be important in the initiation of tolerance and that inhibition of IgE synthesis may be important in long-lived tolerance.

In order to determine whether early introduction of peanut was effective at preventing peanut allergy in the absence of ongoing peanut consumption, the LEAP-On Study was designed (Du Toit et al., 2016). Children (N=566) from the original LEAP cohort, irrespective of whether they were in the original peanut consumer or avoidant group, were asked to completely avoid peanut consumption for 1 year and then their peanut allergy status was determined by OFC, SPT, and specific IgE. Despite high adherence to this protocol of avoidance, the protective effects of early consumption remained and the original peanut consuming group had a 74 percent reduction in peanut allergy at age 6 years compared to the original peanut avoid-

ant group. Another follow-up study, the LEAP Adlib Study, is currently being designed. In this trial the original LEAP participants will continue to be followed up for a 4-year period of ad libitum consumption of peanut to determine whether the effects of early introduction remain protective.

In regard to other foods, observational studies suggest that delayed introduction of egg (Koplin et al., 2010), cow milk (Katz et al., 2010), and wheat (Poole et al., 2006) are associated with an increased risk of those respective food allergies. Various trials are in progress to confirm or refute these observations (see Table 5-1). Early evidence from Koplin and Allen (2013, p. 830) "suggests that if a window of opportunity for promoting tolerance exists, it may be different for each food" (Koplin and Allen, 2013, p. 830). However, further investigation is required. In the large HealthNuts study, where egg allergy was determined by challenge (among other food allergens), it was found that early introduction (age 4 to 6 months) of hen egg in the infant's diet protected against the development of egg allergy, but introduction after 6 months of age was associated with significantly increased risk of developing egg allergy and even more so if introduced after age 9 months (Koplin et al., 2010). The results from the LEAP study (Du Toit et al., 2015) also are supported by data from the Solids Timing for Allergy Research (STAR) trial, which randomized 86 infants with eczema to egg avoidance or early regular egg consumption from age 4 months. The study found a lower, nonsignificant prevalence of egg allergy by 12 months in the intervention group (33% versus 51%; P=0.11) (Palmer et al., 2013). In a large birth cohort study conducted in Israel, IgE-mediated cow milk allergy did not occur in infants (N=13,019) who had received cow milk–based formula regularly in the first 2 weeks of life. In contrast, children who had formula milk introduced at age 3 to 4 months had the highest rate of cow milk allergy (Katz et al., 2010).

The EAT (Enquiring about Tolerance) intervention trial, which has recently been published, also examined the effects of early introduction of common allergenic foods. Unfortunately, compliance with intervention in this trial was low and the intention to treat analysis did not reveal a protective effect from early introduction of solids. In contrast, the per protocol analysis did suggest that early introduction of other common allergenic foods into the diet of infants may protect against the development of food allergies in general (Perkin et al., 2016). In the EAT study, exclusively breastfed infants (N=1,303) were recruited in the general population and randomly assigned at age 3 months to either introduction of six allergenic foods (cooked egg, peanut, cow milk, sesame, white fish, and wheat) (Early Introduction Group) or to the current recommended practice of exclusive breastfeeding until approximately 6 months of age (Standard Introduction Group). The primary outcome was determined to be food allergy between 1 and 3 years of age determined in nearly all participants by DBPCOFC.

The study showed a modest and nonsignificant 20 percent overall decrease in the rate of food allergies in the Early Introduction Group (5.6 percent compared to 7.1 percent in the Standard Introduction Group). However, in a per protocol analysis, the prevalence of any food allergy was significantly lower in the Early Introduction Group compared to the Standard Introduction Group (2.4 percent versus 7.3 percent; P=0.01) representing a 66 percent reduction in the prevalence of overall food allergy. The effects were most apparent for peanut allergy in the per protocol analysis (0 percent in the Early Introduction Group versus 2.5 percent in the Standard Introduction Group; P=0.003) and for egg allergy (1.4 percent versus 5.5 percent; P=0.009). These changes also were accompanied by decreases in SPT to the foods in the Early Introduction Group. A dose–response analysis revealed that 2 g of peanut protein or egg white protein per week appeared to be most protective against these food allergies. Interestingly 2 g of peanut protein per week is the dose that was observed in the Du Toit et al. study in Israel where children appeared to be protected against peanut allergy (Du Toit et al., 2008).

The EAT study shows that early introduction of foods was safe, as the intervention group did not experience an increased number of reactions compared to the controls. However, it is difficult to make any certain conclusions from the EAT study about the efficacy of early introduction of foods, given that efficacy was seen only in the per protocol group. Although careful analysis did not show any evidence of bias that could account for these results, it is not possible to completely exclude unmeasured bias.

A number of factors appeared to be associated with nonadherence to early introduction of foods relating to atopic predisposition. These include ethnicity, family life, readiness to eat solid foods, and parental perception of possible food allergic reactions (IgE- or non-IgE-mediated). The EAT study therefore suggests that if early introduction of allergenic foods from 3 months of age is to be adopted as a prevention strategy, numerous potential obstacles must be overcome with respect to implementation of adherence. Importantly, early introduction of allergens in the LEAP study or the EAT study did not reduce duration of breastfeeding (Feeney et al., 2016). It is noteworthy, however, that the participants in the EAT study are from the general population rather than a high-risk population and therefore any effect size may be less pronounced compared to the LEAP study. Furthermore, the intervention was more complex because it involved six foods, not one.

Diet diversity Two studies have examined the role of diversity of early life food exposures, which may be one factor that coincides temporally with the rise in food allergy, in the development of food sensitization and food allergy. A prospective birth cohort study of 856 children found that

increased diversity of complementary foods introduced in the first year of life was associated with a reduced risk of food allergy (Roduit et al., 2014). In another prospective longitudinal study of 123 participants, the authors found that dietary patterns in the first year of life consisting of more fresh fruit and vegetables and home-prepared meals were associated with less challenge-proven food allergy by the age of 2 years (Grimshaw et al., 2014).

The committee concludes that results of the LEAP trial provide strong evidence that early introduction of peanut (between 4 and 11 months) is protective against peanut allergy in infants who are at high risk (as defined by early onset eczema or coexistent egg allergy). Limited evidence from observational studies also suggests that delaying the introduction of egg, cow milk, and wheat to decrease risk of those food allergies has no benefits. Results from one RCT show a not significant decrease in food allergy if allergenic foods (i.e., cooked egg, peanut, cow milk, sesame, white fish, and wheat) are introduced starting at 3 months of age. More studies are necessary to assess whether early introduction of other allergenic foods, in addition to peanut, affect food allergy.

Nutritional Immunomodulation Hypothesis

Proper functioning of the immune system is crucial to health, and diet is a major and common exogenous factor modulating immunocompetence. Thus, nutrition research has focused on the role of foods or specific food components in enhancing immune system responsiveness to challenges and thus improving health and reducing disease risks (Albers et al., 2005). Along these lines, evidence supports the notion that sensitization or expression of food allergies does not depend exclusively on the food allergens per se, but on the exposure to other immunomodulatory exposures, such as other dietary factors, during specific critical periods. This section provides an overview of the immunomodulatory capacities of selected food components, including vitamin D, selected fatty acids, and folate. Better knowledge of these interactions should provide additional avenues for preventing and/or ameliorating food allergies.

Vitamin D

Vitamin D has become increasingly recognized as an important regulator of immune response (Adams and Hewison, 2008). $1,25(OH)_2D$ can be converted from 25(OH)D locally based on widespread expression of vitamin D activating enzyme CP27B in a broad spectrum of cells involved in immune response, such as macrophages, B cells, and T cells. This active form of vitamin D exerts its function through interaction with the vitamin D receptor (VDR), which is also present in the above immune cells. Vitamin

D has been demonstrated to inhibit the differentiation of B lymphocytes to plasma cells and suppress immunoglobulin production (Chen et al., 2007). However, the effects of vitamin D on T lymphocytes are more complicated. Vitamin D has been shown to inhibit T cell proliferation and production of Th1 cytokines, which induces a shift in the balance between Th1 and Th2-type cytokines toward Th2 dominance (Cantorna et al., 2004; Iho et al., 1985; Reichel et al., 1987). In contrast, in CD4+ and CD8+ T-cells from human cord blood, vitamin D inhibits IL-12-generated interferon (IFN)-γ production and IL-4 production, as well as IL-4-induced expression of IL-13.

It has been hypothesized that in the presence of vitamin D, T regulatory cells function normally to suppress inappropriate Th1 and Th2 responses to environmental exposures leading to disease (Litonjua and Weiss, 2007). Research suggests that vitamin D deficiency might impair epithelial barrier integrity, which would in turn result in increased and inappropriate mucosal exposure to food antigens and also a pro-sensitization immune imbalance that compromises immunological tolerance (Roider et al., 2013).

Two opposing hypotheses have been proposed regarding the connection between vitamin D and allergic disease in general. In 1999, Wjst postulated that excess vitamin D might be associated with an increased risk of allergic disease based on its effects on the shift in the T-cell phenotype from a balance on Th1/Th2 to aTh2 dominance, and parallel patterns of increased oral vitamin D supplementation with a "Western lifestyle" (Wjst, 2008; Wjst and Dold, 1999). In contrast, Litonjua and Weiss raised an opposite hypothesis, suggesting that vitamin D might protect against asthma and allergies (Litonjua and Weiss, 2007, 2008). They believed that the immune effects of vitamin D are probably found on dendritic cells and Treg cells, and that these effects may differ depending on the stage of human development.

Two lines of ecological enquiry support the more recent hypothesis that low vitamin D may increase the risk of food allergy. First, countries further from the Equator (and thus receiving lower ambient ultraviolet radiation) have recorded more pediatric admissions to the hospital for food allergy–related events, and more prescriptions of hypoallergenic formulas for the treatment of cow milk allergy and adrenaline auto injectors for the treatment of anaphylaxis in children, compared to countries closer to the Equator (Camargo et al., 2007; Mullins et al., 2009, 2010; Rudders et al., 2010). These findings appear to be independent of longitude, socioeconomic status, or physician density. Second, children receiving care at a large medical center in Boston for food-related acute allergic reactions were more likely to be born in autumn/winter than in spring/summer (Vassallo et al., 2010). Similar relationships of food allergy to birth seasonality have been reported in the Southern hemisphere (Mullins

et al., 2011). Furthermore, children residing in Australia's southern states have twice the odds (95% CI: 1.2-5.0) of peanut allergy at age 4 to 5 years and three times (95% CI: 1.0-9.0) the odds of egg allergy than children in the northern states (Osborne et al., 2012). A recent study from Australia described that infants with vitamin D insufficiency were three times more likely to have egg allergy than those who had adequate stores of the vitamin, with the odds increasing to 10-fold among those with two or more food allergies. Furthermore, among food-sensitized infants, those with vitamin D insufficiency were six times more likely to be food allergic than tolerant (Allen et al., 2013). These effects were observed among infants with Australian-born parents but not those with parents born outside Australia. Genetic polymorphisms contribute to variation in vitamin D binding protein levels, explaining almost 80 percent of variation in levels (Koplin et al., 2016). Binding protein levels in turn alter the biological availability of serum vitamin D, with lower levels increasing the availability of serum vitamin D ($25OHD_3$). It was recently described that polymorphisms resulting in lower VDR levels appeared to compensate for adverse effects of low serum vitamin D on food allergy risk (Koplin et al., 2016), presumably by increasing the ability to use available vitamin D. These findings suggest that references ranges for optimal levels of serum vitamin D may need to take into account differences in VDR level.

A few studies have been published on the effect of maternal vitamin D status during pregnancy and the development of food allergy in offspring. A follow-up study from an RCT (N=164) reported that Vitamin D supplementation of the mothers during lactation may increase the risk of later food allergy up to 2 years of age (unadjusted analysis), although the authors reported high loss in subjects in the follow-up (Norizoe et al., 2014). However, results from cross-sectional studies (Allen et al., 2013) suggest that vitamin D sufficiency in infants age 1 year may be an important protective factor for food allergy at that age. Another cross-sectional study that followed a German birth cohort for 10 years reported that specific IgE for food allergens (OR: 1.07; 95% CI: 1.02-1.11) at age 10, as well as lifetime prevalence were significantly related to the vitamin D status (Wawro et al., 2014). Conversely, a study in Korea (N=226) showed that vitamin D deficiency increased the risk of sensitization to food allergens (Baek et al., 2014). In a longitudinal study (N=231), Jones et al. showed that maternal intake of supplemental vitamin D was significantly correlated with cord blood $25(OH)D_3$ concentration (Jones et al., 2012). However, the associations between cord blood $25(OH)D_3$ concentration and allergen sensitization, IgE-mediated food allergy, or eczema severity were not significant. Another prospective birth cohort study (N=378) in Germany reported that maternal and cord blood $25(OH)D_3$ was positively associated with

children's risk for food allergy within the first 2 years of life (Weisse et al., 2013).

Liu et al. reported that the combination of persistently low vitamin D status at birth and in early childhood (ages 1 to 3 years) increased the risk of food sensitization (defined as specific IgE ≥0.35 kUA/L to any common food allergen, that is, egg white, milk, peanut, walnut, soy, shrimp, cod fish, and wheat) (aOR: 2.03; 95% CI: 1.02-4.04); the risk was particularly higher among children carrying the C allele of rs2243250 (aOR: 3.23; 95% CI: 1.37-7.60) (N=460) (Liu et al., 2013).

Multiple genes are known to be involved in 25(OH)D_3 metabolism and regulatory pathways: genes encoding the molecules to convert 25(OH)D_3 into its bioactive form 1,25(OH)2D (i.e., *CYP27B1*) and then a water-soluble metabolite (i.e., calcitroic acid; *CYP24A1*), as well as the receptor complex of vitamin D (i.e., *VDR*, *RXRA*, *RXRB*) and vitamin D binding protein (i.e., *GC*). Liu et al. evaluated children in the Boston Birth Cohort (N=649) and did not find an association between vitamin D levels in cord blood and sensitization to food allergens in early childhood (Liu et al., 2011). However, when examined with candidate gene single nucleotide polymorphisms, a significant interaction was identified for an IL-4 gene polymorphism and three other genes, indicating a risk for sensitization. In an Australian study, Koplin et al. investigated whether polymorphisms in a VDR-binding protein gene (low, the GT/TT genotype; high, the GG genotype) could modify the relationship between serum vitamin D and food allergy (Koplin et al., 2016). The study (N=5,276) found that low serum 25(OH)D_3 levels (≤50 nM/L) at age 1 year had a modest association with food allergy, particularly among infants with the GG genotype (aOR: 6.0; 95% CI: 0.9-38.9) but the CI was wide. There was no association with food allergy in children with those with low serum 25(OH)D_3 levels and GT/TT genotypes (aOR: 0.7; 95% CI: 0.2-2.0; P interaction=0.014).

The committee concludes that the quantity of evidence on the role of vitamin D in the development of food allergy during critical developmental windows (in utero, infancy, and early childhood) is limited. Further research is needed to confirm or refute this relationship.

Lipids/Omega-3 Fatty Acids

Dietary fat consumption has been hypothesized to influence atopy development by modulation of IgE production (Black and Sharpe, 1997). Among the different dietary fats, the ones that have been studied most extensively are the omega-3 fatty acids. Omega-3 fatty acids are known to have anti-inflammatory and immune modulator properties (Wall et al., 2010). Current evidence suggests that the intake of omega-3 fatty acids has decreased from ancestral times, whereas the consumption of omega-6 has

probably increased. Consequently, the dietary ratios of omega-6 to omega-3 fatty acids have changed over time from approximately 1:1 to almost 17:1 in certain industrialized societies (Simopoulos, 2002). The parallel increases in this ratio and in the prevalence of allergic disease, as well as information from experimental models, have elicited the hypothesis that dietary omega-3 fatty acids in early life may influence immune system development and immune cell function (Calder, 2013; Shek et al., 2012).

This hypothesis has been tested using a variety of experimental models, and the results of individual studies have been the focus of several reviews and meta-analyses that reveal the uncertainties that currently afflict this area of knowledge. Contributing to the current controversies are (1) the different experimental designs (observational versus RCTs), (2) the times of intervention and follow up, (3) the usually small size of the populations studied, (4) the different approaches to supplying the omega-3 fatty acids and the doses used, (5) the different periods investigated (fetal life, infancy, childhood), (6) the different outcomes examined, and (7) the potential confounder introduced by the wide-ranging presence of pro-allergenic pollutants and contaminants in fish, the major source of dietary omega-3.

The systematic review of Klemens et al., which reviewed the literature from 1950-2010, is considered to be of medium quality (Klemens et al., 2011). The review included three RCTs (Dunstan et al., 2003; Furuhjelm et al., 2009; Lauritzen et al., 2005; total N=264) of omega-3 fatty acids supplementation compared to olive or soy oil during pregnancy and/or lactation in a high-risk population for outcomes of food allergy, as defined by SPT and clinical diagnosis. When supplementation started during pregnancy egg sensitization decreased at 12 months of age (OR: 0.33; 95% CI: 0.16-0.70). Receiving the supplementation during pregnancy and/or lactation and food allergy at age 12 months were not significantly associated.

A recent Cochrane review, which included manuscripts published until August 2014, assessed the effect of omega-3 supplementation in pregnant and/or breastfeeding women on allergy outcomes (food allergy, atopic dermatitis, allergic rhinitis, and asthma/wheeze) in their children (Gunaratne et al., 2015). Overall, the results showed little reduction of allergic disease in the children resulting from maternal omega-3 supplementation during pregnancy and/or breastfeeding. Five trials reported food allergy outcomes (Dunstan et al., 2003; Furuhjelm et al., 2009; Lauritzen et al., 2005; Makrides et al., 2009, 2010). There was only one study where omega-3 supplementation reduced the incidence of IgE-mediated food allergies in children up to 12 months of age (Furuhjelm et al., 2009) (N=117; RR: 0.13; 95% CI: 0.02-0.95). Similarly, another recent review identified three RCTs (Dunstan et al., 2003; Furuhjelm et al., 2009; Palmer et al., 2012) and two follow-up studies (Furuhjelm et al., 2011; Palmer et al., 2013) with pregnant women whose infants were at high risk of atopy. After adjusting for

potential confounders or after long-term follow-up only one study showed an association between maternal omega-3 fatty acid supplementation and lower risk of food sensitization (Newberry et al., 2016).

The committee concludes that the current evidence does not support a link between increased maternal omega-3 intake and a protective effect on childhood food allergy.

Folate

Emerging interest in the role of folate in immune development and allergic disease has been driven by the recent understanding that folate, a dietary methyl donor, can affect immune function and alter gene expression through epigenetic mechanisms (Brown et al., 2014). Concerns have been raised about whether folic acid supplementation during pregnancy and/or early childhood is a potential risk factor for the development of atopic diseases in children. As animal models have demonstrated, maternal supplementation with dietary methyl donors during pregnancy induces hypermethylation of key regulatory genes in lung tissue, resulting in subsequent allergic airway disease in offspring (Hollingsworth et al., 2008). Exposure to folate in utero can affect DNA methylation during fetal development in humans (Amarasekera et al., 2014), which can influence transcriptional activity. For example, hypermethylation can silence the expression of genes. During polarization of naive T helper cells to Th2 cells, methylation of the promoter region of the IFN-γ gene blocks transcription factor binding and thus expression of the IFN-γ gene (Jones and Chen, 2006). Consequently, increased folic acid intake could influence the expression of genes that may be involved in T-cell differentiation during gestation. In turn, this may influence the allergic predisposition in the neonate.

To date, most human studies on this topic have focused on asthma, with very limited number of studies specific to food allergy or food sensitization. An Australian study (N=484) assessed maternal folic acid intake and serum folate levels during the third trimester, and cord blood folate status at birth (N=285), and allergic outcomes at age 12 months, including IgE-mediated food allergy, eczema, and asthma, in offspring (Dunstan et al., 2012, p. 51). In their study, food allergy was defined as "a history of immediate symptoms following contact and/or ingestion and a positive SPT to the implicated food."

However, maternal serum folate status and allergic outcomes were not associated (Dunstan et al., 2012). In a study of 2,834 Dutch children, maternal folic acid supplement intake across the whole pregnancy, and intracellular folate status (measured in the third trimester of pregnancy in 837 [29.5%] participants) was not significantly associated with specific

IgE against hen egg, cow milk, peanut, and aeroallergens at age 2 years or eczema until age 6 to 7 years (Magdelijns et al., 2011).

A recent study that measured serum folate (at ages 2, 4, 6, and 8 years) in 138 U.S. children found that increased serum folate levels at or before age 6 years were significantly associated with increased incidence of sensitization to both food and aeroallergens, but not with serum total IgE, asthma, or wheezing at ages 6 or 9 years (Okupa et al., 2013). In the National Health and Nutrition Examination Survey (NHANES) (which covers ages 2 to 85 years), a cross-sectional study, serum folate levels were inversely associated with atopy, wheeze, and elevated total IgE levels (Matsui and Matsui, 2009).

Of note, the inconsistent results of previous studies are likely due to many reasons, including differences in sample size, participants' ages, clinical characteristics, allergic outcomes, methods used for measurement of folate status, and statistical methods used in the analysis.

The committee concludes that evidence to assess the causal association between folate and the development or prevention of food allergy is lacking. Further research to study this potential association is needed.

Other Nutrients

A prospective cohort study assessed the relationship between maternal dietary antioxidant intake (B carotene, vitamins C and E, copper, and zinc) during pregnancy and food allergy of the child at age 12 months among families at high risk (West et al., 2012). This study of 300 mother-infant dyads found a protective effect of vitamin C intake on food allergy, with higher intakes that were limited to one quartile of vitamin C intake. For copper, intake in the highest quartile also showed a protective effect. However, as previously noted, observational studies suffer from inherent methodological flaws. Thus, proper RCTs are required to determine the causal effect of the maternal diet on the etiology of food allergies in offspring.

The committee concludes that evidence to assess the causal association between other nutrients and the development or prevention of food allergy is lacking.

Other Hypotheses

Do the Obesity and Diabetes Epidemics Have a Role in the Rise of Food Allergy?

The parallel increase in the prevalence of obesity and type 2 diabetes and allergic diseases raises the question of whether these conditions may be linked. Obesity is known to induce systemic inflammation, which

might adversely influence the immature immune system and atopic outcomes. Increased adipose tissue also could lead to reduced adiponectin levels, which in turn down-regulates the secretion of IL-10 and decreases regulatory T cells (Hersoug and Linneberg, 2007). Although the precise mechanism underlying the link between obesity and allergic disease including food allergies remains to be elucidated, the hypothesis is biologically plausible.

Very limited data are available on the association between having overweight or obesity and food allergy. Observational studies have shown that obesity is associated with a higher risk of atopy (elevated specific IgE to allergen) (Ouyang et al., 2009; Visness et al., 2009; Xu et al., 2000). For example, data from the 2005-2006 NHANES demonstrated that children with overweight or obesity had a higher geometric mean of total IgE levels and were at a higher risk of atopy than children with normal weight. This association was driven largely by allergic sensitization to food allergens, and systemic inflammation (measured as serum c-reactive protein) in children with obesity may play a role in the development of allergy (Visness et al., 2009). In contrast, ample studies show the association between overweight and obesity and asthma in both children and adults (Baumann and Lorentz, 2013; Granell et al., 2014).

The role of maternal overweight and obesity and diabetes on the developing fetus and the subsequent risk of allergic diseases has not been well studied but deserve attention. In the prospective Boston Birth cohort, Kumar et al. reported that in term births, gestational diabetes was significantly associated with allergen sensitization in the child, and such association was also driven by food sensitization (Kumar et al., 2009). In contrast, others reported no associations between obesity measures and atopy (Jarvis et al., 2002; Ma et al., 2010), or inverse associations (Van Gysel et al., 2009).

Other Unsubstantiated Hypothesis for the Rise in Food Allergy

Media interest in food allergies has become significant and sustained as food allergies have become more common. As such, public conjectures about potential causes for the rise are widespread. In particular, awareness about unfortunate cases of food-induced anaphylaxis is high. Added to that is the increased awareness by various community or commercial organizations (such as schools, restaurants, airlines, and sporting clubs) of their need to be careful about how they provide foods for food allergic individuals. As a result, communities are greatly interested in why the prevalence of food allergy appears to be rising.

One of the most widely held theories, among the many that abound, as to why food allergy is on the rise holds that it is due to the increasing

consumption of processed foods and food additives. Unfortunately, to date no significant research has been conducted on this issue. Websites and blogs tout the dangers of processed foods and food additives, and evidence from clinical observation suggests that some parents believe that food additives aggravate a range of clinical symptoms and signs, from difficult behavior and autism to gastrointestinal reactions. Clinically, the best way to understand whether a food is aggravating symptoms is to eliminate that food and later challenge with it—provided the risk of anaphylaxis has been excluded. However, the role of additives and preservatives in the development of food allergy in the first place has never been examined at the ecological or epidemiological level. In addition to understanding whether preservatives or additives have a direct toxicological effect on the developing immune system, it would be valuable to assess whether these substances actually influence the composition of the gastrointestinal microbiome.

Concerns over genetically modified crops (Nordlee et al., 1996) has resulted in consideration of the role that such foods may play in aggravating food allergy and in a requirement to assess the potential allergenicity of genetically modified crops (CAC, 2009; FAO/WHO, 2001). Although an online tool recently has been developed to help assess the role a novel protein may play in cross-reactivity (Goodman et al., 2016) based on criteria from the Codex Alimentarius Commission (CAC, 2009), current methodologies are considered inadequate to predict de novo allergenicity. Little or no research exists on whether the increased use of genetically modified crops could be linked to the rise in food allergy.

Numerous lay books and review articles argue that the increased consumption of fast food in the Westernized diet may have a significant impact on immunity (Myles, 2014). Although emerging indirect evidence suggests that fresh fruit and vegetables and food diversity might be important for an optimal and healthy start to life, to date little work has been done on their role specifically in preventing food allergy. Some of the first emerging evidence of diet diversity and its impact on food allergy development has been generated by the EuroPrevall study (Grimshaw et al., 2014). In a nested case-control within-cohort study of 41 infants using gold standard food challenge outcomes and 82 age-matched controls, the authors found that an infant diet with high levels of fruits, vegetables, and home-prepared foods is associated with less food allergy by 2 years of age. As an observational study, these results are subject to confounding but they generate a hypothesis worth testing in systematic trials.

The committee concludes that speculation abounds regarding why food allergy is on the rise. Although some ideas are based in appropriate theoretical frameworks, the absence of RCTs prevents firm conclusions to be drawn on their validity.

OVERALL CONCLUSIONS

The development of food allergies, like other complex diseases, might be regulated by the epigenome and in that way be caused by a genetic predisposition interacting with environmental exposures. The epigenome can be altered throughout the lifespan, but is particularly sensitive to environmental factors during early life periods. There appears to be a window of opportunity in the perinatal and early childhood period that may modulate the functionality of the immune system and related health conditions, specifically food allergies.

Many factors have been postulated to contribute to the onset of sensitization and to food allergies. A few of them have been extensively researched and sufficient evidence exists to support guidelines or to continue research to gain more insights (e.g., about the optimal timing and dosing of early introduction of foods). For other factors, either evidence is lacking about their association with food allergy but the association is biologically plausible (e.g., folate) or limited evidence exists about their association (e.g., vitamin D or fatty acids). For these, a recommendation based on their association with food allergy development cannot be made at this time and more research is needed. For other factors, direct or indirect evidence is lacking, but myths continue to prevail among the public (e.g., food additives).

For some factors (e.g., breastfeeding or vaginal delivery), although the evidence is inconsistent, it would be unethical to pursue RCTs; therefore, the evidence about their contribution to food allergies is derived solely from epidemiological studies. The review of the evidence by the committee neither confirmed nor rebutted current hypotheses related to any association between these factors and the increase in the prevalence of food allergies. The most recent research on the effects of allergen exposure at early age, however, strongly supports the dual allergen exposure hypothesis. The strongest data on potential prevention practices derives from a large RCT supporting the hypothesis that delaying the introduction of peanuts, coupled with high eczema rates, may have contributed to the high prevalence of peanut allergy in the Western world. Similar trials are being conducted for other allergenic foods and some of them are still being analyzed and interpreted (see Table 5-1). The LEAP study found that within a very narrow time range (ages 4 to 11 months), early introduction of peanut is protective against peanut allergy in infants who are at high risk (as defined by early onset eczema or coexistent egg allergy). Other studies have found that delaying introduction of other allergenic foods (cooked egg, cow milk, and wheat) has no benefits.

The lack of strong evidence for a link between most of the potential risk determinants and food allergy has created inconsistencies in public health

advice among different guidelines (see Table 5-2) and corresponding confusion among physicians, patients, and their families. Consensus of infant feeding guidelines to prevent food allergy across different public health authorities is needed for health care providers to counsel patients and their caregivers with consistent recommendations. Moreover, future clinical practice guidelines and public health policy should take into account the way in which a risk factor may differentially affect the risk of disease as well as the behavior of individuals with food allergy or their caregivers.

RECOMMENDATIONS

The committee recommends that public health authorities and clinical practice guidelines include consistent, clear, and evidence-based advice for families and health care providers, including dietitians, about the potential benefits of introducing allergenic foods (e.g., peanut products, egg, dairy, and wheat) in the first year of life to infants, when an infant is developmentally ready (around 6 months of age), but not before 4 months of age, particularly to those at high risk of allergy. Guidelines also should include information about the circumstances in which health care providers should advise their patients about the safest way to introduce in their diet peanut products (and/or other foods, as determined by the results of ongoing research).

In addition, as mentioned in Chapter 6, the committee recommends that public health authorities regularly update food allergy guidelines on diagnosis, prevention, and management based on strong scientific evidence. For example, current evidence is insufficient to associate any of the following behaviors with prevention of food allergy: food allergen avoidance diets for pregnant or lactating women, prolonged allergen avoidance in infancy, vaginal delivery, breastfeeding, infant formulas containing extensively or partially hydrolyzed protein, and supplementation with specific nutrients (e.g., vitamin D, folate, fatty acids) in children or adults.

RESEARCH NEEDS

Considerations for Study Designs

Studies on the etiological factors associated with food allergies frequently present methodological flaws due to various reasons, including lack of accounting for confounding factors (e.g., breastfeeding), use of inaccurate food allergy measures (e.g., self-reporting), or disregard for the

fact that different populations (e.g., those at high risk of developing a food allergy) might respond differently to the various risk factors. For example, due to a variety of differential gene-environment factors (e.g., genetics, epigenetics, microbiomes, and other pre- and postnatal environmental factors), populations will respond differently to interventions. Also, the etiology and early life onset of food allergy seems to be multifactorial, and collecting specimen for future analyses would be advantageous. Future research design on etiological determinants should consider the following:

- Conduct longitudinal birth cohort studies that explore the effects of environmental factors during critical developmental windows (in utero, infancy, and early childhood) on food allergy.
- Couple relevant prenatal, perinatal, and early childhood epidemiological and clinical data with appropriate biospecimen collections (e.g., serum, cord blood, breast milk) for current and future biomarker analyses.
- Design studies so that the responses to various exposures of individuals and populations at high risk and low risk of developing food allergy can be differentiated.
- Use the currently accepted gold standard—double-blind, placebo-controlled oral food challenges (employing standard dosing protocols and scoring systems, so that the results of various studies can better be compared)—as the food allergy outcome in research intervention studies until a simpler reliable method to measure food allergy is identified and validated.
- Account for the potential influence of confounding factors, in addition to age, sex, and geography, such as breastfeeding, composition of breast milk, dietary intake, other allergic disorders in the patient or family history (particularly atopic dermatitis), genetic susceptibility, presence of dogs or cats in the household, number of siblings, history of antibiotic usage, and exposure to agents or practices that might impair skin barrier function.
- Engage patients or groups representing patients so that research designs may take into consideration potential socio-psychological, cultural, and behavioral considerations.

Overall Research Needs

Many genetic and environmental factors could contribute to the onset of sensitization and to food allergy. For the majority of factors reviewed by the committee, some, but largely insufficient or inconsistent, evidence exists at this time about their association with sensitization or food allergy. Nev-

ertheless, health care providers, patients, and their caregivers still need clear prevention approaches and authoritative and clear public health guidelines. Therefore, research needs to continue to support or refute the contribution of these factors to food sensitization or food allergy. The committee recognizes, though, that for other factors direct or indirect evidence is lacking and research is not currently warranted (e.g., food additives). Although some public health guidelines have been developed to guide practices of health care providers and individuals, efforts have not been undertaken to assess the impact of such public health guidelines on practices related to food allergy and on prevalence of food allergy. Prospective studies and behavioral research should be conducted to accomplish the following objectives:

- Examine risk factors for food allergies in all populations (ages, sex, ethnicities, comorbidities, socioeconomic strata), especially in those populations that might have been underrepresented in past research.
- Gain insights about the behaviors of those with (or at risk of) food allergy and their caregivers as well as about the impact of public health guidelines on health care providers and individuals' practices.
- Examine the etiology of the rising prevalence of food allergy within the past two decades, which could identify new targets for allergy prevention and treatment. For example, what changes have occurred in food preparation and consumption behavior in communities and what is their potential relationship to the increase in food allergies? What changes may have occurred in the use of agents (such as detergents) or practices (such as in personal hygiene) that might contribute to impaired skin barrier function?
- Elucidate, through prospective studies, the role of environmental factors and gene-environment interactions in the atopic march and the development of food allergy. For example, do specific factors increase the risk of an individual progressing from eczema to food allergy?
- Explore potentially unidentified risk factors that may influence food allergy. For example, although the data available to date have not shown evidence of a relationship, it is plausible that maternal and early childhood adiposity and metabolic disorders could be risk factors for food allergy development.
- Using prospective birth cohort studies, evaluate the effects of multiple early life factors (individually and in combination) and of possible gene-environmental interactions in the development and

prevention of food allergy in order to inform the design of specific RCTs.
- Identify best practices to engage patients and their families in the planning stages of research studies so that patients' and families' concerns are considered, and assess the value of using these approaches.

Specific Research Needs

In addition, high-quality prospective studies and RCTs are needed on specific risk determinants for which some evidence exists about their effect on food allergy related to the most plausible hypotheses to make meaningful conclusions. These studies should be conducted to accomplish the following objectives:

The Microbial Hypothesis

- Determine, using well-designed prospective studies, the role of mode of birth delivery (vaginal, emergency versus elective cesarean section) and early life microbiome composition on the development of food allergy.
- Assess, through well-designed prospective studies, potential links between food allergy and antibiotic exposure in children (studies should include information on the type, dose, and frequency of antibiotic exposure).
- Determine whether pet ownership is related to food allergy by using well-designed prospective studies.
- Assess, with RCTs, the potential benefits of prebiotics and probiotics to prevent the onset of food allergy.

Allergen Avoidance and Exposure

- Elucidate the relationship, if any, between breastfeeding and the onset of food allergy (may also influence through microbiome modulation) with well-designed prospective studies and take into account the potential effect of differences in breast milk composition.
- Determine, with RCTs, whether consuming or eliminating or avoiding specific allergenic foods during pregnancy and lactation has any benefits.
- Conduct RCTs, similar to the Learning Early About Peanut study, to determine whether early introduction of peanut products has

benefit in individuals other than high-risk infants, who were studied in the original trial.
- Examine early introduction of allergenic foods in addition to peanut to determine whether this approach is beneficial in preventing the development of food allergy.

Nutrition Immunomodulation Hypothesis

- Assess, with RCTs, the potential role of specific nutrients, such as vitamin D, folate, or fatty acids, in preventing food allergy.

REFERENCES

Adams, J. S., and M. Hewison. 2008. Unexpected actions of vitamin D: New perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab* 4(2):80-90.

Adlerberth, I., and A. E. Wold. 2009. Establishment of the gut microbiota in Western infants. *Acta Paediatr* 98(2):229-238.

Agostoni, C., T. Decsi, M. Fewtrell, O. Goulet, S. Kolacek, B. Koletzko, K. F. Michaelsen, L. Moreno, J. Puntis, J. Rigo, R. Shamir, H. Szajewska, D. Turck, and J. van Goudoever. 2008. Complementary feeding: A commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 46(1):99-110.

Albers, R., J. M. Antoine, R. Bourdet-Sicard, P. C. Calder, M. Gleeson, B. Lesourd, S. Samartin, I. R. Sanderson, J. Van Loo, F. W. Vas Dias, and B. Watzl. 2005. Markers to measure immunomodulation in human nutrition intervention studies. *Br J Nutr* 94(3):452-481.

Alduraywish, S. A., C. J. Lodge, B. Campbell, K. J. Allen, B. Erbas, A. J. Lowe, and S. C. Dharmage. 2016. The march from early life food sensitization to allergic disease: A systematic review and meta-analyses of birth cohort studies. *Allergy* 71(1):77-89.

Allen, K. J., and J. J. Koplin. 2015. Why does Australia appear to have the highest rates of food allergy? *Pediatr Clin North Am* 62(6):1441-1451.

Allen, K. J., J. J. Koplin, A. L. Ponsonby, L. C. Gurrin, M. Wake, P. Vuillermin, P. Martin, M. Matheson, A. Lowe, M. Robinson, D. Tey, N. J. Osborne, T. Dang, H. T. Tina Tan, L. Thiele, D. Anderson, H. Czech, J. Sanjeevan, G. Zurzolo, T. Dwyer, M. L. Tang, D. Hill, and S. C. Dharmage. 2013. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *J Allergy Clin Immunol* 131(4):1109-1116.

Amarasekera, M., D. Martino, S. Ashley, H. Harb, D. Kesper, D. Strickland, R. Saffery, and S. L. Prescott. 2014. Genome-wide DNA methylation profiling identifies a folate-sensitive region of differential methylation upstream of ZFP57-imprinting regulator in humans. *Faseb J* 28(9):4068-4076.

Amoli, M. M., S. Hand, A. H. Hajeer, K. P. Jones, S. Rolf, C. Sting, B. H. Davies, and W. E. Ollier. 2002. Polymorphism in the STAT6 gene encodes risk for nut allergy. *Genes Immun* 3(4):220-224.

AND (Academy of Nutrition and Dietetics). 2015. *Practice paper of the Academy of Nutrition and Dietetics: Promoting and supporting breastfeeding*. http://www.eatrightpro.org/resource/practice/position-and-practice-papers/practice-papers/practice-paper-promoting-and-supporting-breastfeeding (accessed July 16, 2016).

Appelt, G. K., M. Chan-Yeung, W. T. A. Watson, H. Dimich-Ward, A. Ferguson, J. Manfreda, and A. B. Becker. 2004. Breastfeeding and food avoidance are ineffective in preventing sensitization in high risk children. *J Allergy Clin Immunol* 113(2):S99.

ASCIA (Australasian Society of Clinical Immunology and Allergy). 2016a. *Food allergy FAQs*. http://www.allergy.org.au/patients/food-allergy/faqs (accessed July 16, 2016).

ASCIA. 2016b. *Guidelines: Infant feeding and allergy prevention*. http://www.allergy.org.au/images/pcc/ASCIA_guidelines_infant_feeding_and_allergy_prevention.pdf (accessed May 25, 2016).

Azad, M. B., T. Konya, D. S. Guttman, C. J. Field, M. R. Sears, K. T. HayGlass, P. J. Mandhane, S. E. Turvey, P. Subbarao, A. B. Becker, J. A. Scott, and A. L. Kozyrskyj. 2015. Infant gut microbiota and food sensitization: Associations in the first year of life. *Clin Exp Allergy* 45(3):632-643.

Azad, M. B., T. Konya, R. R. Persaud, D. S. Guttman, R. S. Chari, C. J. Field, M. R. Sears, P. J. Mandhane, S. E. Turvey, P. Subbarao, A. B. Becker, J. A. Scott, and A. L. Kozyrskyj. 2016. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: A prospective cohort study. *BJOG* 123(6):983-993.

Baek, J. H., Y. H. Shin, I. H. Chung, H. J. Kim, E. G. Yoo, J. W. Yoon, H. M. Jee, Y. E. Chang, and M. Y. Han. 2014. The link between serum vitamin D level, sensitization to food allergens, and the severity of atopic dermatitis in infancy. *J Pediatr* 165(4):849-854.

Ballard, O., and A. L. Morrow. 2013. Human milk composition: Nutrients and bioactive factors. *Pediatr Clin North Am* 60(1):49-74.

Barker, D. J. 1990. The fetal and infant origins of adult disease. *BMJ* 301(6761):1111.

Baumann, S., and A. Lorentz. 2013. Obesity—a promoter of allergy? *Int Arch Allergy Immunol* 162(3):205-213.

Black, P. N., and S. Sharpe. 1997. Dietary fat and asthma: Is there a connection? *Eur Respir J* 10(1):6-12.

Boyce, J. A., A. Assa'ad, A. W. Burks, S. M. Jones, H. A. Sampson, R. A. Wood, M. Plaut, S. F. Cooper, M. J. Fenton, S. H. Arshad, S. L. Bahna, L. A. Beck, C. Byrd-Bredbenner, C. A. Camargo, Jr., L. Eichenfield, G. T. Furuta, J. M. Hanifin, C. Jones, M. Kraft, B. D. Levy, P. Lieberman, S. Luccioli, K. M. McCall, L. C. Schneider, R. A. Simon, F. E. Simons, S. J. Teach, B. P. Yawn, and J. M. Schwaninger. 2010. Guidelines for the diagnosis and management of food allergy in the United States: Report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 126(6 Suppl):S1-S58.

Boyle, R. J., D. Ierodiakonou, T. Khan, J. Chivinge, Z. Robinson, N. Geoghegan, K. Jarrold, T. Afxentiou, T. Reeves, S. Cunha, M. Trivella, V. Garcia-Larsen, and J. Leonardi-Bee. 2016. Hydrolyzed formula and risk of allergic or autoimmune disease: Systematic review and meta-analysis. *BMJ* 352:i974.

Brough, H. A., A. Simpson, K. Makinson, J. Hankinson, S. Brown, A. Douiri, D. C. Belgrave, M. Penagos, A. C. Stephens, W. H. McLean, V. Turcanu, N. Nicolaou, A. Custovic, and G. Lack. 2014. Peanut allergy: Effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. *J Allergy Clin Immunol* 134(4):867-875.

Brown, S. B., K. W. Reeves, and E. R. Bertone-Johnson. 2014. Maternal folate exposure in pregnancy and childhood asthma and allergy: A systematic review. *Nutr Rev* 72(1):55-64.

Brown, S. J., Y. Asai, H. J. Cordell, L. E. Campbell, Y. Zhao, H. Liao, K. Northstone, J. Henderson, R. Alizadehfar, M. Ben-Shoshan, K. Morgan, G. Roberts, L. J. Masthoff, S. G. Pasmans, P. C. van den Akker, C. Wijmenga, J. O. Hourihane, C. N. Palmer, G. Lack, A. Clarke, P. R. Hull, A. D. Irvine, and W. H. McLean. 2011. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol* 127(3):661-667.

Bunyavanich, S., S. L. Rifas-Shiman, T. A. Platts-Mills, L. Workman, J. E. Sordillo, C. A. Camargo, Jr., M. W. Gillman, D. R. Gold, and A. A. Litonjua. 2014. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. *J Allergy Clin Immunol* 133(5):1373-1382.

CAC (Codex Alimentarius Commission). 2009. *Foods derived from modern biotechnology*. Rome: World Health Organization and Food and Agriculture Organization.

Calder, P. C. 2013. n-3 Fatty acids, inflammation and immunity: New mechanisms to explain old actions. *Proc Nutr Soc* 72(3):326-336.

Camargo, C. A., Jr., S. Clark, M. S. Kaplan, P. Lieberman, and R. A. Wood. 2007. Regional differences in EpiPen prescriptions in the United States: The potential role of vitamin D. *J Allergy Clin Immunol* 120(1):131-136.

Campos, E., N. Shimojo, Y. Inoue, T. Arima, S. Suzuki, M. Tomiita, T. Matsuura, A. Hata, Y. Suzuki, M. Aoyagi, and Y. Kohno. 2007. No association of polymorphisms in the 5' region of the CD14 gene and food allergy in a Japanese population. *Allergol Int* 56(1):23-27.

Campos, E. J., N. Shimojo, Y. Suzuki, Y. Mashimo, T. Arima, T. Matsuura, Y. Inoue, A. Yamaide, M. Tomiita, K. Fujii, A. Hata, and Y. Kohno. 2008. IL-10 gene polymorphism, but not TGF-beta1 gene polymorphisms, is associated with food allergy in a Japanese population. *Pediatr Allergy Immunol* 19(8):716-721.

Cantorna, M. T., Y. Zhu, M. Froicu, and A. Wittke. 2004. Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. *Am J Clin Nutr* 80(6 Suppl): 1717S-1720S.

Chen, S., G. P. Sims, X. X. Chen, Y. Y. Gu, S. Chen, and P. E. Lipsky. 2007. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J Immunol* 179(3):1634-1647.

Chen, T. K., J. H. Lee, H. H. Yu, Y. H. Yang, L. C. Wang, Y. T. Lin, and B. L. Chiang. 2012. Association between human IL-10 gene polymorphisms and serum IL-10 level in patients with food allergy. *J Formos Med Assoc* 111(12):686-692.

Cuello-Garcia, C. A., J. L. Brozek, A. Fiocchi, R. Pawankar, J. J. Yepes-Nunez, L. Terracciano, S. Gandhi, A. Agarwal, Y. Zhang, and H. J. Schunemann. 2015. Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 136(4):952-961.

Cuello-Garcia, C. A., A. Fiocchi, R. Pawankar, J. J. Yepes-Nunez, G. P. Morgano, Y. Zhang, K. Ahn, S. Al-Hammadi, A. Agarwal, S. Gandhi, K. Beyer, W. Burks, G. W. Canonica, M. Ebisawa, R. Kamenwa, B. W. Lee, H. Li, S. Prescott, J. J. Riva, L. Rosenwasser, H. Sampson, M. Spigler, L. Terracciano, A. Vereda, S. Waserman, H. J. Schunemann, and J. L. Brozek. 2016. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Prebiotics. *World Allergy Organ J* 9:10.

de Silva, D., M. Geromi, S. Halken, A. Host, S. S. Panesar, A. Muraro, T. Werfel, K. Hoffmann-Sommergruber, G. Roberts, V. Cardona, A. E. Dubois, L. K. Poulsen, R. Van Ree, B. Vlieg-Boerstra, I. Agache, K. Grimshaw, L. O'Mahony, C. Venter, S. H. Arshad, and A. Sheikh. 2014. Primary prevention of food allergy in children and adults: Systematic review. *Allergy* 69(5):581-589.

Depner, M., M. J. Ege, J. Genuneit, J. Pekkanen, M. Roponen, M. R. Hirvonen, J. C. Dalphin, V. Kaulek, S. Krauss-Etschmann, J. Riedler, C. Braun-Fahrlander, C. Roduit, R. Lauener, P. I. Pfefferle, J. Weber, and E. von Mutius. 2013. Atopic sensitization in the first year of life. *J Allergy Clin Immunol* 131(3):781-788.

DGAC (Dietary Guidelines Advisory Committee). 2015. Scientific Report of the 2015 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Health and Human Services and Secretary of Agriculture. U.S. Department of Agriculture, Agriculture Research Service, Washington DC.

Dharmage, S. C., A. J. Lowe, M. C. Matheson, J. A. Burgess, K. J. Allen, and M. J. Abramson. 2014. Atopic dermatitis and the atopic march revisited. *Allergy* 69(1):17-27.

Dominguez-Bello, M. G., E. K. Costello, M. Contreras, M. Magris, G. Hidalgo, N. Fierer, and R. Knight. 2010. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* 107(26):11971-11975.

Dowhower Karpa, K., I. M. Paul, J. A. Leckie, S. Shung, N. Carkaci-Salli, K. E. Vrana, D. Mauger, T. Fausnight, and J. Poger. 2012. A retrospective chart review to identify perinatal factors associated with food allergies. *Nutr J* 11:87.

Du Toit, G., Y. Katz, P. Sasieni, D. Mesher, S. J. Maleki, H. R. Fisher, A. T. Fox, V. Turcanu, T. Amir, G. Zadik-Mnuhin, A. Cohen, I. Livne, and G. Lack. 2008. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 122(5):984-991.

Du Toit, G., G. Roberts, P. H. Sayre, M. Plaut, H. T. Bahnson, H. Mitchell, S. Radulovic, S. Chan, A. Fox, V. Turcanu, and G. Lack. 2013. Identifying infants at high risk of peanut allergy: The Learning Early About Peanut Allergy (LEAP) screening study. *J Allergy Clin Immunol* 131(1):135-143.

Du Toit, G., G. Roberts, P. H. Sayre, H. T. Bahnson, S. Radulovic, A. F. Santos, H. A. Brough, D. Phippard, M. Basting, M. Feeney, V. Turcanu, M. L. Sever, M. Gomez Lorenzo, M. Plaut, and G. Lack. 2015. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 372(9):803-813.

Du Toit, G., P. H. Sayre, G. Roberts, M. L. Sever, K. Lawson, H. T. Bahnson, H. A. Brough, A. F. Santos, K. M. Harris, S. Radulovic, M. Basting, V. Turcanu, M. Plaut, and G. Lack. 2016. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 374(15):1435-1443.

Dunstan, J. A., T. A. Mori, A. Barden, L. J. Beilin, A. L. Taylor, P. G. Holt, and S. L. Prescott. 2003. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: A randomized, controlled trial. *J Allergy Clin Immunol* 112(6):1178-1184.

Dunstan, J., C. West, S. McCarthy, J. Metcalfe, S. Meldrum, W. Oddy, M. Tulic, N. D'Vaz, and S. Prescott. 2012. The relationship between maternal folate status in pregnancy, cord blood folate levels, and allergic outcomes in early childhood. *Allergy: Eur J Allergy Clin Immunol* 67(1):50-57.

Ege, M. J., I. Herzum, G. Buchele, S. Krauss-Etschmann, R. P. Lauener, M. Roponen, A. Hyvarinen, D. A. Vuitton, J. Riedler, B. Brunekreef, J. C. Dalphin, C. Braun-Fahrlander, J. Pekkanen, H. Renz, E. von Mutius. 2008. Prenatal exposure to a farm environment modifies atopic sensitization at birth. *J Allergy Clin Immunol* 122(2):407-412.

Eggesbo, M., G. Botten, H. Stigum, P. Nafstad, and P. Magnus. 2003. Is delivery by cesarean section a risk factor for food allergy? *J Allergy Clin Immunol* 112(2):420-426.

Eggesbo, M., G. Botten, H. Stigum, S. O. Samuelsen, B. Brunekreef, and P. Magnus. 2005. Cesarean delivery and cow milk allergy/intolerance. *Allergy* 60(9):1172-1173.

Faa, G., C. Gerosa, D. Fanni, S. Nemolato, P. van Eyken, and V. Fanos. 2013. Factors influencing the development of a personal tailored microbiota in the neonate, with particular emphasis on antibiotic therapy. *J Matern Fetal Neonatal Med* 26(Suppl 2):35-43.

Falth-Magnusson, K., and N. I. Kjellman. 1987. Development of atopic disease in babies whose mothers were receiving exclusion diet during pregnancy—A randomized study. *J Allergy Clin Immunol* 80(6):868-875.

FAO/WHO (Food and Agriculture Organization/World Health Organization). 2001. *Evaluation of allergenicity of genetically modified foods. Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology*. Rome: Food and Agricultural Organization/World Health Organization.

Fasano, A. 2000. Regulation of intercellular tight junctions by zonula occludens toxin and its eukaryotic analogue zonulin. *Ann N Y Acad Sci* 915:214-222.

Feeney, M., G. Du Toit, G. Roberts, P. H. Sayre, K. Lawson, H. T. Bahnson, M. L. Sever, S. Radulovic, M. Plaut, and G. Lack. 2016. Impact of peanut consumption in the LEAP Study: Feasibility, growth, and nutrition. *J Allergy Clin Immunol* 138(4):1108-1118.

Fleischer, D. M., J. M. Spergel, A. H. Assa'ad, and J. A. Pongracic. 2013. Primary prevention of allergic disease through nutritional interventions. *J Allergy Clin Immunol Pract* 1(1):29-36.

Fleischer, D. M., S. Sicherer, M. Greenhawt, D. Campbell, E. Chan, A. Muraro, S. Halken, Y. Katz, M. Ebisawa, L. Eichenfield, H. Sampson, G. Lack, G. Du Toit, G. Roberts, H. Bahnson, M. Feeney, J. Hourihane, J. Spergel, M. Young, A. As'aad, K. Allen, S. Prescott, S. Kapur, H. Saito, I. Agache, C. A. Akdis, H. Arshad, K. Beyer, A. Dubois, P. Eigenmann, M. Fernandez-Rivas, K. Grimshaw, K. Hoffman-Sommergruber, A. Host, S. Lau, L. O'Mahony, C. Mills, N. Papadopoulos, C. Venter, N. Agmon-Levin, A. Kessel, R. Antaya, B. Drolet, and L. Rosenwasser. 2015. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *J Allergy Clin Immunol* 136(2):258-261.

Fooladi, A. A., S. Khani, H. M. Hosseini, S. F. Mousavi, E. M. Aghdam, and M. R. Nourani. 2013. Impact of altered early infant gut microbiota following breastfeeding and delivery mode on allergic diseases. *Inflamm Allergy Drug Targets* 12(6):410-418.

Frazier, A. L., C. A. Camargo, Jr., S. Malspeis, W. C. Willett, and M. C. Young. 2014. Prospective study of peripregnancy consumption of peanuts or tree nuts by mothers and the risk of peanut or tree nut allergy in their offspring. *JAMA Pediatr* 168(2):156-162.

Furuhjelm, C., K. Warstedt, J. Larsson, M. Fredriksson, M. F. Bottcher, K. Falth-Magnusson, and K. Duchen. 2009. Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. *Acta Paediatr* 98(9):1461-1467.

Furuhjelm, C., K. Warstedt, M. Fageras, K. Falth-Magnusson, J. Larsson, M. Fredriksson, and K. Duchen. 2011. Allergic disease in infants up to 2 years of age in relation to plasma omega-3 fatty acids and maternal fish oil supplementation in pregnancy and lactation. *Pediatr Allergy Immunol* 22(5):505-514.

Galli, S. J., P. Starkl, T. Marichal, and M. Tsai. 2016. Mast cells and IgE in defense against venoms: Possible "good side" of allergy? *Allergol Int* 65(1):3-15.

Gaudieri, S., M. Lucas, A. Lucas, E. McKinnon, H. Albloushi, A. Rauch, J. di Iulio, D. Martino, S. L. Prescott, and M. K. Tulic. 2012. Genetic variations in IL28B and allergic disease in children. *PLoS One* 7(1):e30607.

Goldberg, M., E. Eisenberg, A. Elizur, N. Rajuan, M. Rachmiel, A. Cohen, G. Zadik-Mnuhin, and Y. Katz. 2013. Role of parental atopy in cow's milk allergy: A population-based study. *Ann Allergy Asthma Immunol* 110(4):279-283.

Goldman, A. S. 2000. Modulation of the gastrointestinal tract of infants by human milk. Interfaces and interactions. An evolutionary perspective. *J Nutr* 130(2S Suppl):426S-431S.

Goodman, R. E., M. Ebisawa, F. Ferreira, H. A. Sampson, R. van Ree, S. Vieths, J. L. Baumert, B. Bohle, S. Lalithambika, J. Wise, and S. L. Taylor. 2016. AllergenOnline: A peer-reviewed, curated allergen database to assess novel food proteins for potential cross-reactivity. *Molec Nutr Food Res* 60(5):1183-1198.

Gottgens, B. 2012. Genome-scale technology driven advances to research into normal and malignant haematopoiesis. *Scientifica (Cairo)* 2012:437956.

Granell, R., A. J. Henderson, D. M. Evans, G. D. Smith, A. R. Ness, S. Lewis, T. M. Palmer, and J. A. Sterne. 2014. Effects of BMI, fat mass, and lean mass on asthma in childhood: A Mendelian randomization study. *PLoS Med* 11(7):e1001669.

Greer, F. R., S. H. Sicherer, and A. W. Burks. 2008. Effects of early nutritional interventions on the development of atopic disease in infants and children: The role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 121(1):183-191.

Grimshaw, K. E., K. Allen, C. A. Edwards, K. Beyer, A. Boulay, L. B. van der Aa, A. Sprikkelman, S. Belohlavkova, M. Clausen, R. Dubakiene, E. Duggan, M. Reche, L. V. Marino, P. Norhede, L. Ogorodova, A. Schoemaker, A. Stanczyk-Przyluska, Z. Szepfalusi, E. Vassilopoulou, S. H. Veehof, B. J. Vlieg-Boerstra, M. Wjst, and A. E. Dubois. 2009. Infant feeding and allergy prevention: A review of current knowledge and recommendations. A EuroPrevall state of the art paper. *Allergy* 64(10):1407-1416.

Grimshaw, K. E. C., J. Maskell, E. M. Oliver, R. C. G. Morris, K. D. Foote, E. N. C. Mills, B. M. Margetts, and G. Roberts. 2014. Diet and food allergy development during infancy: Birth cohort study findings using prospective food diary data. *J Allergy Clin Immunol* 133(2):511-519.

Gunaratne, A. W., M. Makrides, and C. T. Collins. 2015. Maternal prenatal and/or postnatal n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation for preventing allergies in early childhood. *Cochrane Database Syst Rev* 7:CD010085.

Hand, S., C. Darke, J. Thompson, C. Stingl, S. Rolf, K. P. Jones, and B. H. Davies. 2004. Human leucocyte antigen polymorphisms in nut-allergic patients in South Wales. *Clin Exp Allergy* 34(5):720-724.

Hansen, C. H., D. S. Nielsen, M. Kverka, Z. Zakostelska, K. Klimesova, T. Hudcovic, H. Tlaskalova-Hogenova, and A. K. Hansen. 2012. Patterns of early gut colonization shape future immune responses of the host. *PLoS One* 7(3):e34043.

Hersoug, L. G., and A. Linneberg. 2007. The link between the epidemics of obesity and allergic diseases: Does obesity induce decreased immune tolerance? *Allergy* 62(10):1205-1213.

Hollingsworth, J. W., S. Maruoka, K. Boon, S. Garantziotis, Z. Li, J. Tomfohr, N. Bailey, E. N. Potts, G. Whitehead, D. M. Brass, and D. A. Schwartz. 2008. In utero supplementation with methyl donors enhances allergic airway disease in mice. *J Clin Invest* 118(10):3462-3469.

Hong, X., and X. Wang. 2014. Epigenetics and development of food allergy (FA) in early childhood. *Curr Allergy Asthma Rep* 14(9):460.

Hong, X., G. Wang, X. Liu, R. Kumar, H. J. Tsai, L. Arguelles, K. Hao, C. Pearson, K. Ortiz, A. Bonzagni, S. Apollon, L. Fu, D. Caruso, J. A. Pongracic, R. Schleimer, P. G. Holt, H. Bauchner, and X. Wang. 2011. Gene polymorphisms, breast-feeding, and development of food sensitization in early childhood. *J Allergy Clin Immunol* 128(2):374-381.

Hong, X., K. Hao, C. Ladd-Acosta, K. D. Hansen, H. J. Tsai, X. Liu, X. Xu, T. A. Thornton, D. Caruso, C. A. Keet, Y. Sun, G. Wang, W. Luo, R. Kumar, R. Fuleihan, A. M. Singh, J. S. Kim, R. E. Story, R. S. Gupta, P. Gao, Z. Chen, S. O. Walker, T. R. Bartell, T. H. Beaty, M. D. Fallin, R. Schleimer, P. G. Holt, K. C. Nadeau, R. A. Wood, J. A. Pongracic, D. E. Weeks, and X. Wang. 2015. Genome-wide association study identifies peanut allergy-specific loci and evidence of epigenetic mediation in US children. *Nat Commun* 6:6304.

Hong, X., C. Ladd-Acosta, K. Hao, B. Sherwood, H. Ji, C. A. Keet, R. Kumar, D. Caruso, X. Liu, G. Wang, Z. Chen, Y. Ji, G. Mao, S. O. Walker, T. R. Bartell, Z. Ji, Y. Sun, H. J. Tsai, J. A. Pongracic, D. E. Weeks, and X. Wang. 2016. Epigenome-wide association study links site-specific DNA methylation changes with cow's milk allergy. *J Allergy Clin Immunol* 138(3):908-911.

Horimukai, K., K. Morita, M. Narita, M. Kondo, H. Kitazawa, M. Nozaki, Y. Shigematsu, K. Yoshida, H. Niizeki, K. Motomura, H. Sago, T. Takimoto, E. Inoue, N. Kamemura, H. Kido, J. Hisatsune, M. Sugai, H. Murota, I. Katayama, T. Sasaki, M. Amagai, H. Morita, A. Matsuda, K. Matsumoto, H. Saito, and Y. Ohya. 2014. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 134(4):824-830.

Hu, Y., J. Chen, and H. Li. 2010. Comparison of food allergy prevalence among Chinese infants in Chongqing, 2009 versus 1999. *Pediatr Int* 52(5):820-824.

Iho, S., F. Kura, H. Sugiyama, T. Takahashi, and T. Hoshino. 1985. The role of monocytes in the suppression of PHA-induced proliferation and IL 2 production of human mononuclear cells by 1,25-dihydroxyvitamin D3. *Immunol Lett* 11(5-6):331-336.

Ivakhnenko, O., and S. Nyankovskyy. 2013. Effect of the specific infant formula mixture of oligosaccharides on local immunity and development of allergic and infectious disease in young children: Randomized study. *Pediatria Polska* 88(5):398-404.

Jarvis, D., S. Chinn, J. Potts, and P. Burney. 2002. Association of body mass index with respiratory symptoms and atopy: Results from the European Community Respiratory Health Survey. *Clin Exp Allergy* 32(6):831-837.

Jones, A. C., E. A. Miles, J. O. Warner, B. M. Colwell, T. N. Bryant, and J. A. Warner. 1996. Fetal peripheral blood mononuclear cell proliferative responses to mitogenic and allergenic stimuli during gestation. *Pediatr Allergy Immunol* 7(3):109-116.

Jones, A. P., D. Palmer, G. Zhang, and S. L. Prescott. 2012. Cord blood 25-hydroxyvitamin D3 and allergic disease during infancy. *Pediatrics* 130(5):e1128-e1135.

Jones, B., and J. Chen. 2006. Inhibition of IFN-gamma transcription by site-specific methylation during T helper cell development. *EMBO J* 25(11):2443-2452.

Katz, Y., N. Rajuan, M. R. Goldberg, E. Eisenberg, E. Heyman, A. Cohen, and M. Leshno. 2010. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 126(1):77-82.

Kelly, D., T. King, and R. Aminov. 2007. Importance of microbial colonization of the gut in early life to the development of immunity. *Mutat Res* 622(1-2):58-69.

Klemens, C. M., D. R. Berman, and E. L. Mozurkewich. 2011. The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: A systematic review. *BJOG* 118(8):916-925.

Kong, X. Y., Y. Yang, J. Guan, and R. Z. Wang. 2014. Probiotics' preventive effect on pediatric food allergy: A meta-analysis of randomized controlled trials. *Chin Med Sci J* 29(3):144-147.

Koplin, J. J., and K. J. Allen. 2013. Optimal timing for solids introduction—why are the guidelines always changing? *Clin Exp Allergy* 43(8):826-834.

Koplin, J. J., N. J. Osborne, M. Wake, P. E. Martin, L. C. Gurrin, M. N. Robinson, D. Tey, M. Slaa, L. Thiele, L. Miles, D. Anderson, T. Tan, T. D. Dang, D. J. Hill, A. J. Lowe, M. C. Matheson, A. L. Ponsonby, M. L. Tang, S. C. Dharmage, and K. J. Allen. 2010. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 126(4):807-813.

Koplin, J. J., S. C. Dharmage, A. L. Ponsonby, M. L. Tang, A. J. Lowe, L. C. Gurrin, N. J. Osborne, P. E. Martin, M. N. Robinson, M. Wake, D. J. Hill, and K. J. Allen. 2012a. Environmental and demographic risk factors for egg allergy in a population-based study of infants. *Allergy* 67(11):1415-1422.

Koplin, J. J., M. L. Tang, P. E. Martin, N. J. Osborne, A. J. Lowe, A. L. Ponsonby, M. N. Robinson, D. Tey, L. Thiele, D. J. Hill, L. C. Gurrin, M. Wake, S. C. Dharmage, and K. J. Allen. 2012b. Predetermined challenge eligibility and cessation criteria for oral food challenges in the HealthNuts population-based study of infants. *J Allergy Clin Immunol* 129(4):1145-1147.

Koplin, J. J., R. L. Peters, A. L. Ponsonby, L. C. Gurrin, D. Hill, M. L. Tang, S. C. Dharmage, and K. J. Allen. 2014. Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents. *Allergy* 69(12):1639-1647.

Koplin, J. J., N. H. Suaini, P. Vuillermin, J. A. Ellis, M. Panjari, A. L. Ponsonby, R. L. Peters, M. C. Matheson, D. Martino, T. Dang, N. J. Osborne, P. Martin, A. Lowe, L. C. Gurrin, M. L. Tang, M. Wake, T. Dwyer, J. Hopper, S. C. Dharmage, and K. J. Allen. 2016. Polymorphisms affecting vitamin D-binding protein modify the relationship between serum vitamin D (25[OH]D3) and food allergy. *J Allergy Clin Immunol* 137(2):500-506.

Kozyrskyj, A. 2015. *Infant gut microbial markers of food sensitization at age 1*. Presented at Comittee Workshop, August 31, 2015. Washington, DC.

Kramer, M. S., and R. Kakuma. 2012. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 9:Cd000133.

Kumar, R., F. Ouyang, R. E. Story, J. A. Pongracic, X. Hong, G. Wang, C. Pearson, K. Ortiz, H. Bauchner, and X. Wang. 2009. Gestational diabetes, atopic dermatitis, and allergen sensitization in early childhood. *J Allergy Clin Immunol* 124(5):1031-1038.

Kusunoki, T., I. Okafuji, T. Yoshioka, M. Saito, R. Nishikomori, T. Heike, M. Sugai, A. Shimizu, and T. Nakahata. 2005. SPINK5 polymorphism is associated with disease severity and food allergy in children with atopic dermatitis. *J Allergy Clin Immunol* 115(3):636-638.

Lack, G. 2012. Update on risk factors for food allergy. *J Allergy Clin Immunol* 129(5): 1187-1197.

Lack, G., D. Fox, K. Northstone, and J. Golding. 2003. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 348(11):977-985.

Langley-Evans, S. 1997. Fetal programming of immune function and respiratory disease. *Clin Exp Allergy* 27(12):1377-1379.

Lau, M. Y., S. C. Dharmage, J. A. Burgess, A. J. Lowe, C. J. Lodge, B. Campbell, and M. C. Matheson. 2014. CD14 polymorphisms, microbial exposure and allergic diseases: A systematic review of gene-environment interactions. *Allergy* 69(11):1440-1453.

Lauritzen, L., T. M. Kjaer, M. B. Fruekilde, K. F. Michaelsen, and H. Frokiaer. 2005. Fish oil supplementation of lactating mothers affects cytokine production in 2 1/2-year-old children. *Lipids* 40(7):669-676.

Li, M., J. B. Liu, Q. Liu, M. Yao, R. Cheng, H. Xue, H. Zhou, and Z. Yao. 2012. Interactions between *FLG* mutations and allergens in atopic dermatitis. *Arch Dermatol Res* 304(10):787-793.

Li, M., M. Wang, and S. M. Donovan. 2014. Early development of the gut microbiome and immune-mediated childhood disorders. *Semin Reprod Med* 32(1):74-86.

Liao, S. L., S. H. Lai, K. W. Yeh, Y. L. Huang, T. C. Yao, M. H. Tsai, M.C. Hua, and J. L. Huang. 2014. Exclusive breastfeeding is associated with reduced cow's milk sensitization in early childhood. *Pediatr Allergy Immunol* 25(5):456-461.

Lilja, G., A. Dannaeus, K. Falth-Magnusson, V. Graff-Lonnevig, S. G. Johansson, N. I. Kjellman, and H. Oman. 1988. Immune response of the atopic woman and foetus: Effects of high- and low-dose food allergen intake during late pregnancy. *Clin Allergy* 18(2):131-142.

Litonjua, A. A., and S. T. Weiss. 2007. Is vitamin D deficiency to blame for the asthma epidemic? *J Allergy Clin Immunol* 120(5):1031-1035.

Litonjua, A. A., and S. T. Weiss. 2008. Reply. *J Allergy Clin Immunol* 121(4):1066.

Liu, X., T. H. Beaty, P. Deindl, S. K. Huang, S. Lau, C. Sommerfeld, M. D. Fallin, W. H. Kao, U. Wahn, and R. Nickel. 2004. Associations between specific serum IgE response and 6 variants within the genes IL4, IL13, and IL4RA in German children: The German Multicenter Atopy Study. *J Allergy Clin Immunol* 113(3):489-495.

Liu, X., S. Zhang, H. J. Tsai, X. Hong, B. Wang, Y. Fang, X. Liu, J. A. Pongracic, and X. Wang. 2009. Genetic and environmental contributions to allergen sensitization in a Chinese twin study. *Clin Exp Allergy* 39(7):991-998.

Liu, X., G. Wang, X. Hong, D. Wang, H. J. Tsai, S. Zhang, L. Arguelles, R. Kumar, H. Wang, R. Liu, Y. Zhou, C. Pearson, K. Ortiz, R. Schleimer, P. G. Holt, J. Pongracic, H. E. Price, C. Langman, and X. Wang. 2011. Gene-vitamin D interactions on food sensitization: A prospective birth cohort study. *Allergy* 66(11):1442-1448.

Liu, X., L. Arguelles, Y. Zhou, G. Wang, Q. Chen, H. J. Tsai, X. Hong, R. Liu, H. E. Price, C. Pearson, S. Apollon, N. Cruz, R. Schleimer, C. B. Langman, J. A. Pongracic, and X. Wang. 2013. Longitudinal trajectory of vitamin D status from birth to early childhood in the development of food sensitization. *Pediatr Res* 74(3):321-326.

Lodge, C. J., K. J. Allen, A. J. Lowe, and S. C. Dharmage. 2013. Overview of evidence in prevention and aetiology of food allergy: A review of systematic reviews. *Int J Environ Res Public Health* 10(11):5781-5806.

Lodge, C. J., D. J. Tan, M. X. Lau, X. Dai, R. Tham, A. J. Lowe, G. Bowatte, K. J. Allen, and S. C. Dharmage. 2015. Breastfeeding and asthma and allergies: A systematic review and meta-analysis. *Acta Paediatr* 104(467):38-53.

Loo, E. X., G. V. Llanora, Q. Lu, M. M. Aw, B. W. Lee, and L. P. Shek. 2014. Supplementation with probiotics in the first 6 months of life did not protect against eczema and allergy in at-risk Asian infants: A 5-year follow-up. *Int Arch Allergy Immunol* 163(1):25-28.

Lowe, A. J., C. S. Hosking, C. M. Bennett, K. J. Allen, C. Axelrad, J. B. Carlin, M. J. Abramson, S. C. Dharmage, and D. J. Hill. 2011. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: A randomized controlled trial. *J Allergy Clin Immunol* 128(2):360-365.

Lowe, A. J., S. C. Dharmage, K. J. Allen, M. L. Tang, and D. J. Hill. 2013. The role of partially hydrolyzed whey formula for the prevention of allergic disease: Evidence and gaps. *Expert Rev Clin Immunol* 9(1):31-41.

Luccioli, S., Y. Zhang, L. Verrill, M. Ramos-Valle, and E. Kwegyir-Afful. 2014. Infant feeding practices and reported food allergies at 6 years of age. *Pediatrics* 134(Suppl 1):S21-S28.

Ma, J., L. Xiao, and S. B. Knowles. 2010. Obesity, insulin resistance and the prevalence of atopy and asthma in US adults. *Allergy* 65(11):1455-1463.

Madore, A. M., V. T. Vaillancourt, Y. Asai, R. Alizadehfar, M. Ben-Shoshan, D. L. Michel, A. L. Kozyrskyj, A. Becker, M. Chan-Yeung, A. E. Clarke, P. Hull, D. Daley, A. J. Sandford, and C. Laprise. 2013. HLA-DQB1*02 and DQB1*06:03P are associated with peanut allergy. *Eur J Hum Genet* 21(10):1181-1184.

Magdelijns, F. J., M. Mommers, J. Penders, L. Smits, and C. Thijs. 2011. Folic acid use in pregnancy and the development of atopy, asthma, and lung function in childhood. *Pediatrics* 128(1):e135-144.

Mailhol, C., F. Giordano-Labadie, V. Lauwers-Cances, A. Ammoury, C. Paul, and F. Rance. 2014. Point prevalence and risk factors for food allergy in a cohort of 386 children with atopic dermatitis attending a multidisciplinary dermatology/paediatric allergy clinic. *Eur J Dermatol* 24(1):63-69.

Makrides, M., R. A. Gibson, A. J. McPhee, C. T. Collins, P. G. Davis, L. W. Doyle, K. Simmer, P. B. Colditz, S. Morris, L. G. Smithers, K. Willson, and P. Ryan. 2009. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: A randomized controlled trial. *JAMA* 301(2):175-182.

Makrides, M., R. A. Gibson, A. J. McPhee, L. Yelland, J. Quinlivan, P. Ryan, and Domino Investigative Team. 2010. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: A randomized controlled trial. *JAMA* 304(15):1675-1683.

Marichal, T., P. Starkl, L. L. Reber, J. Kalesnikoff, H. C. Oettgen, M. Tsai, M. Metz, and S. J. Galli. 2013. A beneficial role for immunoglobulin E in host defense against honeybee venom. *Immunity* 39(5):963-975.

Marrs, T., K. D. Bruce, K. Logan, D. W. Rivett, M. R. Perkin, G. Lack, and C. Flohr. 2013. Is there an association between microbial exposure and food allergy? A systematic review. *Pediatr Allergy Immunol* 24(4):311-320.

Martin, P. E., J. J. Koplin, J. K. Eckert, A. J. Lowe, A. L. Ponsonby, N. J. Osborne, L. C. Gurrin, M. N. Robinson, D. J. Hill, M. L. K. Tang, S. C. Dharmage, and K. J. Allen. 2013. The prevalence and socio-demographic risk factors of clinical eczema in infancy: A population-based observational study. *Clin Exp Allergy* 43(6):642-651.

Martin, P. E., J. K. Eckert, J. J. Koplin, A. J. Lowe, L. C. Gurrin, S. C. Dharmage, P. Vuillermin, M. L. Tang, A. L. Ponsonby, M. Matheson, D. J. Hill, and K. J. Allen. 2015. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy* 45(1):255-264.

Martin, R., A. J. Nauta, K. Ben Amor, L. M. Knippels, J. Knol, and J. Garssen. 2010. Early life: Gut microbiota and immune development in infancy. *Benef Microbes* 1(4):367-382.

Martino, D., J. E. Joo, A. Sexton-Oates, T. Dang, K. Allen, R. Saffery, and S. Prescott. 2014. Epigenome-wide association study reveals longitudinally stable DNA methylation differences in CD4+ T cells from children with IgE-mediated food allergy. *Epigenetics* 9(7):998-1006.

Matsui, E. C., and W. Matsui. 2009. Higher serum folate levels are associated with a lower risk of atopy and wheeze. *J Allergy Clin Immunol* 123(6):1253-1259.

McAndrew, F., J. Thompson, L. Fellows, A. Large, M. Speed, and M. J. Renfrew. 2012. *Infant feeding survey.* Leeds, England: Health and Social Care Information Centre, IFF Research.

McGowan, E. C., G. R. Bloomberg, P. J. Gergen, C. M. Visness, K. F. Jaffee, M. Sandel, G. O'Connor, M. Kattan, J. Gern, and R. A. Wood. 2015. Influence of early-life exposures on food sensitization and food allergy in an inner-city birth cohort. *J Allergy Clin Immunol* 135(1):171-178.

McLoughlin, R. M., and K. H. Mills. 2011. Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma. *J Allergy Clin Immunol* 127(5):1097-1107; quiz 1108-1109.

Metsala, J., A. Lundqvist, M. Kaila, M. Gissler, T. Klaukka, and S. M. Virtanen. 2010. Maternal and perinatal characteristics and the risk of cow's milk allergy in infants up to 2 years of age: A case-control study nested in the Finnish population. *Am J Epidemiol* 171(12):1310-1316.

Metsala, J., A. Lundqvist, L. J. Virta, M. Kaila, M. Gissler, and S. M. Virtanen. 2013. Mother's and offspring's use of antibiotics and infant allergy to cow's milk. *Epidemiology* 24(2):303-309.

Mullins, R. J., S. Clark, and C. A. Camargo, Jr. 2009. Regional variation in epinephrine autoinjector prescriptions in Australia: More evidence for the vitamin D-anaphylaxis hypothesis. *Ann Allergy Asthma Immunol* 103(6):488-495.

Mullins, R. J., S. Clark, and C. A. Camargo, Jr. 2010. Regional variation in infant hypoallergenic formula prescriptions in Australia. *Pediatr Allergy Immunol* 21(2 Pt 2):e413-e420.

Mullins, R. J., S. Clark, C. Katelaris, V. Smith, G. Solley, and C. A. Camargo, Jr. 2011. Season of birth and childhood food allergy in Australia. *Pediatr Allergy Immunol* 22(6):583-589.

Muraro, A., S. Halken, S. H. Arshad, K. Beyer, A. E. Dubois, G. Du Toit, P. A. Eigenmann, K. E. Grimshaw, A. Hoest, G. Lack, L. O'Mahony, N. G. Papadopoulos, S. Panesar, S. Prescott, G. Roberts, D. de Silva, C. Venter, V. Verhasselt, A. C. Akdis, and A. Sheikh. 2014. Primary prevention of food allergy. *Allergy* 69(5):590-601.

Muto, T., A. Fukuoka, K. Kabashima, S. F. Ziegler, K. Nakanishi, K. Matsushita, and T. Yoshimoto. 2014. The role of basophils and proallergic cytokines, TSLP and IL-33, in cutaneously sensitized food allergy. *Int Immunol* 26(10):539-549.

Myers, J. M. B., N. Wang, G. K. LeMasters, D. I. Bernstein, T. G. Epstein, M. A. Lindsey, M. B. Ericksen, R. Chakraborty, P. H. Ryan, M. S. Villareal, J. W. Burkle, J. E. Lockey, T. Reponen, and G. K. K. Hershey. 2010. Genetic and environmental risk factors for childhood eczema development and allergic sensitization in the CCAAPS Cohort. *J Invest Derm* 130(2):430-437.

Myles, I. A. 2014. Fast food fever: Reviewing the impacts of the Western diet on immunity. *Nutr J* 13:61.

Neeland, M. R., D. J. Martino, and K. J. Allen. 2015. The role of gene-environment interactions in the development of food allergy. *Expert Rev Gastroenterol Hepatol* 9(11):1317-1318.

Negoro, T., K. Orihara, T. Irahara, H. Nishiyama, K. Hagiwara, R. Nishida, H. Takagi, K. Satoh, Y. Yamamoto, S. Shimizu, T. Hagiwara, M. Ishii, T. Tanioka, Y. Nakano, K. Takeda, I. Yoshimura, Y. Iikura, and T. Tobe. 2006. Influence of SNPs in cytokine-related genes on the severity of food allergy and atopic eczema in children. *Pediatr Allergy Immunol* 17(8):583-590.

Newberry, S. J., M. Chung, M. Booth, M. A. Maglione, A. M. Tang, C. E. O'Hanlon, D. D. Wang, A. Okunogbe, C. Huang, A. Motala, M. Timmer, W. Dudley, R. Shanman, T. R. Coker, and P. G. Shekelle. 2016. *Omega-3 fatty acids and maternal and child health: An updated systematic review.* Evidence Report/Technology Assessment No. 224. AHRQ Publication No. 16-E003-EF. Rockville, MD: Agency for Healthcare Research and Quality.

NHMRC (National Health and Medical Research Council). 2013. *Infant feeding guidelines*. Canberra, Australia: National Health and Medical Research Council. https://www.eatforhealth.gov.au/guidelines (accessed November 14, 2016).

NHS (National Health Service). 2015a. *Pregnancy and baby: Food allergies in babies*. http://www.nhs.uk/conditions/pregnancy-and-baby/pages/food-allergies-in-children.aspx (accessed June 23, 2016).

NHS. 2015b. *Pregnancy and baby: Your baby's first solid foods*. http://www.nhs.uk/conditions/pregnancy-and-baby/pages/solid-foods-weaning.aspx (accessed July 16, 2016).

Nordlee, J. A., S. L. Taylor, J. A. Townsend, L. A. Thomas, and R. K. Bush. 1996. Identification of a Brazil-nut allergen in transgenic soybeans. *N Engl J Med* 334(11):688-692.

Norizoe, C., N. Akiyama, T. Segawa, H. Tachimoto, H. Mezawa, H. Ida, and M. Urashima. 2014. Increased food allergy and vitamin D: Randomized, double-blind, placebo-controlled trial. *Pediatr Int* 56(1):6-12.

Noti, M., B. S. Kim, M. C. Siracusa, G. D. Rak, M. Kubo, A. E. Moghaddam, Q. A. Sattentau, M. R. Comeau, J. M. Spergel, and D. Artis. 2014. Exposure to food allergens through inflamed skin promotes intestinal food allergy through the thymic stromal lymphopoietin-basophil axis. *J Allergy Clin Immunol* 133(5):1390-1399.

Okupa, A. Y., R. F. Lemanske, Jr., D. J. Jackson, M. D. Evans, R. A. Wood, and E. C. Matsui. 2013. Early-life folate levels are associated with incident allergic sensitization. *J Allergy Clin Immunol* 131(1):226-228.

Osborn, D. A., and J. Sinn. 2006. Formulas containing hydrolyzed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev*(4):CD003664.

Osborn, D. A., and J. Sinn. 2009. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants (Review). *Cochrane Database Syst Rev* (1): CD003664.

Osborne, N. J., O. C. Ukoumunne, M. Wake, and K. J. Allen. 2012. Prevalence of eczema and food allergy is associated with latitude in Australia. *J Allergy Clin Immunol* 129(3):865-867.

Ouyang, F., R. Kumar, J. Pongracic, R. E. Story, X. Liu, B. Wang, H. Xing, X. Liu, Z. Li, W. Zhang, Y. Fang, S. Zhang, X. Xu, and X. Wang. 2009. Adiposity, serum lipid levels, and allergic sensitization in Chinese men and women. *J Allergy Clin Immunol* 123(4):940-948.

Oxelius, V. A., R. Krueger, S. Ahlstedt, T. Keil, S. Lau, and U. Wahn. 2015. Innate IgG molecules and innate B cells expressed by immunoglobulin constant heavy G chain (Fcγ) genetic marker genes are involved in the 'allergic march' of IgE sensitization in children. *Int Arch Allergy Immunol* 166(1):25-29.

Pabst, O., and A. M. Mowat. 2012. Oral tolerance to food protein. *Mucosal Immunol* 5(3):232-239.

Palm, N. W., R. K. Rosenstein, S. Yu, D. D. Schenten, E. Florsheim, and R. Medzhitov. 2013. Bee venom phospholipase A2 induces a primary type 2 response that is dependent on the receptor ST2 and confers protective immunity. *Immunity* 39(5):976-985.

Palmer, D. J., T. Sullivan, M. S. Gold, S. L. Prescott, R. Heddle, R. A. Gibson, and M. Makrides. 2012. Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: Randomised controlled trial. *BMJ* 344:e184.

Palmer, D. J., J. Metcalfe, M. Makrides, M. S. Gold, P. Quinn, C. E. West, R. Loh, and S. L. Prescott. 2013. Early regular egg exposure in infants with eczema: A randomized controlled trial. *J Allergy Clin Immunol* 132(2):387-392.

Panjari, M., J. J. Koplin, S. C. Dharmage, R. L. Peters, L. C. Gurrin, S. M. Sawyer, V. McWilliam, J. K. Eckert, D. Vicendese, B. Erbas, M. C. Matheson, M. L. Tang, J. Douglass, A. L. Ponsonby, T. Dwyer, S. Goldfeld, and K. J. Allen. 2016. Nut allergy prevalence and differences between Asian-born children and Australian-born children of Asian descent: A state-wide survey of children at primary school entry in Victoria, Australia. *Clin Exp Allergy* 46(4):602-609.

Pele, F., E. Bajeux, H. Gendron, C. Monfort, F. Rouget, L. Multigner, J. F. Viel, and S. Cordier. 2013. Maternal fish and shellfish consumption and wheeze, eczema and food allergy at age two: A prospective cohort study in Brittany, France. *Environ Health* 12:102.

Perkin, M. R., K. Logan, A. Tseng, B. Raji, S. Ayis, J. Peacock, H. Brough, T. Marrs, S. Radulovic, J. Craven, C. Flohr, and G. Lack. 2016. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 374(18):1733-1743.

Peters, R. L., S. C. Dharmage, L. C. Gurrin, J. J. Koplin, A. L. Ponsonby, A. J. Lowe, M. L. Tang, D. Tey, M. Robinson, D. Hill, H. Czech, L. Thiele, N. J. Osborne, and K. J. Allen. 2014. The natural history and clinical predictors of egg allergy in the first 2 years of life: A prospective, population-based cohort study. *J Allergy Clin Immunol* 133(2):485-491.

Peters, R. L., K. J. Allen, S. C. Dharmage, C. J. Lodge, J. J. Koplin, A. L. Ponsonby, M. Wake, A. J. Lowe, M. L. Tang, M. C. Matheson, and L. C. Gurrin. 2015. Differential factors associated with challenge-proven food allergy phenotypes in a population cohort of infants: A latent class analysis. *Clin Exp Allergy* 45(5):953-963.

Poole, J. A., K. Barriga, D. Y. Leung, M. Hoffman, G. S. Eisenbarth, M. Rewers, and J. M. Norris. 2006. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics* 117(6):2175-2182.

Praveen, P., F. Jordan, C. Priami, and M. J. Morine. 2015. The role of breast-feeding in infant immune system: A systems perspective on the intestinal microbiome. *Microbiome* 3:41.

Prescott, S. L., C. Macaubas, B. J. Holt, T. B. Smallacombe, R. Loh, P. D. Sly, and P. G. Holt. 1998. Transplacental priming of the human immune system to environmental allergens: Universal skewing of initial T cell responses toward the Th2 cytokine profile. *J Immunol* 160(10):4730-4737.

Prescott, S. L., P. Smith, M. Tang, D. J. Palmer, J. Sinn, S. J. Huntley, B. Cormack, R. G. Heine, R. A. Gibson, and M. Makrides. 2008. The importance of early complementary feeding in the development of oral tolerance: Concerns and controversies. *Pediatr Allergy Immunol* 19(5):375-380.

Prince, B. T., M. J. Mandel, K. Nadeau, and A. M. Singh. 2015. Gut microbiome and the development of food allergy and allergic disease. *Pediatr Clin North Am* 62(6):1479-1492.

Pyrhonen, K., S. Nayha, L. Hiltunen, and E. Laara. 2013. Caesarean section and allergic manifestations: Insufficient evidence of association found in population-based study of children aged 1 to 4 years. *Acta Paediatr* 102(10):982-989.

Reichel, H., H. P. Koeffler, A. Tobler, and A. W. Norman. 1987. 1 alpha,25-Dihydroxyvitamin D3 inhibits gamma-interferon synthesis by normal human peripheral blood lymphocytes. *Proc Natl Acad Sci U S A* 84(10):3385-3389.

Roduit, C., R. Frei, M. Depner, B. Schaub, G. Loss, J. Genuneit, P. Pfefferle, A. Hyvarinen, A. M. Karvonen, J. Riedler, J. C. Dalphin, J. Pekkanen, E. von Mutius, C. Braun-Fahrlander, and R. Lauener. 2014. Increased food diversity in the first year of life is inversely associated with allergic diseases. *J Allergy Clin Immunol* 133(4):1056-1064.

Roider, E., T. Ruzicka, and J. Schauber. 2013. Vitamin D, the cutaneous barrier, antimicrobial peptides and allergies: Is there a link? *Allergy Asthma Immunol Res* 5(3):119-128.

Rudders, S. A., J. A. Espinola, and C. A. Camargo, Jr. 2010. North-south differences in US emergency department visits for acute allergic reactions. *Ann Allergy Asthma Immunol* 104(5):413-416.

Saarinen, K. M., K. Juntunen-Backman, A. L. Jarvenpaa, P. Kuitunen, L. Lope, M. Renlund, M. Siivola, and E. Savilahti. 1999. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: A prospective study of 6209 infants. *J Allergy Clin Immunol* 104(2 Pt 1):457-461.

Sampson, H. A., R. Gerth van Wijk, C. Bindslev-Jensen, S. Sicherer, S. S. Teuber, A. W. Burks, A. E. Dubois, K. Beyer, P. A. Eigenmann, J. M. Spergel, T. Werfel, and V. M. Chinchilli. 2012. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 130(6):1260-1274.

Senechal, H., S. Geny, F. X. Desvaux, M. Busson, C. Mayer, Y. Aron, J. P. Oster, J. C. Bessot, G. Peltre, G. Pauli, and E. Swierczewski. 1999. Genetics and specific immune response in allergy to birch pollen and food: Evidence of a strong, positive association between atopy and the HLA class II allele HLA-DR7. *J Allergy Clin Immunol* 104(2 Pt 1):395-401.

Shek, L. P., M. F. Chong, J. Y. Lim, S. E. Soh, and Y. S. Chong. 2012. Role of dietary long-chain polyunsaturated fatty acids in infant allergies and respiratory diseases. *Clin Dev Immunol* 2012:730568.

Sicherer, S. H., T. J. Furlong, H. H. Maes, R. J. Desnick, H. A. Sampson, and B. D. Gelb. 2000. Genetics of peanut allergy: A twin study. *J Allergy Clin Immunol* 106(1 Pt 1):53-56.

Siegel, A. M., K. D. Stone, G. Cruse, M. G. Lawrence, A. Olivera, M. Y. Jung, J. S. Barber, A. F. Freeman, S. M. Holland, M. O'Brien, N. Jones, C. G. Nelson, L. B. Wisch, H. H. Kong, A. Desai, O. Farber, A. M. Gilfillan, J. Rivera, and J. D. Milner. 2013. Diminished allergic disease in patients with STAT3 mutations reveals a role for STAT3 signaling in mast cell degranulation. *J Allergy Clin Immunol* 132(6):1388-1396.

Simopoulos, A. P. 2002. The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed Pharmacother* 56(8):365-379.

Simpson, E. L., J. R. Chalmers, J. M. Hanifin, K. S. Thomas, M. J. Cork, W. H. McLean, S. J. Brown, Z. Chen, Y. Chen, and H. C. Williams. 2014. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 134(4):818-823.

Starkl, P., T. Marichal, N. Gaudenzio, L. L. Reber, R. Sibilano, M. Tsai, and S. J. Galli. 2016. IgE antibodies, FcεRIα, and IgE-mediated local anaphylaxis can limit snake venom toxicity. *J Allergy Clin Immunol* 137(1):246-257.

Stelmach, I., M. Bobrowska-Korzeniowska, K. Smejda, P. Majak, J. Jerzynska, W. Stelmach, K. Polanska, W. Sobala, J. Krysicka, and W. Hanke. 2014. Risk factors for the development of atopic dermatitis and early wheeze. *Allergy Asthma Proc* 35(5):382-389.

Strachan, D. P. 1989. Hay fever, hygiene, and household size. *BMJ* 299(6710):1259-1260.

Strid, J., J. Hourihane, I. Kimber, R. Callard, and S. Strobel. 2005. Epicutaneous exposure to peanut protein prevents oral tolerance and enhances allergic sensitization. *Clin Exp Allergy* 35(6):757-766.

Sudo, N., S. Sawamura, K. Tanaka, Y. Aiba, C. Kubo, and Y. Koga. 1997. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol* 159(4):1739-1745.

Tan, H. T., J. A. Ellis, J. J. Koplin, M. C. Matheson, L. C. Gurrin, A. J. Lowe, P. E. Martin, T. D. Dang, M. Wake, M. L. Tang, A. L. Ponsonby, S. C. Dharmage, and K. J. Allen. 2012a. Filaggrin loss-of-function mutations do not predict food allergy over and above the risk of food sensitization among infants. *J Allergy Clin Immunol* 130(5):1211-1213.

Tan, T. H., J. A. Ellis, R. Saffery, and K. J. Allen. 2012b. The role of genetics and environment in the rise of childhood food allergy. *Clin Exp Allergy* 42(1):20-29.

Tey, D., K. J. Allen, R. L. Peters, J. J. Koplin, M. L. K. Tang, L. C. Gurrin, A.-L. Ponsonby, A. J. Lowe, M. Wake, and S. C. Dharmage. 2014. Population response to change in infant feeding guidelines for allergy prevention. *J Allergy Clin Immunol* 133(2):476-484.

Togias, A., S. F. Cooper, M. L. Acebal, A. Assa'ad, L. Baker, L. A. Beck, J. Block, C. Byrd-Bredbenner, E. S. Chan, L. F. Eichenfield, D. M. Fleischer, G. J. Fuchs III, G. T. Furuta, M. J. Greenhawt, R. S. Gupta, M. Habich, S. M. Jones, K. Keaton, A. Muraro, M. Plaut, L. J. Rosenwasser, D. Rotrosen, H. A. Sampson, L. Schneider, S. H. Sicherer, R. Sidbury, J. Spergel, D. R. Stukus, C. Venter, and J. A. Boyce. 2017. Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases–sponsored expert panel. *Allergy Asthma Clin Immunol* 13(1):1-20.

Torgerson, T. R., A. Linane, N. Moes, S. Anover, V. Mateo, F. Rieux-Laucat, O. Hermine, S. Vijay, E. Gambineri, N. Cerf-Bensussan, A. Fischer, H. D. Ochs, O. Goulet, and F. M. Ruemmele. 2007. Severe food allergy as a variant of IPEX syndrome caused by a deletion in a noncoding region of the FOXP3 gene. *Gastroenterology* 132(5):1705-1717.

Tsai, H. J., R. Kumar, J. Pongracic, X. Liu, R. Story, Y. Yu, D. Caruso, J. Costello, A. Schroeder, Y. Fang, H. Demirtas, K. E. Meyer, M. R. O'Gorman, and X. Wang. 2009. Familial aggregation of food allergy and sensitization to food allergens: A family-based study. *Clin Exp Allergy* 39(1):101-109.

Van Gysel, D., E. Govaere, K. Verhamme, E. Doli, and F. De Baets. 2009. Body mass index in Belgian schoolchildren and its relationship with sensitization and allergic symptoms. *Pediatr Allergy Immunol* 20(3):246-253.

Vassallo, M. F., A. Banerji, S. A. Rudders, S. Clark, and C. A. Camargo, Jr. 2010. Season of birth and food-induced anaphylaxis in Boston. *Allergy* 65(11):1492-1493.

Venkataraman, D., N. Soto-Ramirez, R. J. Kurukulaaratchy, J. W. Holloway, W. Karmaus, S. L. Ewart, S. H. Arshad, and M. Erlewyn-Lajeunesse. 2014. Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence. *J Allergy Clin Immunol* 134(4):876-882.

Visness, C. M., S. J. London, J. L. Daniels, J. S. Kaufman, K. B. Yeatts, A. M. Siega-Riz, A. H. Liu, A. Calatroni, and D. C. Zeldin. 2009. Association of obesity with IgE levels and allergy symptoms in children and adolescents: Results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 123(5):1163-1169.

von Berg, A., B. Filipiak-Pittroff, U. Kramer, E. Link, C. Bollrath, I. Brockow, S. Koletzko, A. Grubl, J. Heinrich, H. E. Wichmann, C. P. Bauer, D. Reinhardt, and D. Berdel. 2008. Preventive effect of hydrolyzed infant formulas persists until age 6 years: Long-term results from the German Infant Nutritional Intervention Study (GINI). *J Allergy Clin Immunol* 121(6):1442-1447.

von Berg, A., B. Filipiak-Pittroff, U. Kramer, B. Hoffmann, E. Link, C. Beckmann, U. Hoffmann, D. Reinhardt, A. Grubl, J. Heinrich, H. E. Wichmann, C. P. Bauer, S. Koletzko, and D. Berdel. 2013a. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-Year results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunol* 131(6):1565-1573.

von Berg, A., S. Koletzko, B. Filipiak-Pittroff, J. Heinrich, C. P. Bauer, U. Kramer, B. Hoffmann, and D. Berdel. 2013b. The German Infant Nutritional Intervention (GINI) study and formulation issues. Reply. *J Allergy Clin Immunol* 132(3):770-771.

Wall, R., R. P. Ross, G. F. Fitzgerald, and C. Stanton. 2010. Fatty acids from fish: The anti-inflammatory potential of long-chain omega-3 fatty acids. *Nutr Rev* 68(5):280-289.

Wawro, N., J. Heinrich, E. Thiering, J. Kratzsch, B. Schaaf, B. Hoffmann, I. Lehmann, C. P. Bauer, S. Koletzko, A. von Berg, D. Berdel, and J. Linseisen. 2014. Serum 25(OH)D concentrations and atopic diseases at age 10: Results from the GINIplus and LISAplus birth cohort studies. *BMC Pediatr* 14:286.

Weisse, K., S. Winkler, F. Hirche, G. Herberth, D. Hinz, M. Bauer, S. Roder, U. Rolle-Kampczyk, M. von Bergen, S. Olek, U. Sack, T. Richter, U. Diez, M. Borte, G. I. Stangl, and I. Lehmann. 2013. Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. *Allergy* 68(2):220-228.

West, C. E., J. Dunstan, S. McCarthy, J. Metcalfe, N. D'Vaz, S. Meldrum, W. H. Oddy, M. K. Tulic, and S. L. Prescott. 2012. Associations between maternal antioxidant intakes in pregnancy and infant allergic outcomes. *Nutrients* 4(11):1747-1758.

West, C. E., M. L. Hammarstrom, and O. Hernell. 2013. Probiotics in primary prevention of allergic disease—Follow-up at 8-9 years of age. *Allergy* 68(8):1015-1020.

West, C. E., H. Renz, M. C. Jenmalm, A. L. Kozyrskyj, K. J. Allen, P. Vuillermin, and S. L. Prescott. 2015. The gut microbiota and inflammatory noncommunicable diseases: Associations and potentials for gut microbiota therapies. *J Allergy Clin Immunol* 135(1):3-13.

Wetzig, H., R. Schulz, U. Diez, O. Herbarth, B. Viehweg, and M. Borte. 2000. Associations between duration of breast-feeding, sensitization to hens' eggs and eczema infantum in one and two year old children at high risk of atopy. *Int J Hyg Environ Health* 203(1):17-21.

WHO (World Health Organization). 2003. *Prevention of allergy and allergic asthma. Based on the WHO/WAO meeting on the prevention of allergy and allergic asthma.* Geneva, Switzerland: WHO.

WHO. 2016. *Infant and young child feeding*. http://who.int/mediacentre/factsheets/fs342/en (accessed June 5, 2016).

Wjst, M. 2008. Allergy risk of vitamin D supplements has been described in various settings. *J Allergy Clin Immunol* 121(4):1065-1066; author reply 1066.

Wjst, M., and S. Dold. 1999. Genes, factor X, and allergens: What causes allergic diseases? *Allergy* 54(7):757-759.

Woo, J. G., A. Assa'ad, A. B. Heizer, J. A. Bernstein, and G. K. Hershey. 2003. The –159 C→T polymorphism of CD14 is associated with nonatopic asthma and food allergy. *J Allergy Clin Immunol* 112(2):438-444.

Xu, B., M. R. Jarvelin, and J. Pekkanen. 2000. Body build and atopy. *J Allergy Clin Immunol* 105(2 Pt 1):393-394.

Zhang, Y., F. Collier, G. Naselli, R. Saffery, M. L. Tang, K. J. Allen, A. L. Ponsonby, L. C. Harrison, and P. Vuillermin. 2016. Cord blood monocyte-derived inflammatory cytokines suppress IL-2 and induce nonclassic "TH2-type" immunity associated with development of food allergy. *Sci Transl Med* 8(321):321ra8.

6

Management in the Health Care Setting

Proper management in the health care setting begins with an appropriate diagnosis of food allergy so that the patient can be instructed on specifically which foods can trigger allergic symptoms. Once a diagnosis is established, management relies on educating the patient and family on avoiding the allergen and preparing to treat allergic symptoms, including severe allergic reactions (i.e., anaphylaxis) promptly and appropriately. Additionally, daily management of food allergy carries potential nutritional, social, and emotional ramifications that should be addressed. Achieving these goals requires significant patient and family education and counseling. Emerging approaches for treatment show promise for altering the threshold of reactivity, making exposure to small amounts of the food less problematic, and future treatments will ideally result in elimination of the allergy.

This chapter covers management of diagnosed food allergy from the perspective of a health care setting and includes topics such as the impact of food allergy on affected individuals and families and the current understanding of food allergy treatment. Dietary issues with regard to prevention are discussed in Chapter 5. This chapter also highlights the importance of educating health care providers about food allergy and management advice for the home, public environments, and high-risk scenarios. From a developmental and ecological perspective, the instructions provided at the health care setting represents only one aspect of successful management because successful adherence depends on management and sensitivity toward food allergy from all societal sectors, including families, schools, food service, and the community. Chapter 7 focuses on management of food allergies in

other settings such as schools, restaurants, and travel, and on the safety of manufactured products.

APPROACH TO LITERATURE REVIEW

The topics addressed in this chapter did not undergo individual systematic review or meta-analysis. The primary resources for discussion, findings, conclusions, and recommendations were derived from various guidelines (see Chapter 1, Table 1-1, for a description of the guidelines): the National Institute of Allergy and Infectious Diseases/National Institutes of Health (NIAID/NIH)-supported Guidelines (Boyce et al., 2010) and its associated literature reviews, the European Academy of Allergy & Clinical Immunology (EEACI) Guidelines (Muraro et al., 2014a,b) and associated systematic reviews (de Silva et al., 2014; Dhami et al., 2014), the American Academy of Allergy, Asthma & Immunology (AAAAI) Guidelines (Sampson et al., 2014); the AAAAI Practice parameter (Lieberman et al., 2015), and American Academy of Pediatrics (AAP) Clinical Reports (Sicherer et al., 2007, 2010). Additional PubMed searches were performed to identify items in the literature to supplement the discussion on specific topics, especially for papers published after the aforementioned reports. Meta-analyses and systematic reviews were selected when available.

ALLERGEN AVOIDANCE AND RECOGNITION OF AND PREPAREDNESS TO TREAT ALLERGIC REACTIONS AND ANAPHYLAXIS

General Principles of Management, Avoidance, Cross-Contact, Hidden Ingredients, Routes of Exposure

The primary advice for managing a diagnosed food allergy, whether immunoglobulin E (IgE)-mediated or non-IgE-mediated, is to avoid ingesting the culprit food allergen(s) (Boyce et al., 2010; Muraro et al., 2014b; Sampson et al., 2014). Of course, no randomized clinical trials (RCTs) have been conducted to evaluate this approach, but not ingesting the allergen is a rational management strategy for a diagnosed food allergy. No evidence exists that avoidance affects the natural course of atopic dermatitis, asthma, or eosinophilic esophagitis (Allen et al., 2009; Boyce et al., 2010). Maternal avoidance of a food allergen may be needed in some cases if the infant, diagnosed with a food allergy, experiences reactions from the maternally-ingested allergen while breastfeeding (Jarvinen et al., 1999; Lifschitz et al., 1988; Monti et al., 2006).

Achieving avoidance of a food allergen entails numerous considerations involved in obtaining or preparing allergen-safe foods. For example, *cross-*

contact is a term describing a situation where an unintended allergen may be present in an otherwise allergen-free food because of contact between the unsafe and safe food. Examples of cross-contact include having a knife used in peanut butter placed into a jar of jelly, using a fryer with oil exposed to fish and egg ingredients used for potatoes, and placing a spoon used to stir a milk-containing soup into a milk-free one.

The possibility of *hidden ingredients* is also a concern (see also Chapter 7). For example, an individual with food allergy may not have expected that chili or spaghetti sauce may contain peanut flour, that peanut butter may be used to seal the ends of an egg roll, or that "non-dairy" creamers contain casein, the major allergenic protein in cow milk.

Avoiding ingestion of a food allergen requires patient education about obtaining safe foods in numerous settings, for example reading labels on packaged foods,[1] asking before ordering in restaurants and food service, and preparing safe meals at home. Standard cleaning procedures, such as using wet wipes and washing hands with running water and soap, typically suffice to remove allergen from surfaces. However, topical antibacterial hand cleaning agents do not neutralize allergens (Perry et al., 2004). Ingestion contact with an allergen occurs from sharing utensils or straws or from intimate kissing where saliva containing the allergen may transfer to the allergic individual (Eriksson et al., 2003; Hallett et al., 2002; Maloney et al., 2006). Young children may need supervision when around food allergens to avoid taking or being fed the allergen, or having hand-to-mouth transfer of food allergens.

The primary route of exposure that triggers serious reactions—for example, severe anaphylaxis or fatal reactions—is through ingestion (Fleischer et al., 2012; Sampson et al., 2014). Modest allergen contact with intact skin is unlikely to trigger serious reactions (Simonte et al., 2003; Wainstein et al., 2007), but transfer from hand to the mouth can be a concern, and the eyelid may swell significantly with direct contact. Aerosolizing[2] food proteins (e.g., from boiling milk, frying egg or fish, cooking with wheat flours) may trigger reactions, often respiratory symptoms, depending on proximity, amount aerosolized, and patient-specific factors, such as asthma and degree of sensitivity (Roberts et al., 2002). Aerosol exposure can be a concern in occupational settings (e.g., "baker's asthma"). Peanut butter, an oily substance, does not aerosolize enough to trigger reactions (Simonte et al., 2003).

[1] The section on packaged foods below describes the current regulatory frameworks for food labeling of packaged foods that attempt to inform consumers of the presence of an allergen in a food.

[2] Aerosolizing is the process or act of converting some physical substance into the form of particles small and light enough to be carried on the air.

The complexities of avoidance management requires a proper diagnosis followed by a comprehensive approach to educating patients, families, caregivers, and others on appropriate measures. Mistakes and subsequent allergic reactions are common. A prospective study of 512 infants with food allergy followed for a median of 36 months noted 1,171 reactions among 367 children (Fleischer et al., 2012). Common reasons for reactions included accidental exposure, label reading errors, and cross-contact, but the study also noted some exposures were purposeful, suggesting they were done presumably to test whether the allergy was active. Additionally, the source of ingested foods during accidental exposure included siblings, relatives, and other caregivers. This study reflects the many potential sources of error in avoidance management and the need for comprehensive education. A 2015 systematic review regarding unexpected allergic reactions in those older than age 12 years (Versluis et al., 2015) identified 18 observational and 6 qualitative studies. The authors noted that current knowledge about the frequency of unexpected reactions is limited, that reactions can be severe and fatal, and that most reactions were noted to have taken place at home though other locations, such as restaurants and others' homes, were common. They also identified various labeling issues and risky behaviors as problems and concluded that patient education and dietary instruction are needed.

EDUCATING PATIENTS ABOUT ALLERGEN AVOIDANCE

This section presents several topics where health care providers should provide advice to their patients with food allergy. Many of the topics relate to allergen avoidance, the main advice given to patients. They include strictness of allergen avoidance, avoidance and comorbidities, and concerns about cross-reactive foods. These topics are covered to various degrees in Boyce et al. (2010); Muraro et al. (2014b); and Sampson et al. (2014). The topic of nonstrict avoidance is discussed in more detail in the review by Kim and Sicherer (2010).

Strictness of Allergen Avoidance

Typically persons with a food allergy are advised to strictly avoid the trigger food (Boyce et al., 2010; Kim and Sicherer, 2010; Muraro et al., 2014b; Sampson et al., 2014). However, individuals with a mild allergy, particularly allergies related to pollen-food allergy syndrome, may not need to strictly avoid the trigger fruit or vegetable. Similarly, those with food-associated, exercise-induced anaphylaxis may only need to avoid the identified trigger only in the hours before exercise. A majority of children with cow milk or egg allergy are able to ingest extensively heated forms of these

foods, for example when baked into a muffin. Additionally, circumstantial evidence from observational studies suggests that ingesting these forms does not impede recovery from these allergies and may speed tolerance induction (Kim et al., 2011; Leonard et al., 2012; Nowak-Wegrzyn et al., 2008; Tey et al., 2012). For individuals with a high threshold of reactivity, allowing ingestion of sub-threshold amounts of the allergen has not been studied. Limited evidence from a study of young children suggests that an isolated exposure to egg, milk, or peanut resulting in an allergic reaction does not increase allergen-specific IgE responses (Sicherer et al., 2016). More studies are needed to understand circumstances where nonstrict avoidance would suffice. In some situations, nonstrict avoidance is an option that can be considered under medical guidance. For example, as presented in Chapter 7, this committee recommends the implementation of a risk-based approach for labeling foods with unintended allergens which, under medical consultation, should improve the ability of individuals with food allergy to decide whether they can safely consume a specific packaged food.

Allergen Avoidance and Relationship to Comorbid Asthma, Atopic Dermatitis, and Allergic Rhinitis

Food allergen avoidance is generally not recommended as a primary means to address treatment of asthma, atopic dermatitis, or allergic rhinitis. However, avoidance is warranted when a specific food allergy is diagnosed in a patient with those diagnoses (Boyce et al., 2010; Sampson et al., 2014). If a food allergy is diagnosed, limited evidence suggests that avoiding the allergen may improve atopic dermatitis (Agata et al., 1993; Bath-Hextall et al., 2009; Boyce et al., 2010; Lever et al., 1998). Studies have suggested that following extended elimination of a food that had not previously caused serious reactions, for example only flare of atopic dermatitis, re-exposure to the food could result in acute systemic allergic reactions (Chang et al., 2016; David, 1984; Flinterman et al., 2006). Although this observation raises caution, no RCTs have been performed to confirm this association.

Concerns About Cross-Reactive Foods

Food with proteins that are homologous[3] to a food protein to which an individual is allergic may present a reaction risk (Boyce et al., 2010; Sampson et al., 2014). For example, an individual with a peanut allergy may be at higher risk for allergy to beans (e.g., soy) because both foods

[3] Homology between proteins is defined in terms of shared ancestry and is typically inferred from the similarity of their amino acid sequence.

are legumes. However, clinical cross-reactivity varies among families of foods and also among individuals depending upon their allergy profile. Unfortunately, testing has limited value because sensitization to foods with homologous proteins, evidenced by positive skin prick tests (SPTs) or the presence of food-specific IgE antibodies, is much more common than is clinical allergy (Boyce et al., 2010; Sampson et al., 2014; Sicherer, 2001) (see Chapter 4 for a detailed discussion of testing). Foods with high likelihood of clinically relevant cross-reactivity include milk from cows and goats; tree nuts, specifically cashew with pistachio and walnut with pecan; various fish with each other; and between crustacean shellfish, such as shrimp and lobster. In contrast, grains and legumes have less co-allergy. Decisions about avoiding related foods may rely also on factors such as concerns about accidental exposure from misidentification or cross contact. For example, an individual with food allergy who tolerates walnut but not cashew may decide to avoid all tree nuts to avoid cross-contact or misidentification. Therefore, advice about the need to avoid potentially cross-reactive foods is individualized and may require extensive testing with oral food challenges (OFCs). Adherence is, obviously, more difficult. Education of patients and families about these concerns is required for proper management.

ADVICE ON ALLERGEN AVOIDANCE IN VARIOUS SETTINGS OF CONCERN

Packaged Foods

Laws governing the labeling of allergens in packaged foods vary by country (Akiyama et al., 2011; Gendel, 2012) and are described in Chapter 7. Health care providers should discuss current labeling laws in counseling those who have a diagnosed food allergy. The current U.S. labeling law, the Food Allergen Labeling and Consumer Protection Act of 2004, requires manufacturers to use plain English terms to identify milk, egg, wheat, soy, peanut, tree nuts, fish, and crustacean shellfish ingredients. These may be included in the ingredient list and/or in a separate "contains" statement. Highly refined oils are exempt based on removal of protein by the process. The individual name of the food is required for categorical foods (e.g., walnut, cashew, shrimp, tuna, cod). Noncrustacean seafood, such as clam, oyster, scallop, is not included in the laws. Foods that are known to cause serious allergic reactions are not necessarily included on the label, for example, sesame and mustard (Caballero et al., 2002; Dalal et al., 2012) because they are not included in the U.S. list of priority allergens (see Chapter 7).

In the United States and some other countries, when manufacturers perceive the possibility of allergens being unintentionally included in the

product, they may voluntarily use precautionary or advisory terminology, such as "may contain X," "in a facility with X," and other such terms. Studies suggest varied risks with such products (Crotty and Taylor, 2010; Decastelli et al., 2012; Ford et al., 2010; Hefle et al., 2007; Robertson et al., 2013; Zurzolo et al., 2013) and consumers should be counseled that the terms do not reflect degree of risk. As Chapter 7 concludes, labeling laws help consumers to identify most, but not all, allergens, and advisory labeling has resulted in an unregulated proliferation of warnings that are not well understood by consumers or health care providers, and appears to result in risk-taking behavior. For example, findings from a recent survey administered in 16 countries suggest limited understanding among individuals with food allergy about food allergen thresholds (Marchisotto et al., 2016). In addition to managing the risks from packaged foods by replacing the current food allergen precautionary advisory labeling system, as recommended in Chapter 7, risks from consuming packaged foods should be communicated to individuals with food allergy and their caregivers by effective counseling in the health care setting.

Management at Home

Management of food allergen avoidance in the home requires constant vigilance regarding cross contact, label reading, and hidden ingredients. Typical cleaning methods should remove allergens from utensils, dishes, and surfaces. Depending on age and developmental ability, different safeguards may be needed to protect a child from ingesting the avoided allergen. For example, allergens may need to be kept out of reach of younger children who are not aware of the danger. Families may need to consider keeping the food-allergic individual away from the allergen during food preparation areas if aerosolization is likely (e.g., frying fish or eggs, boiling milk, steaming lobster, preparing food with wheat flours or powdered milk). Maintaining a continuous safe environment is challenging and time consuming. Health care providers should review these issues with patients and families.

Management in Food Service Settings and During Travel

People who are food allergic must navigate multiple issues when dining away from home, including avoiding cross-contact and hidden ingredients in foods served at food service establishments such as restaurants, ice cream parlors, bakeries, grocery stores with prepared foods, and food carts (see also Chapter 8). Informing the establishment about the allergy is the patient's or family's responsibility, but the establishment also must be able to take precautions to provide safe food to the public. Factors contributing

to risk could be the presence of allergens in the source ingredients or cross-contact with allergens at the buffets and food preparation areas.

It may be beneficial for the health care provider to understand and review with patients that a variety of errors can occur in the restaurant setting, whether from the consumer or the establishment's personnel (Ahuja and Sicherer, 2007; Furlong et al., 2001). Errors from the consumer could be due to poor communication of the allergy, assumptions made by the consumer about the safety of the foods, and selection of restaurants that may pose additional challenges depending on their allergy (e.g., seafood restaurant for an individual with shellfish allergy). Among 5,149 persons in a self-report registry for peanut and tree nut allergy, composed mostly of children, 13.7 percent reported reactions in food establishments (Furlong et al., 2001). Following a survey of a random subgroup of 129, lack of communication of the allergy was reported for 45 percent of the reactions. Reported rationales included assuming visual inspection would suffice, thinking the allergy was not too severe, and presuming the food should be safe. These findings suggest a benefit for health care personnel in advising patients with food allergy to openly and specifically discuss their allergy with staff of food establishments.

Errors on the part of the restaurant personnel can include misunderstanding of an allergy diagnosis compared with a less dangerous intolerance or preference, poor communication within the establishment, staff failure to prevent cross-contact or to know about hidden ingredients, among others (Ahuja and Sicherer, 2007). Surveys of restaurant personnel in Brighton, United Kingdom (Bailey et al., 2011) and New York City (Ahuja and Sicherer, 2007) showed that restaurant personnel, including chefs, may indicate confidence in providing a safe meal for a food-allergic consumer, but have knowledge deficits about allergy, cross-contact, and general food allergy management. These findings suggest that health care providers should discuss strategies such as encouraging patients with food allergy to review cross contact and hidden ingredients with staff when obtaining restaurant meals (i.e., educate or confirm knowledge of staff).

Travel presents additional potential obstacles for persons with food allergy (Barnett et al., 2012). A lack of global uniform guidelines requires consumers with food allergy to navigate different regulations, or regions with no regulations, internationally. Language barriers may prevent safe communication. Travel to remote regions raises concerns about obtaining safe food and managing a reaction. Several studies have reported allergic reactions on airplanes based on self-report of having unintentionally ingested or been exposed to allergens (Comstock et al., 2008; Greenhawt et al., 2013; Sicherer et al., 1999). These issues, highlighted further in Chapter 8, suggest that individuals and families with food allergy be counseled to consider their allergies when traveling and to call ahead to notify

transportation services, carry medications, ensure safe food is available, and, for younger children, inspect and wipe seating areas for residual food before the child has contact with the space.

Management in Schools and Child Care Centers

Supervision of children and procedures to provide safe foods in early care and education settings, schools, and summer camp settings is required to avoid allergen exposure and to recognize and promptly treat allergic or anaphylactic reactions. A number of recommendations and guidelines have been developed that focus on advice to school personnel, health care providers, patients, and families (CDC, 2013; Eldredge and Schellhase, 2012; Ford et al., 2014; Leo and Clark, 2012; Muraro et al., 2014d; Robinson and Ficca, 2012; Sheetz et al., 2004; Sicherer et al., 2010; Vale et al., 2015; Young et al., 2009). A discussion about approaches to providing a safe experience for children with food allergies when away from home, including the responsibilities of the school staff, is provided in Chapter 8. This chapter focuses on the responsibilities and challenges of the health care provider, parents, and students. These issues also can extend to additional settings away from home, such as religious events, sports, afterschool clubs and camps, among other supervised settings for children (Sampson et al., 2014).

For the child with possible food allergy who attends a school setting, the responsibilities of the child's physician or health care provider may include confirming the diagnosis, providing a written emergency care plan, providing advice about general management to the family and school personnel, and giving necessary medication prescriptions. As reviewed in Chapter 4, ascertaining a diagnosis and whether a child has a potentially life-threatening food allergy can be difficult. Briefly, these elements for diagnosis include deciphering a true allergy, judging its potential severity, and considering comorbid conditions such as asthma.

The physician or health care provider may work with the patient and family to notify the school about a potentially life-threatening food allergy, including providing a written plan, often referred to as an Emergency Action or Emergency Care Plan for Anaphylaxis or Allergy and Anaphylaxis. Unfortunately, no standard, evidence-based plans have been developed and so numerous forms with many different approaches are used. This may represent a significant gap in providing standard care. Survey studies suggest that an insufficient number of students with food allergy have a management plan, or that the plan may not be followed (Ewan and Clark, 2001; Gupta et al., 2014). No comprehensive studies have been conducted that provide evidence for a validated, brief written emergency plan for individual or general use. Various organizations or schools have

developed plans. Studies have identified key factors that might be included on standardized written plans, or compared plans for determination of preferences, or identified variations in using these plans, but systematic studies are lacking (Banerjee et al., 2007; Ewan and Clark, 2001; Powers et al., 2007; Weiss et al., 2004; Worth et al., 2010). Key features typically include the date, the child's name, recent weight, identifying information (child's picture, if provided), specifics about the food allergy or allergies, emergency medications and doses, descriptions of possible symptoms and related treatment instructions, advice to activate emergency services, and family contact information. Development of evidence-based, universal plans could potentially improve understanding and emergency care.

A number of factors must be considered when developing emergency plans for medical management of anaphylaxis and, more specifically, for treatment in a school setting. For example, regarding management in general, no diagnostic test exists to predict or confirm anaphylaxis, and specific symptoms may vary, resulting in treatment quandaries. Although diagnostic features of anaphylaxis have been published, (Sampson et al., 2006b), it is prudent to inject epinephrine (adrenaline) before observing symptoms diagnostic of anaphylaxis. Therefore, the decision to inject epinephrine may vary based on the patient's history, foods involved, and likelihood of an ingestion of the avoided food at the onset of mild symptoms that could be attributed to other causes and are not (yet) anaphylaxis (i.e., throat discomfort may be an early symptom of a viral infection or an initial symptoms of food allergy). For example, if an allergen was ingested that previously caused anaphylaxis, it may be advisable to inject epinephrine at the time of first symptoms, or if an allergen was definitely ingested and previously known to have caused severe anaphylaxis, it may be advisable to inject epinephrine before symptoms occur (AAAAI BOD, 1998; Sicherer et al., 2010). The supervising adult may need to differentiate a mild allergic symptom from anaphylaxis, deciding when to administer epinephrine. This can be difficult, even for experienced professionals. Current advice emphasizes educating parents and school personnel that (1) antihistamines cannot be depended on to treat anaphylaxis but are adjunctive therapies to treat an allergic reaction, (2) inhaled bronchodilators must not be depended on to treat anaphylaxis but may be given for respiratory reactions, and (3) intramuscular epinephrine is safe and, if a possibility of a severe allergic reaction exists, should be administered (side effects are mild and may include temporary fast heart rate, jitteriness, flushing, or paleness) (Sicherer et al., 2007, 2010). Administration of medications in U.S. schools has been addressed in general guidance documents (Council on School Health, 2009). However, no studies provide sufficient evidence for validation of the options discussed above.

Given the complexity of food allergy diagnosis and emergency treat-

ment, the physician may need to consider whether a licensed health care professional is available to assist the child. When one is not available, a plan that is different from one when a professional is involved must be developed. For example, a licensed health professional may administer an antihistamine for mild allergic symptoms and observe for progression of symptoms before administering epinephrine, whereas a nonlicensed, not medically trained individual may not be expected to make this kind of medical or nursing assessment. In this case, the advice may be to promptly give the epinephrine by auto-injector and call for activation of emergency medical services immediately. No studies have addressed the various approaches upon which to develop best practices in this regard.

In addition to the above issues of medical management, the physician or health care professional should address age-specific concerns (for example, the inability of preschool age children to self-monitor taking unsafe foods or the potential risk-taking activities of adolescents), potential risks, bullying, and general management. Medical identification jewelry is encouraged. Avoidance measures should be discussed and are reviewed in the *CDC Voluntary Guidelines for Managing Food Allergies in Schools and Early Care and Education Programs* (CDC, 2013). Avoidance advice may vary by age, allergy, developmental abilities, nutritional status, socioeconomic status, and other factors, and counseling may be adjusted according to the needs of the child and the circumstances of the school. However, little information is available to inform best practices on avoidance (Banejee et al., 2007; Cicutto et al., 2012; Vale et al., 2015; Worth et al., 2010). Families and patients should be educated about how and when to administer self-injectable epinephrine, the importance of avoidance strategies (e.g., no food sharing), when to have children notify an adult of any symptoms or if they may have eaten an unsafe food. The diagnosis, treatment plan, and prescriptions should be reviewed periodically and updated at least yearly. Families and schools also need to be alert to the expiration dates on epinephrine auto-injectors.

Finally, the physician and family will need to provide the school with a list of foods to be avoided and possible substitutions. Some school food programs may require physician-recommended substitutions. Additional issues from the community perspective are discussed in Chapter 8 of this report.

Educational Needs

Although it is incumbent upon health care providers to educate patients and families, these providers have noted deficits in understanding food allergy and anaphylaxis management, as described in Chapter 2. Managing food allergy requires educating all those who are involved in measures

associated with avoiding and treating allergic reactions. However, numerous studies suggest that many different stakeholders, including physicians, have deficits in their understanding of these basic concepts (Desjardins et al., 2013; Morawetz et al., 2014). For example, in an Internet survey of medical professionals, only 23 percent recognized risk factors for anaphylaxis and only 55 percent identified a case of anaphylaxis that had no hives (Wang et al., 2014). Another Web-based study of 407 primary care physicians noted a fair allergy and anaphylaxis knowledge base but specific deficits were noted, such as only 23 percent recognizing that cheese is unsafe for those with milk allergy and fewer than 30 percent indicating comfort with laboratory tests or caring for children with food allergies (Gupta et al., 2010b). Surveys of emergency department management of anaphylaxis suggest serious undertreatment of anaphylaxis and lack of referral (Clark et al., 2004). When allergy referral is achieved, previously unknown triggers are often identified (Campbell et al., 2015b).

Surveys of the general public (Gupta et al., 2009) and parents of children with food allergy (Gupta et al., 2010a) also show a variety of knowledge deficits. Studies have identified errors in using epinephrine autoinjectors among patients and health care providers (Arga et al., 2011; Brown et al., 2013; Guerlain et al., 2010; Sicherer et al., 2000). A Canadian survey of 184 respondents of caregivers of children who had experienced a first allergic reaction within the past year identified gaps in the caregivers having received food allergy and anaphylaxis education and coping strategies for fear and anxiety (Abdurrahman et al., 2013). In a qualitative manner, they found three primary areas of deficit: lack of receiving information on recognizing and managing food allergy–related reactions, long wait times to see an allergist, and significant family anxiety. Surveys of school nurses revealed the need for better understanding of emergency plan development, staff education, and delegation and avoidance measures (Carlisle et al., 2010). Surveys of pediatric dietitians (Groetch et al., 2010; Maslin et al., 2014) revealed that they considered they had moderate knowledge for educating families and evaluating safe foods and low knowledge for creating diagnostic food challenges. Knowledge deficits about food allergy also have been noted among child care providers (Greiwe et al., 2015), emergency response providers (Jacobsen et al., 2012), restaurant personnel (Ahuja and Sicherer, 2007; Bailey et al., 2011), and teachers (Ercan et al., 2012; Polloni et al., 2013). Overall, stakeholders are currently insufficiently educated and seek more information on food allergy.

Studies suggest that educating health care providers is valuable and that patients and their families may benefit from being directed to various educational resources. A number of studies report successful educational materials or programs for various stakeholders, including in-person and online programs, many of which have not been validated (Bailey et al.,

2014; Bansal et al., 2005; Camargo et al., 2007; Cavanaugh and Strickland, 2011; Chokshi et al., 2015; Desai et al., 2015; Hernandez-Trujillo and Simons, 2013; Reeves et al., 2015; Rosen et al., 2014; Sasaki et al., 2015; Shah et al., 2013; van Os-Medendorp et al., 2015; Wahl et al., 2015; White et al., 2015; Yu et al., 2008). One study found that providing simple guidelines improved anaphylaxis management in the emergency department (Desai et al., 2015). In one program that health care professionals can use with parents of children with food allergy (Sicherer et al., 2012), significant improvements were seen in the correct number of auto-injector activation steps, comfort with using the auto-injector, knowledge test scores, and the annualized rate of allergic reactions fell on average from 1.77 (historical) the year prior, to 0.42 ($P<0.001$) after the program. A number of smartphone and tablet applications are also emerging for managing food allergy (Cuervo-Pardo et al., 2015).

Food anaphylaxis can occur in any setting but proper emergency management can resolve a life-threatening occurrence. Therefore, the public, particularly first responders and aiders, need to be prepared to assist in such food-related severe reactions. There is not, however, a national standardized curriculum that includes required elements for emergency care training. Overall, food allergy anaphylaxis is not included in training curricula of organizations that offer various certifications on emergency training or specialized training for professionals such as pediatric specialization for child care providers or training for Emergency Medical Service personnel.

In summary, education of stakeholders is key for food allergy management because knowledge deficits are significant. There is a clear unmet need for education. Evidence indicates that adopting a multidisciplinary clinical approach and providing educational materials may improve knowledge, correct use of epinephrine, and reduce reactions. Although various educational programs are available or in development, most have not been extensively studied. Studies on widespread implementation also are lacking.

High-Risk Groups

Several guidelines (e.g., Muraro et al., 2014b; Sampson et al., 2014) emphasize that certain factors may increase the risk for anaphylaxis. Examples of factors that may increase risks include coexisting asthma, allergies to specific foods (e.g., peanut, tree nuts), degree of sensitivity and extent of eliciting factors (e.g., illness, exercise, medications, alcohol). The relative contributions of all of these are not established. Risk factors identified in case series of fatal food allergic reactions include adolescence or young adult age group, comorbid asthma, ingestion of peanut or tree nuts (although fatal reactions can occur from other allergens, such as

milk), delayed treatment with epinephrine, lack of skin symptoms (perhaps resulting in delayed recognition and treatment), and previously diagnosed food allergy (Bock et al., 2001, 2007; Pumphrey, 2000; Pumphrey and Gowland, 2007; Sampson et al., 1992). The AAAAI Guidelines (Sampson et al., 2014) suggests discussing self-care management techniques especially with high-risk patients, described as adolescents, young adults, and patients with asthma.

Adolescents and young adults, including those in college, may be at higher risk of fatal food-induced anaphylaxis for a variety of reasons (Akeson et al., 2007; Greenhawt et al., 2009; Macadam et al., 2012; Marrs and Lack, 2013; Monks et al., 2010; Mullins, 2003; Noimark et al., 2012; Sampson et al., 2006a). They may not understand or recognize, or may deny symptoms indicating anaphylaxis. For example, in a survey of 174 adolescents with food allergy, 61 percent did not report having anaphylaxis but described symptoms such as throat swelling, trouble breathing, and loss of consciousness (Sampson et al., 2006a). In this same study, risk-taking behaviors included not always carrying epinephrine (39 percent), purposefully ingesting unsafe food (54 percent), and ingesting foods with advisory labeling for their allergen (42 percent). The motivation behind risk-taking behaviors may include poor understanding of risk, convenience, not wanting to feel different from peers, bullying, lack of recollection of allergic reactions, success having survived self-resolving reactions without the need for treatment, fear of injections, overreliance on emergency medications on hand to justify unsafe eating behaviors, and other behavioral and psychosocial factors (Akeson et al., 2007; Greenhawt et al., 2009; Macadam et al., 2012; MacKenzie et al., 2010; Marrs and Lack, 2013; Monks et al., 2010; Noimark et al., 2012; Sampson et al., 2006a). Potential for interventions also are noted in several studies. In one study, 68 percent of adolescents with food allergy indicated a belief that educating their friends would make living with food allergy easier (Sampson et al., 2006a). In another study of adolescents with food allergy, adherence to self-care was reported by 16 percent of participants, and was more likely if the adolescents belonged to an allergy support group (odds ratio [OR]: 2.54; 95% confidence interval [CI]: 1.04-6.20), had a written management plan (OR: 3.22; 95% CI: 1.18-8.81), perceived having a more severe allergy (OR: 1.24; 95% CI: 1.01-1.52), and perceived fewer management barriers (OR: 0.87; 95% CI: 0.79-0.96) (Jones et al., 2015). Approaches for providing care and better education have not been systematically studied, but suggestions have included targeting knowledge, preparedness, empowerment, and beliefs (Marrs and Lack, 2013).

Advice on Allergens in Nonfood Items and Alcoholic Beverages

Allergens in Pet Foods, Cosmetics, and Topical Products

A variety of noningested products include allergens, which requires caution on the part of consumers when allergen disclosures may not be included. Examples include pet foods containing milk, soy, fish, or nut ingredients, and lotions with nut ingredients. Most of these products are not ingested, so the risk of anaphylaxis would be relatively low but studies have not delineated the risks. These products have no labeling requirements relating to food allergens. Physicians may discuss these potential risks with patients who have food allergy, especially with toddlers who may otherwise have access to these products and could ingest them accidentally.

Allergens in Vaccines, Medications, and Dietary Supplements

Physicians and patients with food allergy must consider potential food allergen exposures in vaccines, medications, and dietary supplement products (e.g., vitamins, probiotics), which are not regulated by labeling laws. Also, excipients (i.e., substances added to medications to improve various characteristics) may be food or derived from foods (Kelso, 2014). These include milk proteins; soy derivatives; oils from sesame, peanut, fish or soy; and beef or fish gelatin. The medications involved include vaccines; anesthetics; and oral, topical, and injected medications. With perhaps the exception of gelatin, reactions appear to be rare overall, likely because little residual protein is included in the final preparation of these items. The specific risk for each medication is not known.

Vaccines also may contain food allergens, such as egg protein or gelatin. Expert opinion based on many studies suggests that the yearly influenza vaccination and the measles, mumps, and rubella vaccines should not be deferred based on egg allergy (e.g., Turner et al., 2015). In contrast, the yellow fever and rabies vaccines should not be given to persons with severe egg allergy unless testing with the vaccine is undertaken first (Kelso et al., 2012, 2013).

Allergens in Alcoholic Beverages

Allergic or allergic-like reactions can occur from alcoholic beverages. These products are not included in allergen labeling laws and counseling of patients may be warranted. However, the literature on the allergenicity of alcoholic beverages is sparse. Persons with alcohol dehydrogenase deficiency may experience dose-related symptoms that mimic allergy, including flushing, nausea, vomiting, and sometimes wheezing. Sulfites, often found

in wine, may induce asthma symptoms. Wines may be clarified by processes that use allergens such as egg, but the final product may not likely contain residual protein (Rolland et al., 2008). Beer may have residual proteins from barley or other grains that can trigger reactions (Quercia et al., 2012). Distilled alcohol should be free from protein. Many alcoholic beverages are made from potential allergens, for example amaretto from almonds, frangelico from hazelnuts, and Irish cream from milk, but the residual allergenicity of these products has not been studied.

EMERGENCY MANAGEMENT OF ALLERGIC REACTIONS

The physician must counsel patients with food allergy, and their families, on recognizing and treating food-induced anaphylaxis. The following discusses some of the challenges involved in diagnosis and treatment of anaphylaxis at the level of first aid and physician care. The previous section "Management in Schools and Child Care Centers" includes additional information regarding written emergency plans and emergency medical identification jewelry.

Definition of Anaphylaxis, Diagnosis, and Differential Diagnosis

Anaphylaxis has been described as a severe, life-threatening, generalized or systemic hypersensitivity reaction (Muraro et al., 2014a). Life-threatening breathing, airway, or circulatory problems may occur and skin and mucosal changes usually, although not always, occur. A consensus definition was proposed in 2006, describing anaphylaxis as "a serious allergic reaction that is rapid in onset and may cause death" (Sampson et al., 2006b, p. 392). Diagnostic criteria based on consensus were published in 2006 (Sampson et al., 2006b) and some validation has been performed (Campbell et al., 2012; Harduar-Morano et al., 2010). Diagnosis may need to differentiate anaphylaxis from fainting, cardiac events, mild allergic reactions, asthma, choking, panic attacks, and many other ailments. However, no simple tests exist to confirm anaphylaxis or to predict those at risk. Serum tryptase, a mediator released from mast cells, may not be increased with food-induced anaphylaxis, although severity of the episode and differences from baseline may be relevant (De Schryver et al., 2016; Lin et al., 2000a; Sahiner et al., 2014; Sala-Cunill et al., 2013; Wongkaewpothong et al., 2014). Histamine measurements are difficult to obtain. As reviewed previously, allergy tests are not good predictors of severity of reactions. Overall, anaphylaxis is a clinical diagnosis and no rapid diagnostic test is available.

Nature of Anaphylaxis

Anaphylaxis involves more than one organ system (e.g., skin, respiratory tract, and/or gastrointestinal [GI] tract) (Boyce et al., 2010). The skin is involved in 80 to 90 percent of episodes, respiratory symptoms in up to 70 percent, GI in up to 40 percent, and cardiovascular symptoms in up to 35 percent (Boyce et al., 2010; Dhami et al., 2014; Lieberman et al., 2015; Muraro et al., 2014a; Sampson et al., 2014). Symptoms include flushing, pruritus, hives (urticaria), nasal congestion and rhinorrhea, throat itching and swelling (edema), choking, wheezing, coughing, trouble breathing, altered breathing sounds or trouble speaking, cramping abdominal pain, nausea, vomiting, diarrhea, dizziness, high or slow heart rate, sleepiness, confusion, loss of consciousness, anxiety, feeling of doom, seizure, and uterine cramps.

Food-induced anaphylaxis typically occurs within minutes to several hours of ingestion of the food (but may be longer for mammalian meat, alpha-gal-related reactions (Boyce et al., 2010; Sampson et al., 2014; Tripathi et al., 2015). The reaction usually develops and resolves completely within hours, but a biphasic course has been described where symptoms resolve but recur hours later, a phenomenon that is described for 1 to 20 percent of cases (Alqurashi et al., 2015; Ellis and Day, 2007; Lee and Greenes, 2000; Lee et al., 2015b; Lieberman, 2005; Mehr et al., 2009; Sampson et al., 1992). Biphasic reactions may be more likely with severe or undertreated reactions, but are unpredictable, and observation in an emergency department for at least 4 to 6 hours is recommended (Boyce et al., 2010). Rarely, symptoms can last for many hours or days (Sampson et al., 1992). Deaths have been reported from 30 minutes to 2 hours after exposure (Bock et al., 2001, 2007; Sampson et al., 1992). No biomarkers are available that adequately predict severity or whether a biphasic reaction will develop. Reactions could be worse, milder, or similar from time to time, presumably because of many variables including overall sensitivity, amount of allergen ingested, and other factors.

Risk Factors (Asthma, Certain Foods, Cofactors) and Risk Assessment

A number of comorbid diseases may affect the severity and treatment response of anaphylaxis (Boyce et al., 2010; Dhami et al., 2014; Lieberman et al., 2015; Muraro et al., 2014a; Sampson et al., 2014). Asthma is a significant risk factor for death, especially in adolescents and young adults (Bock et al., 2001, 2007; Pumphrey, 2000; Pumphrey and Gowland, 2007; Sampson et al., 1992). Cardiac disease is a risk factor for middle-aged or older adults (Pumphrey, 2000; Pumphrey and Gowland, 2007). Allergies to some foods are associated with more severe reactions (e.g., peanut, tree

nuts, milk, fish, shellfish, seeds, and egg) than others (fruits and vegetables). Additional risks for more severe reactions include underlying mastocytosis and lung disease diagnosis. Various medications may affect response to treatment, including beta-adrenergic antagonists, angiotensin-converting enzyme inhibitors, and alpha adrenergic blockers. No simple means exist to predict the severity of reactions or to clearly identify an individual at risk.

Medical Treatment of Anaphylaxis

Epinephrine, typically prescribed as auto-injectors for self-injection for first aid management, is first-line therapy for food-induced anaphylaxis and is recommended to be injected intramuscularly (anterolateral thigh into the vastus lateralis muscle) (Boyce et al., 2010; Lieberman et al., 2015; Muraro et al., 2014a; Sampson et al., 2014). Epinephrine should be administered promptly for anaphylaxis and when clinical features are likely to evolve into anaphylaxis (AAAAI BOD, 1994; Muraro et al., 2014a). Delay in providing therapy with epinephrine is associated with increased risk of death and morbidity. Epinephrine has a variety of actions that improve breathing and circulation and may reduce the release of additional inflammatory mediators. Treating anaphylaxis with epinephrine has no absolute contraindications.

A Cochrane Systematic Review (Sheikh et al., 2012a) of the effectiveness of epinephrine auto-injectors in relieving respiratory, cardiovascular, and other symptoms during anaphylaxis in the community setting sought randomized or quasi-randomized trials comparing auto-injectors to no intervention or other interventions and found no qualifying studies out of 1,328 references that were reviewed. Nonetheless, the conclusion was to recommend epinephrine auto-injectors as the most effective first-line treatment for anaphylaxis in the community, with a recommendation for trials comparing different doses and devices as well as syringe and ampule.

According to the NIAID/NIH-supported Guidelines, a prescription for an epinephrine auto-injector, typically two doses, should be given to those who have experienced anaphylaxis as well as patients with diagnosed food allergy who have asthma and those with allergy to foods that typically cause severe reactions (e.g., peanut, tree nuts, fish, shellfish). A prescription for anyone with a diagnosed food allergy may be considered because subsequent reaction severity is hard to predict (Boyce et al., 2010). The EAACI Anaphylaxis Guidelines (Muraro et al., 2014b) additionally comment upon a prescription being indicated when a person has had previous mild to moderate symptoms from trace food exposure, mild to moderate symptoms to a food and travel to areas remote from medical care is planned, and for teenagers or young adults with food allergy (excluding oral allergy syndrome). The AAAAI Practice Parameter on anaphylaxis discusses additional con-

siderations, such as allergy to mustard, peach, or apple, for those patients in Mediterranean regions (who tend to have more severe reactions to these fruits), and people having past reactions with throat tightness, those having food allergy and airway anatomy that predisposes to obstruction, or those having contact allergic reactions to specific foods. This document also concluded that physician discretion is needed (Lieberman et al., 2015).

Consensus has emerged on the use of premeasured auto-injector doses of 0.15 mg for those weighing 16.5 (7.5 kg) up to 55 pounds (25 kg), and a dose of 0.3 mg for those 55 pounds and greater (Boyce et al., 2010; Muraro et al., 2014a; Sampson et al., 2014). Controversy exists regarding the auto-injectors use for infants weighing less than 7.5 kg (or less than 10 kg in some guidelines [Boyce et al., 2010, Sampson et al., 2014]) and for individuals with obesity (Sicherer et al., 2007; Simons et al., 2014, 2015). Although dosing at 0.01 mg/kg epinephrine intramuscularly has been recommended, the ideal dose has not been determined through studies (Lieberman et al., 2015). Additional studies and potentially a wider range of fixed-dose auto-injectors may be beneficial.

First aid management also includes activating emergency services (calling for help, dialing 911 or equivalent), evaluating airway breathing and circulation, and providing cardiorespiratory resuscitation, if needed. It may be beneficial to place the patient in a recumbent position with the legs elevated if tolerated (although bringing a patient to a standing position may result in death, and caution is needed during transport (Pumphrey, 2003). The patient may require more than one dose of intramuscular epinephrine, as studies suggest this may occur in 10 to 20 percent of cases (Jarvinen et al., 2008; Oren et al., 2007). The intramuscular epinephrine dose can be repeated (e.g., in approximately 5 minutes from the last dose), as warranted by symptoms (Muraro et al., 2014a). Side effects of epinephrine may include restlessness, headache, dizziness, palpitations, pallor, flushing, and tremor. Rarely, epinephrine can lead to severe side effects, such as myocardial infarction or intracranial hemorrhage, but these severe side effects almost exclusively occur from overdose, which is more likely if errors in intravenous administration occur, rather than intramuscular injection from auto-injectors (Campbell et al., 2015a).

Additional treatment of anaphylaxis is considered adjunctive to epinephrine and may include bronchodilator medications, H1 and H2 antihistamines, corticosteroids, vasopressors, glucagon, atropine, supplemental oxygen, intravenous fluids, and patient positioning (Boyce et al., 2010; Lieberman et al., 2015; Muraro et al., 2014a; Sampson et al., 2014). Most of these adjunctive therapies would be available following first aid management and would be administered by emergency personnel or by emergency department staff.

Systemic antihistamines are often used during anaphylaxis. Systematic

reviews to assess the benefit or harm of H1 antihistamines for the treatment of anaphylaxis have been conducted. Randomized and quasi-randomized controlled trials to compare this therapy with placebo or no intervention have been sought. However, no studies have satisfied inclusion criteria (Nurmatov et al., 2014b; Sheikh et al., 2007). The medications presumably help to relieve cutaneous symptoms but no studies regarding effect on other symptoms of anaphylaxes or progression of reactions have been conducted. Combination treatment with H1 and H2 antihistamines may have additional efficacy compared to H1 antihistamines alone for cutaneous symptoms (Lin et al., 2000b; Runge et al., 1992). Oral (in preference to intravenous) administration is recommended for relief of cutaneous symptoms (Ellis and Brown, 2013; Muraro et al., 2014a) to avoid hypotension related to rapid intravenous administration. The onset of action of antihistamines (e.g., liquids, rapid disintegrating tablets) is approximately 30 minutes. Studies to determine the benefit or harm of antihistamines in anaphylaxis would be useful.

Oral or intravenous glucocorticoids are often used in anaphylaxis to theoretically prevent protracted symptoms or late onset of symptoms and also to address concomitant asthma. A systematic review was undertaken with the intention to perform a meta-analysis to assess benefits and harms of glucocorticoid treatment during anaphylaxis, but no randomized or quasi-randomized controlled trials comparing glucocorticoids to any control were identified and so no meta-analysis could be undertaken (Choo et al., 2012). Therefore, therapy with glucocorticoids, which have a slow onset of action, are used in anaphylaxis without clear evidence and are based on expert opinion (Boyce et al., 2010; Muraro et al., 2014a; Sampson et al., 2014). Studies on the utility of glucocorticoids in anaphylaxis could inform therapeutic approaches.

No consensus in the literature exists on the optimal time for observation of the patient who has experienced anaphylaxis, although 4 to 6 hours has been suggested, or longer if the patient experienced hypotension (Boyce et al., 2010; Muraro et al., 2014a; Sampson et al., 2014).

Post-Anaphylaxis Long-Term Management

Based on current guidelines, discharge planning or long-term management should include a written anaphylaxis emergency action plan, encouraging medical identification jewelry, and having epinephrine auto-injectors (typically two) always available, a plan for monitoring auto-injector expiration, a plan for arranging further evaluation as needed, printed information about anaphylaxis and its treatment, and consideration for referral to specialist for further evaluation. It also is recommended to have instructions on the proper use of epinephrine auto-injectors and indications for use, advice

about allergen avoidance, and additional information regarding a dietitian consult and support groups (Boyce et al., 2010; Lieberman et al., 2015; Muraro et al., 2014a; Sampson et al., 2014). As reviewed above, discharge and long-term management of patients with food allergy who are at risk for anaphylaxis has some potential pitfalls. Nutritional and psychological concerns are described below.

NUTRITIONAL CONSIDERATIONS

Adequate nutrition is important for normal child development and growth. When allergen avoidance is the one recommendation to minimize the risk of an allergic reaction, children could end up deficient on specific nutrients or calories if attention to their nutrition is not considered.

The NIAID/NIH-supported Guidelines suggest nutritional counseling and regular growth monitoring for all children with food allergies (Boyce et al., 2010) and the EAACI Guideline suggested that, ideally, the patient would receive proper counseling by a dietitian with specific competence in food allergy, recognizing this is particularly important for infants and children and may vary by age and foods avoided (Muraro et al., 2014b).

The most common allergenic foods contain nutrients whose removal may reduce diet quality (i.e., lead to nutrient deficiencies) and, therefore, may be detrimental to health, particularly for an infant or child. For example, cow milk has protein, fat, calcium, vitamin D, and riboflavin; wheat in fortified cereals contains carbohydrates, iron, thymine, niacin, riboflavin, and folate; egg includes protein, fat, iron, and riboflavin; and fish and shellfish are sources of protein, fat, and omega-3 fatty acids. When cow milk is avoided, substitutions are typically needed to account for lost nutrients (Fiocchi et al., 2010). For example, an infant or toddler who does not use cow milk may require breast milk or a human milk substitute, and older toddlers may require a calcium supplement and/or fortified alternative beverages, such as soy milk or rice, almond, oat, or coconut beverages, depending on other components of the diet and as tolerated. However, these beverages are not equivalent to cow milk in terms of fat, protein, calories, and other essential nutrients (Groetch et al., 2013). Specifically, an infant with a diagnosed cow milk allergy will typically tolerate formulas approved for use in these circumstances, such as extensively hydrolyzed casein–based or amino acid–based formula, or soy formula, as medically necessary following a diagnostic evaluation. However, partially hydrolyzed milk–based formula is not typically appropriate for an infant with a diagnosed cow milk allergy (Lee et al., 2015a). Infants with food allergy may have nutritional concerns related to their elimination diets or to underlying chronic illness. For example atopic dermatitis or GI inflammation can interfere

with nutrient absorption or result in increased caloric needs (Jarvinen et al., 2013).

No RCTs have addressed whether food allergen avoidance affects growth and nutritional status of infants and children. Multiple studies, primarily observational and cross-sectional, suggest that food allergy may be associated with impaired growth (Cho et al., 2011; Christie et al., 2002; Flammarion et al., 2011; Hobbs et al., 2015; Isolauri et al., 1998; Mehta et al., 2014; Meyer et al., 2012, 2014; Mori et al., 2015; Mukaida et al., 2010; Nachshon et al., 2014; Vieira et al., 2010). It has particularly been noted that growth may be impaired in those avoiding cow milk (Hobbs et al., 2015; Isolauri et al., 1998; Mehta et al., 2014; Mukaida et al., 2010; Tiainen et al., 1995). For example, Tiainen et al. (1995) compared 18 children (mean age 2 years, range 1 to 3.5 years) with cow milk allergy and 20 healthy controls and found that although total energy intake between the two groups did not differ, the children with milk allergy had lower protein and higher fat intake compared to controls, and the allergic children also had a lower height for age percentile (–0.6 versus 0.2 SD units; $P<0.05$). Long-term outcomes for those on a childhood milk avoidance diet can include increased risk of reduced bone mineral density and increased risk of early osteoporosis (Nachshon et al., 2014). A small (N=39) prospective study from the United Kingdom found that milk avoidance in early life can have a long-term effect on food intake and preferences (Maslin et al., 2016).

Having multiple food allergies appears to put children at increased risk of decreased growth, due to the reduced food and total energy intake (Cho et al., 2011; Christie et al., 2002; Flammarion et al., 2011; Hobbs et al., 2015; Meyer et al., 2012, 2014; Mukaida et al., 2010; Vieira et al., 2010). For example, Christie et al. compared children with food allergy to healthy controls and found that children with two or more food allergies were shorter than those with one, and children with cow milk or multiple food allergies were less likely to consume sufficient dietary calcium (Christie et al., 2002). Meyer et al. noted that children with food allergies were more underweight than the general UK population, which was linked to the number of foods excluded (Meyer et al., 2014). However, they also noted cases of obesity despite dietary elimination. A systematic review of nutrient intake and growth in children with multiple IgE-mediated food allergies identified six studies and concluded that "children with multiple food allergies have a higher risk of impaired growth and may have a higher risk of inadequate nutrient intake than children without food allergies" (Sova et al., 2013, p. 669). Although data are limited (Berni Canani et al., 2014; Christie et al., 2002), dietary counseling can potentially improve macro and micro nutrient intake and growth outcomes without evidence of inducing overweight status. Evidence-based specific dietary guidance for children with food allergy is lacking (Groetch et al., 2013; Meyer et al.,

2012). However, the data suggest that by individualizing dietary counseling, dietary intakes and nutritional status can be improved and growth impairment may be prevented.

QUALITY OF LIFE AND MENTAL HEALTH CONSIDERATIONS

Daily management of food allergy is focused on avoiding trigger foods and recognizing and managing allergic reactions, some of which are life-threatening. These considerations practically affect the routine of daily living and also carry psychological burdens that can result in anxiety and stress. Measurement of health-related quality of life (HRQL) helps determine the impact of disease on an individual, which may vary among individuals even if disease severity is similar. Tools to measure HRQL may be generic or disease specific. Generic instruments allow comparison between disorders, while disease-specific instruments are more sensitive for measuring the burden of disease and identifying changes caused by interventions.

A systematic review was undertaken to identify validated instruments specific to food allergy disease (Salvilla et al., 2014). Seventeen eligible studies were retrieved and seven disease specific HRQL instruments were subjected to detail quality appraisal. These seven were found to have robust psychometric properties (Cohen et al., 2004; DunnGalvin et al., 2008; Flokstra-de Blok et al., 2008, 2009a,b; MacKenzie et al., 2012; Resnick et al., 2010) and to be suitable for use in children, adolescents, parents and caregivers, and adults. The authors also concluded that further work is required to understand clinically important differences in score appraisal of patients with food allergy. Using this systematic review, guidelines were developed for using specific instruments based on the type of food allergy, research or clinical applications, inclusion or exclusion of comorbidities, patient age, language and cultural issues, the preferred respondent, and target population (Muraro et al., 2014c). This review pointed out that the instruments have been used in research settings only to provide quantitative information on the HRQL of patients with IgE-mediated food allergy and to assess the effect of interventions and determine outcomes. Studies to recommend use of these instruments at the individual patient level are insufficient. Additionally, the review offered a number of research recommendations, including a need to: determine optimum methods of administration, frequency, and interpretation; identify which instruments, if any, are valid to guide clinical practice of individual patients; determine efficacy of the instruments for evaluating medical and technological advances, patient satisfaction and quality of care, and health and regulatory policy; include these instruments to explain different pathways in the development, expression, and impact of chronic diseases; articulate norms for age, sex, and country or culture; explain the relationship between responses to both proxy and

self-report measures; develop optimum methods for evaluating measures in patients with comorbid conditions; and, determine how quality-adjusted life years for food allergy can be developed to help inform policy.

Aside from validated HRQL instruments, the practical emotional concerns of daily management of food allergies can result in distress. Indeed, the NIAID/NIH-supported Guidelines recommends that patients with food allergy and their caregivers be given information on food allergen avoidance and emergency management that is age and culturally appropriate because management can have substantial daily consequences, including anxiety and diminished quality of life (Boyce et al., 2010). Food-specific HRQL instruments generally query on issues such as holiday plans, restaurants, social activities, time for preparing meals or other meal-related events, taking precautions, troubles in having to carry medications, worry about health issues, not being able to get help for a reaction, other's lack of understanding about the allergy, attending school or work activities safely, having a normal life, anxiety, and worry about the allergy or reactions (Cohen et al., 2004; DunnGalvin et al., 2008; Flokstra-de Blok et al., 2008, 2009a,b; MacKenzie et al., 2012; Resnick et al., 2010). The degree of impact on HRQL can vary based on knowledge of food allergies, age, having had experiences such as emergency room visit for anaphylaxis, an injection of epinephrine, or multiple food allergies, or allergies to specific foods (e.g., milk or egg compared to peanut or tree nut), and the impact can be complex due to interactions among various factors (Springston et al., 2010; Ward and Greenhawt, 2015; Wassenberg et al., 2012).

Various factors may affect the distress, anxiety, and psychological aspects of a food allergy diagnosis and management. Additionally, the impact may vary based on age, role, and time living with a diagnosis. Compared to mothers of children without chronic illness, mothers of children with food allergy have increased anxiety and stress (Lau et al., 2014). For example, a study of families with a child having peanut allergy revealed that mothers compared to fathers reported lower psychological and physical quality of life and more stress and anxiety (King et al., 2009). This study also found that children with food allergy had greater separation anxiety than their siblings. Another study noted that mothers of children with food allergy were more empowered than fathers of children with food allergy, but empowerment was not associated with higher HRQL (Warren et al., 2015). One study found that maternal anxiety and a child's attitude toward food allergy were associated with child distress for children ages 8 to 17 years (Lebovidge et al., 2009). Another study found that child anxiety and parental stress significantly predicted parental report of their child's HRQL, and that child anxiety, parenting stress, length of diagnosis, and receiving epinephrine predicted self-reported HRQL (Roy and Roberts, 2011). A study using various scales to determine anxiety and depression found that

among parents being evaluated for a first-time allergy clinic appointment for suspected food allergy in their child, 33 percent reported mild to severe anxiety and 18 percent reported depression, with no significant change 1 month after the visit (Knibb and Semper, 2013).

Studies have focused on teens and young adults as well. A small qualitative study of adolescents and their parents found that having a child with anaphylaxis can have a significant long-term psychological impact on the parents, and in some cases, this anxiety may be transferred to the adolescents (Akeson et al., 2007). In a large study of adolescents (N=1,420) followed longitudinally, having food allergy was associated with more symptoms of separation and generalized anxiety, attention deficit and hyperactivity disorder, and anorexia nervosa. Over time, adolescents with food allergy experienced increases in generalized anxiety disorder and depression, but having food allergy was not associated with a higher likelihood of having a diagnosed psychiatric disorder (Shanahan et al., 2014). An online study of 86 food-allergic and 344 healthy adults ages 18 to 22 years evaluated autonomy, anxiety, depression, and perception of parental behavior. The study indicated that, although food allergic young adults did not differ from healthy ones, those who experienced anaphylaxis described their disease as more severe, were more worried, and indicated their parents as more protective then those who had not experienced anaphylaxis (Herbert and Dahlquist, 2008). Additionally, for adolescents and young adults, having a food allergy may be associated with dating anxiety, interference with physical intimacy, and fear of a negative evaluation by peers (Hullmann et al., 2012).

Bullying has been another focus of study among psychosocial aspects of food allergy. Episodes of bullying appear to be more common among children with food allergy compared to peers and can take the form of verbal and physical events (Lieberman et al., 2010). Bullying is significantly associated with decreased quality of life and increased distress in parents and children. Parents often may not know about their child being bullied (Shemesh et al., 2013). When parents were aware of bullying, the child's quality of life was better and distress was reduced. Food-related bullying often persists over time, although it is less likely to continue if parents intervene (Annunziato et al., 2014). The AAAAI Guidelines specifically suggests that physicians inquire about behavioral changes because of food allergy–related bullying (Sampson et al., 2014).

Overall, the relationship of a chronic disease such as food allergy and psychosocial problems is complex. A systematic review and meta-analysis of 43 studies suggested a positive association between psychosocial factors and future atopic disorders and current atopic disorders and future poor mental health, but studies of food allergy were insufficient to comment on this disease separately (Chida et al., 2008). Determinants of food allergy–

related cognition, emotion, and behavior are complex and understudied (DunnGalvin et al., 2009).

Interventions pertaining to reducing the psychosocial impact of food allergy are few. It appears that food allergy interventions themselves can result in improvement. For example, measures of food-specific HRQOL showed improvement for those on desensitization therapy in small or uncontrolled studies (Arasi et al., 2014; Carraro et al., 2012; Factor et al., 2012; Otani et al., 2014). Also, anxiety may decrease and HRQL may improve following a diagnostic OFC, whether the outcome confirms an allergy or not (Franxman et al., 2015; Knibb et al., 2012; Soller et al., 2014; van der Velde et al., 2012; Zijlstra et al., 2010). However, no comprehensive, evidence-based protocols exist for the clinical management of psychosocial concerns related to food allergy, and studies are few. Availability of a 24-hour helpline for expert management improved quality of life for participants randomized to this intervention (Kelleher et al., 2013). A pilot study of a telephone-based intervention teaching parents self-regulation for chronic disease management resulted in improvement in some components of HRQL (Baptist et al., 2012). Data to understand the value of support groups for food allergy are limited (Sharma et al., 2012).

Referral to a mental health professional would presumably be of value, if indicated, to improve psychosocial health concerns. Unfortunately, one study of mental health screening of families with food allergy failed to result in a greater consultation rate with a mental health professional compared to a referral by the patient's allergist (Shemesh et al., 2015). An expert review on the topic of addressing the psychosocial aspect of food allergy on a patient-level basis suggested that medical providers can validate feelings, normalize the challenge of balancing management with participation in daily activities, and provide education about food allergy and its psychosocial impact, with referral to a mental health expert when indicated (Herbert et al., 2016).

In conclusion, food allergy may affect different aspects of mental health and HRQL. Health professionals should address these issues. However, more information is needed to refine understanding about identification, prevention, and management of these issues.

TREATMENT MODALITIES UNDER INVESTIGATION

The following summarizes approaches under investigation to treat food allergy. This is not meant to be a comprehensive review of risks and benefits of these approaches, nor a compendium of all approaches under study, but rather an overview with summaries of expert reports and suggested additional references. The committee did not make an assessment in regard to

which treatment modalities have more promise in the future nor where the research gaps exist.

A number of food allergy treatment strategies are under investigation. Examples that are furthest along in study and are allergen-specific include oral, sublingual, and epicutaneous immunotherapy.

Oral immunotherapy (OIT) involves ingesting the food allergen in gradually increasing amounts. Protocols typically begin with ingestion of trace amounts, building up to a small dose on a first day and then increasing the dose, which is taken daily, on a biweekly basis toward a daily "maintenance" dose. Sublingual immunotherapy (SLIT) takes a similar approach but the allergen is retained for a period under the tongue and much lower doses are used compared to OIT. Epicutaneous immunotherapy (EPIT) involves placement of a membrane impregnated with allergen on the skin. These therapies are often evaluated in context of promoting "desensitization" to the targeted food allergen. That is, these treatment approaches may raise the threshold of reactivity while the therapy is in progress, while cessation of therapy may result in loss of protection. A curative therapy would not depend upon daily treatments to maintain a threshold where the food can be ingested without concerns for dose ingested or other factors that may alter the safe ingestion of the food (e.g., concomitant exercise, illness). Approaches that are not allergen-specific also have been suggested. For example, omalizumab is a humanized monoclonal antibody against IgE that is approved for use in recalcitrant allergic asthma and for chronic hives. It may increase the threshold of reactivity to allergens and may, in co-administration with OIT, allow more rapid dosing with fewer symptoms (Begin et al., 2014; Schneider et al., 2013; Wood et al., 2015). Studies with a similar agent suggested an increased threshold to peanut during oral food challenges (Leung et al., 2003).

The 2010 NIAID/NIH-supported Guidelines concluded that allergen-specific immunotherapy is not recommended, and also did not recommend immunotherapy with cross-reactive allergens (i.e., pollen allergens to treat oral allergy syndrome) (Boyce et al., 2010). The 2014 EAACI Guidelines concluded that allergen-specific immunotherapy is promising, but is associated with risks, including anaphylaxis and is not recommended for routine clinical use (Muraro et al., 2014b). These Guidelines (p. 1019) also stated that "the use of anti-IgE alone or in combination with specific immunotherapy is currently not recommended . . . although it represents a promising treatment modality." In addition, the 2010 NIAID/NIH-supported Guidelines and the EACCI Guidelines both recommend not using pollen immunotherapy to primarily treat food allergy. The AAAAI Guidelines similarly concluded that immunotherapeutic approaches such as OIT show promise, but are not ready for implementation in clinical practice because

of inadequate evidence of therapeutic benefit over risks (Sampson et al., 2014).

The field of allergen-specific immunotherapy is rapidly progressing. A number of systematic reviews and meta-analyses have addressed the utility of immunotherapy (primarily OIT and SLIT) for food allergy. A 2012 meta-analysis of milk OIT identified five trials. The authors noted the poor quality of the trials and concluded that treatment could lead to desensitization in a majority of individuals. Although most were mild, a major drawback was the frequency of side effects (Yeung et al., 2012). A 2014 systematic review and meta-analysis of milk oral OIT identified six qualifying articles and concluded that it was effective for treating IgE-mediated cow milk allergy because significantly more patients were desensitized on treatment compared to those on an avoidance diet. The treatment was considered reasonably safe because side effects were mild to moderate and intramuscular epinephrine was rarely required (Martorell Calatayud et al., 2014). A 2012 review and meta-analysis of peanut OIT (Sheikh et al., 2012b) identified six qualifying studies with 85 participants, but given the case series design of all the studies, they were considered to have high risk of bias.[4] The authors noted suggestive evidence that treatment could increase the threshold for many participants but that adverse reactions were common. Although most were minor, some were potentially life-threatening. They concluded that the treatment was promising for short- or medium-term management of carefully selected patients, but that more robust studies were needed and that OIT should not be administered outside of carefully designed clinical trials. A 2014 meta-analysis (Sun et al., 2014) of RCTs of peanut OIT and SLIT identified three studies with a total of 86 participants. These immunotherapies were determined to have a positive effect on peanut allergy (OR: 38.44; 95% CI: 6-246). The authors cautioned that the findings were based on a small number of trials and larger, well-designed and double-blind RCTs are needed. A 2013 review of pediatric SLIT (Larenas-Linnemann et al., 2013) concluded that food OIT was more promising than SLIT, but few studies were included. A 2014 meta-analysis (Nurmatov et al., 2014a) identified 21 eligible trials of OIT or SLIT to foods. The meta-analysis revealed a lower risk of reactions on treatment (risk ratio [RR]: 0.21; 95% CI: 0.12-0.38). Additionally, SPT responses significantly decreased (mean difference: –2.96 millimeters [mm]; 95% CI: –4.48 to –1.45), and allergen-specific IgG4 concentrations increased by an average of 19.9 (95% CI: 17.1-22.6) µg/ml. Safety data showed an increased risk of local oral-pharyngeal and gastrointestinal adverse reactions with treatment (RR: 1.47; 95% CI: 1.11-1.95).

[4] Case series design studies are considered to be vulnerable to selection bias because they, for example, might draw their patients from a particular population and might not represent the wider population.

Also, a non-significant increased average risk of systemic adverse reactions occurred with treatment (RR: 1.08; 95% CI: 0.97-1.19). The authors concluded that OIT can induce immunomodulatory changes and thereby promote desensitization. However, based on limited evidence on long-term efficacy and safety, as well as cost-effectiveness, they concluded that the treatment should not currently be used outside of experimental conditions.

Overall, these reviews and meta-analyses are in agreement with the guidelines noted above. However, OIT is being used clinically by a number of practice settings with various motivations (Greenhawt and Vickery, 2015; Pajno et al., 2014). Phase 3 studies are currently under way for OIT and EPIT. Numerous other approaches have been tried or are in development, such as a panoply of biologics, immune adjuvants, modified protein vaccines, traditional Chinese medicine practices, probiotics, and many others (Bauer et al., 2015; Keet and Wood, 2014; Kumar et al., 2013; Le and Burks, 2014; Nermes et al., 2013; Nowak-Wegrzyn and Sampson, 2011; Oyoshi et al., 2014; Sato et al., 2014; Senti and Kundig, 2016). Clearly, many strategies can be pursued to address treatment of food allergy.

OVERALL CONCLUSIONS

Management in the health care setting involves education about the daily strategies that patients need to follow to avoid allergen ingestion and to recognize and treat reactions promptly. Although these management approaches begin in the health care setting, success often requires involvement at the community level (see Chapter 8). Allergen avoidance, usually strict avoidance even of trace amounts of allergen, is the primary means of management. This requires significant education and caution throughout the day. In addition, it relies upon others in the community to provide safety, seriously affects quality of life, and increases anxiety. Counseling about avoidance involves emphasizing key concerns, such as cross-contact and hidden ingredients and discussing foods related to the diagnosed allergens, which may need to be avoided upon a full food allergy evaluation. Counseling is directed to managing food allergies at home, reading labels (and knowing about products that are not included in mandatory labeling laws), asking questions when eating in restaurants and during travel, and, for children, avoiding food allergens when away from home (e.g., at schools, camp, or when with friends and relatives). Such counseling should address common pitfalls that have been identified in a variety of studies. However, data to be able to provide individualized risk assessments upon which to base instructions regarding avoidance and emergency management are limited. Also, limited programs exist for educating patients, caregivers, and other stakeholders, with few evidence-based programs to ensure effectiveness, and limited information exists on implementation. Adolescents

and young adults appear to be at increased risk for fatal anaphylaxis, and their risk-taking behavior has been identified as a possible cause.

Emergency management depends upon recognizing a reaction and promptly instituting therapy. Epinephrine is the primary treatment for anaphylaxis, with auto-injectors having fixed doses used for first-aid care. However, dosing of epinephrine has not been extensively studied and current auto-injectors may not provide appropriate doses for infants or individuals with obesity. Anaphylaxis is often underrecognized and undertreated. A number of risk factors have been identified for anaphylaxis, but there are no means to reliably predict severity of anaphylaxis. Medications used as primary and adjunctive therapy for anaphylaxis have not been studied. Post-anaphylaxis care includes observation in the medical setting to ensure resolution of symptoms, prescription of medications, education on avoidance and management, and possibly referral for additional testing and management. However, numerous pitfalls to these strategies have been identified.

Avoidance diets, particularly ones involving milk or multiple foods, can affect nutrition and growth and dietitian intervention is warranted. However, data on best practices are limited. Considering the significant impact of food allergy on quality of life and emotional status, information on how best to approach these issues is severely lacking. In addition, data on aspects of management for adults are sparse.

Emerging studies show promising results for desensitizing specific allergens but more information is needed about the safest and most effective approaches and how they may be individualized based on patients allergies and needs.

The committee did not wish to repeat all reasonable management recommendations that are already noted in professional guidelines, committee reports, and practice parameters. However, the committee emphasizes some key research recommendations in alignment with such reports where the study findings suggest areas of high need and frequent deficits in management.

RECOMMENDATIONS

Numerous clinical guidelines and parameters provide advice for health care providers and patients and their caregivers on diagnosing, preventing, and managing food allergy. The committee generally supports current guidelines and U.S. practice parameters for food allergy management and the committee emphasizes those areas where improvements would lead to significant changes in the quality of life of patients and their caregivers, such as training and education of the general public and all stakeholders.

Public Health Authorities, Health Care Providers, and Their Patients and Caregivers

The committee recommends that the Centers for Disease Control and Prevention work with other public health authorities to plan and initiate a public health campaign for the general public, individuals with food allergy, and all relevant stakeholders to increase awareness and empathy as well as to dispel misconceptions about food allergy and its management.

For example, as part of that campaign and taking advantage of the popularity of digital media among the public, particularly children and adolescents, public health authorities could develop effective media engagement programs. To plan for this campaign and develop media programs, public health authorities could conduct formative research with all potential audiences.

The committee recommends that public health authorities, such as the National Institutes of Health and the World Health Organization, and professional organizations, such as the American Academy of Pediatrics; the American Academy of Allergy, Asthma & Immunology; American Academy of Family Physicians; and the Academy of Nutrition and Dietetics, regularly update guidelines on diagnosis, prevention, and management of food allergy based on strong scientific evidence, as emerging scientific data become available.

For example, current evidence is insufficient to associate any of the following behaviors with prevention of food allergy: food allergen avoidance diets for pregnant or lactating women, prolonged allergen avoidance in infancy, vaginal delivery, breastfeeding, infant formulas containing extensively or partially hydrolyzed protein, and supplementation with specific nutrients (e.g., vitamin D, folate, fatty acids) in children or adults.

The committee recommends that medical schools as well as residency and fellowship programs and other relevant schools include training for health care providers in the management of food allergy and anaphylaxis. Health care providers, including dietitians and mental health professionals, also should receive training on approaches to counseling patients and their caregivers. Counseling training is envisioned to be provided, in part, by professional organizations through various means, including the Internet.

The following elements of food allergy training are appropriate for all health care providers, including emergency medical technicians, emergency room staff, nurses, dietitians, and others:

- *Emergency management*. This includes training to recognize and manage an anaphylaxis emergency, such as the use of intramuscular epinephrine as a first line of emergency management for episodes of anaphylaxis.
- *Counseling on food allergy management and anaphylaxis*. This includes identifying food allergies as well as managing and treating them in various settings (e.g., home, school, restaurants), as well as emergency management of anaphylaxis.

As appropriate, physicians and other health care providers also may receive training to provide the following:

- *Nutrition counseling*. This includes discussion of safe and nutritionally adequate avoidance diets to individuals with food allergies, particularly children and their caregivers. The training also could include offering referral to a dietitian when needed and as part of reimbursable care. In addition, dietitians may receive training in providing individualized dietary advice to people with food allergies and their caregivers.
- *Psychosocial counseling*. This includes identifying and discussing with patients and caregivers psychosocial concerns (e.g., bullying), validation of feelings, and balancing management with participation in daily activities. Training also could include offering referral to a mental health professional when needed and as part of reimbursable care. In addition, mental health professionals may receive training in counseling individuals with food allergy and their caregivers.

The committee recommends that health care providers counsel patients and their caregivers on food allergies following the most recent food allergy guidelines and emphasizing the need to take age-appropriate responsibility for managing their food allergy. Counseling is particularly important for those at high risk of food allergy and severe food allergy reactions, such as adolescents, young adults, and those with both food allergy and asthma.

The committee recommends that health care providers and others use intramuscular epinephrine (adrenaline) in all infants, children, and adults as a first line of emergency management for episodes of food allergy anaphylaxis. The Food and Drug Administration should evaluate the need for, and, if indicated, industry should develop an auto-injector with 0.075 mg epinephrine specifically designed for use in infants.

Current auto-injectors have 0.15 mg or 0.30 mg epinephrine, which is not suitable for infants. Consensus is currently lacking on first aid management using available auto-injectors when managing infants. A dose of 0.075 mg from an auto-injector could fill this gap. Labeling the auto-injectors in a standard manner to differentiate doses also could be beneficial.

Training First Responders and First Aiders

The committee recommends that organizations, such as the American Red Cross or the National Safety Council, who provide emergency training (e.g., first aid training, basic life support) to the general public and to first responders and first aid personnel in various professions and workplaces, include food allergy and anaphylaxis management in their curricula.

RESEARCH NEEDS

Health Care Settings

Food allergy management primarily requires avoiding the trigger allergen(s), but this approach requires extreme care; knowledge of cross-contact, hidden ingredients, and the effect of processing; and knowledge of ingredients through label reading and other methods. It is prone to accidents resulting in allergic reactions. Numerous obstacles arise for food-allergic consumers attempting to obtain safe meals outside the home. Surveys among individuals with food allergy, caregivers, and health care providers reveal deficiencies in food allergy knowledge and concerns about accidents, especially among adolescents and young adults. Only limited programs are available for educating individuals, caregivers, and health care providers on strategies to obtain and provide safe meals outside the home, with few validated programs and limited information on implementation. In addition, validated, evidence-based dietary guidance is lacking for those avoiding allergens, such as milk or multiple foods. Knowledge about potential interventions that health professionals could use to improve individual

psychosocial status, such as to improve quality of life or alleviate anxiety, also is lacking.

In regard to management, some areas of research need further study. For example, no means are currently available to reliably predict severity of anaphylaxis, which would be valuable for health care providers, individuals with food allergy, and their caregivers. In terms of managing anaphylaxis, underuse of epinephrine, the primary treatment for anaphylaxis, is common but the reasons are unknown. In addition, the fixed doses of epinephrine in auto-injectors may not be appropriate for infants or for individuals with obesity. Also, medications used as primary and adjunctive therapy for anaphylaxis (e.g., epinephrine dosing, bronchodilators, antihistamines, corticosteroids) have not been studied. Standardized emergency plans for individuals that can be used by caregivers at home or school also do not exist.

To address those gaps in knowledge, the following research areas should be pursued on all affected populations (ages, sexes, ethnicities, comorbidities, socioeconomic strata), especially on underrepresented populations:

- Determine the effectiveness of evidence-based guidelines and evidence-based educational programs on food allergy management, including avoidance of allergens and emergency management of allergic reactions and anaphylaxis, for health care providers and for patients, particularly for high-risk groups.
- Assess the following management issues:
  - the effectiveness of approaches other than strict allergen avoidance
  - the role of food allergy in other chronic allergic conditions
  - the identification of means to recognize clinically relevant versus nonrelevant allergen cross-reactivity
- Identify risk factors and biomarkers of food-induced anaphylaxis, particularly to identify individuals at high risk of severe reactions.
- Assess the safety and efficacy of adjunctive therapies for anaphylaxis, especially bronchodilators, antihistamines, and corticosteroids.
- Devise safe and effective therapies for food allergy, including those that can induce long-term desensitization and tolerance (i.e., sustained remission), and ideally a true cure.
- Improve understanding of the nutritional needs of persons on food allergen avoidance diets, how best to determine their need for dietitian evaluation/management, and how to develop evidence-based medical nutrition therapy.

- Evaluate whether consulting with a dietitian or a mental health professional improves quality of life and understand barriers to referring patients to dietitians or mental health professionals.
- Explore the best means to identify and intervene about psychosocial concerns associated with managing food allergy.
- Identify best practices for providing a uniform written emergency action plan for anaphylaxis. Consider using the recent American Academy of Pediatrics guidelines as the reference for a best practice study.
- Determine the proper dose of epinephrine in infants less than 10 kg and in individuals with obesity.
- Characterize risks associated with non-oral allergen exposures (e.g., skin-exposure and inhalation).

REFERENCES

AAAAI BOD (American Academy of Allergy, Asthma & Immunology Board of Directors). 1994. The use of epinephrine in the treatment of anaphylaxis. AAAI Board of Directors. *J Allergy Clin Immunol* 94(4):666-668.

AAAAI BOD. 1998. Anaphylaxis in schools and other childcare settings. AAAAI Board of Directors. American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 102(2):173-176.

Abdurrahman, Z. B., M. Kastner, C. Wurman, L. Harada, L. Bantock, H. Cruickshank, and S. Waserman. 2013. Experiencing a first food allergic reaction: A survey of parent and caregiver perspectives. *Allergy Asthma Clin Immunol* 9(1):18.

Agata, H., N. Kondo, O. Fukutomi, S. Shinoda, and T. Orii. 1993. Effect of elimination diets on food-specific IgE antibodies and lymphocyte proliferative responses to food antigens in atopic dermatitis patients exhibiting sensitivity to food allergens. *J Allergy Clin Immunol* 91(2):668-679.

Ahuja, R., and S. H. Sicherer. 2007. Food-allergy management from the perspective of restaurant and food establishment personnel. *Ann Allergy Asthma Immunol* 98(4):344-348.

Akeson, N., A. Worth, and A. Sheikh. 2007. The psychosocial impact of anaphylaxis on young people and their parents. *Clin Exp Allergy* 37(8):1213-1220.

Akiyama, H., T. Imai, and M. Ebisawa. 2011. Japan food allergen labeling regulation—History and evaluation. *Adv Food Nutr Res* 62:139-171.

Allen, C. W., A. S. Kemp, and D. E. Campbell. 2009. Dietary advice, dietary adherence and the acquisition of tolerance in egg-allergic children: A 5-yr follow-up. *Pediatr Allergy Immunol* 20(3):213-218.

Alqurashi, W., I. Stiell, K. Chan, G. Neto, A. Alsadoon, and G. Wells. 2015. Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis. *Ann Allergy Asthma Immunol* 115(3):217-223.

Annunziato, R. A., M. Rubes, M. A. Ambrose, C. Mullarkey, E. Shemesh, and S. H. Sicherer. 2014. Longitudinal evaluation of food allergy-related bullying. *J Allergy Clin Immunol Pract* 2(5):639-641.

Arasi, S., I. M. Otani, E. Klingbeil, P. Begin, C. Kearney, T. L. Dominguez, W. M. Block, G. O'Riordan, and K. C. Nadeau. 2014. Two year effects of food allergen immunotherapy on quality of life in caregivers of children with food allergies. *Allergy Asthma Clin Immunol* 10(1):57.

Arga, M., A. Bakirtas, F. Catal, O. Derinoz, K. Harmanci, C. H. Razi, S. Ergocen, M. S. Demirsoy, and I. Turktas. 2011. Training of trainers on epinephrine autoinjector use. *Pediatr Allergy Immunol* 22(6):590-593.

Bailey, S., R. Albardiaz, A. J. Frew, and H. Smith. 2011. Restaurant staff's knowledge of anaphylaxis and dietary care of people with allergies. *Clin Exp Allergy* 41(5):713-717.

Bailey, S., T. Billmeier Kindratt, H. Smith, and D. Reading. 2014. Food allergy training event for restaurant staff; a pilot evaluation. *Clin Transl Allergy* 4:26.

Banerjee, D. K., R. S. Kagan, E. Turnbull, L. Joseph, Y. St Pierre, C. Dufresne, K. Gray-Donald, and A. E. Clarke. 2007. Peanut-free guidelines reduce school lunch peanut contents. *Arch Dis Child* 92(11):980-982.

Bansal, P. J., R. Marsh, B. Patel, and M. C. Tobin. 2005. Recognition, evaluation, and treatment of anaphylaxis in the child care setting. *Ann Allergy Asthma Immunol* 94(1):55-59.

Baptist, A. P., S. I. Dever, M. J. Greenhawt, N. Polmear-Swendris, M. S. McMorris, and N. M. Clark. 2012. A self-regulation intervention can improve quality of life for families with food allergy. *J Allergy Clin Immunol* 130(1):263-265.

Barnett, J., N. Botting, M. H. Gowland, and J. S. Lucas. 2012. The strategies that peanut and nut-allergic consumers employ to remain safe when travelling abroad. *Clin Transl Allergy* 2(1):12.

Bath-Hextall, F., F. M. Delamere, and H. C. Williams. 2009. Dietary exclusions for improving established atopic eczema in adults and children: Systematic review. *Allergy* 64(2):258-264.

Bauer, R. N., M. Manohar, A. M. Singh, D. C. Jay, and K. C. Nadeau. 2015. The future of biologics: Applications for food allergy. *J Allergy Clin Immunol* 135(2):312-323.

Begin, P., T. Dominguez, S. P. Wilson, L. Bacal, A. Mehrotra, B. Kausch, A. Trela, M. Tavassoli, E. Hoyte, G. O'Riordan, A. Blakemore, S. Seki, R. G. Hamilton, and K. C. Nadeau. 2014. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. *Allergy Asthma Clin Immunol* 10(1):7.

Berni Canani, R., L. Leone, E. D'Auria, E. Riva, R. Nocerino, S. Ruotolo, G. Terrin, L. Cosenza, M. Di Costanzo, A. Passariello, A. Coruzzo, C. Agostoni, M. Giovannini, and R. Troncone. 2014. The effects of dietary counseling on children with food allergy: A prospective, multicenter intervention study. *J Acad Nutr Diet* 114(9):1432-1439.

Bock, S. A., A. Munoz-Furlong, and H. A. Sampson. 2001. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 107(1):191-193.

Bock, S. A., A. Munoz-Furlong, and H. A. Sampson. 2007. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol* 119(4):1016-1018.

Boyce, J. A., A. Assa'ad, A. W. Burks, S. M. Jones, H. A. Sampson, R. A. Wood, M. Plaut, S. F. Cooper, M. J. Fenton, S. H. Arshad, S. L. Bahna, L. A. Beck, C. Byrd-Bredbenner, C. A. Camargo, Jr., L. Eichenfield, G. T. Furuta, J. M. Hanifin, C. Jones, M. Kraft, B. D. Levy, P. Lieberman, S. Luccioli, K. M. McCall, L. C. Schneider, R. A. Simon, F. E. Simons, S. J. Teach, B. P. Yawn, and J. M. Schwaninger. 2010. Guidelines for the diagnosis and management of food allergy in the United States: Report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 126(6 Suppl):S1-S58.

Brown, J., D. Tuthill, M. Alfaham, and E. Spear. 2013. A randomized maternal evaluation of epinephrine autoinjection devices. *Pediatr Allergy Immunol* 24(2):173-177.

Caballero, T., M. S. San-Martin, M. A. Padial, J. Contreras, R. Cabanas, P. Barranco, and M. C. Lopez-Serrano. 2002. Clinical characteristics of patients with mustard hypersensitivity. *Ann Allergy Asthma Immunol* 89(2):166-171.

Camargo, C. A., Jr., S. Clark, M. S. Kaplan, P. Lieberman, and R. A. Wood. 2007. Regional differences in EpiPen prescriptions in the United States: The potential role of vitamin D. *J Allergy Clin Immunol* 120(1):131-136.

Campbell, R. L., J. B. Hagan, V. Manivannan, W. W. Decker, A. R. Kanthala, M. F. Bellolio, V. D. Smith, and J. T. Li. 2012. Evaluation of National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria for the diagnosis of anaphylaxis in emergency department patients. *J Allergy Clin Immunol* 129(3):748-752.

Campbell, R. L., M. F. Bellolio, B. D. Knutson, V. R. Bellamkonda, M. G. Fedko, D. M. Nestler, and E. P. Hess. 2015a. Epinephrine in anaphylaxis: Higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. *J Allergy Clin Immunol Pract* 3(1):76-80.

Campbell, R. L., M. A. Park, M. A. Kueber, Jr., S. Lee, and J. B. Hagan. 2015b. Outcomes of allergy/immunology follow-up after an emergency department evaluation for anaphylaxis. *J Allergy Clin Immunol Pract* 3(1):88-93.

Carlisle, S. K., P. A. Vargas, S. Noone, P. Steele, S. H. Sicherer, A. W. Burks, and S. M. Jones. 2010. Food allergy education for school nurses: A needs assessment survey by the Consortium of Food Allergy Research. *J Sch Nurs* 26(5):360-367.

Carraro, S., A. C. Frigo, M. Perin, S. Stefani, C. Cardarelli, S. Bozzetto, E. Baraldi, and S. Zanconato. 2012. Impact of oral immunotherapy on quality of life in children with cow milk allergy: A pilot study. *Int J Immunopathol Pharmacol* 25(3):793-798.

Cavanaugh, R., and C. J. Strickland. 2011. Research to practice: Developing an integrated anaphylaxis education curriculum for school nurses. *J Sch Nurs* 27(3):197-208.

CDC (Centers for Disease Control and Prevention). 2013. *Voluntary guidelines for managing food allergies in schools and early care and education programs*. Washington, DC: U.S. Department of Health and Human Services.

Chang, A., R. Robison, M. Cai, and A. M. Singh. 2016. Natural history of food-triggered atopic dermatitis and development of immediate reactions in children. *J Allergy Clin Immunol Pract* 4(2):229-236.

Chida, Y., M. Hamer, and A. Steptoe. 2008. A bidirectional relationship between psychosocial factors and atopic disorders: A systematic review and meta-analysis. *Psychosom Med* 70(1):102-116.

Cho, H. N., S. Hong, S. H. Lee, and H. Y. Yum. 2011. Nutritional status according to sensitized food allergens in children with atopic dermatitis. *Allergy Asthma Immunol Res* 3(1):53-57.

Chokshi, N. Y., D. Patel, and C. M. Davis. 2015. Long-term increase in epinephrine availability associated with school nurse training in food allergy. *J Allergy Clin Immunol Pract* 3(1):128-130.

Choo, K. J., F. E. Simons, and A. Sheikh. 2012. Glucocorticoids for the treatment of anaphylaxis. *Cochrane Database Syst Rev* 4:CD007596.

Christie, L., R. J. Hine, J. G. Parker, and W. Burks. 2002. Food allergies in children affect nutrient intake and growth. *J Am Diet Assoc* 102(11):1648-1651.

Cicutto, L., B. Julien, N. Y. Li, N. U. Nguyen-Luu, J. Butler, A. Clarke, S. J. Elliott, L. Harada, S. McGhan, D. Stark, T. K. Vander Leek, and S. Waserman. 2012. Comparing school environments with and without legislation for the prevention and management of anaphylaxis. *Allergy* 67(1):131-137.

Clark, S., S. A. Bock, T. J. Gaeta, B. E. Brenner, R. K. Cydulka, and C. A. Camargo. 2004. Multicenter study of emergency department visits for food allergies. *J Allergy Clin Immunol* 113(2):347-352.

Cohen, B. L., S. Noone, A. Munoz-Furlong, and S. H. Sicherer. 2004. Development of a questionnaire to measure quality of life in families with a child with food allergy. *J Allergy Clin Immunol* 114(5):1159-1163.

Comstock, S. S., R. DeMera, L. C. Vega, E. J. Boren, S. Deane, L. A. Haapanen, and S. S. Teuber. 2008. Allergic reactions to peanuts, tree nuts, and seeds aboard commercial airliners. *Ann Allergy Asthma Immunol* 101(1):51-56.

Council on School Health. 2009. Policy statement—guidance for the administration of medication in school. *Pediatrics* 124(4):1244-1251.

Crotty, M. P., and S. L. Taylor. 2010. Risks associated with foods having advisory milk labeling. *J Allergy Clin Immunol* 125(4):935-937.

Cuervo-Pardo, L., M. A. Barcena-Blanch, A. Gonzalez-Estrada, and B. Schroer. 2015. Apps for food allergy: A critical assessment. *J Allergy Clin Immunol Pract* 3(6):980-981.

Dalal, I., M. Goldberg, and Y. Katz. 2012. Sesame seed food allergy. *Curr Allergy Asthma Rep* 12(4):339-345.

David, T. J. 1984. Anaphylactic shock during elimination diets for severe atopic eczema. *Arch Dis Child* 59(10):983-986.

De Schryver, S., M. Halbrich, A. Clarke, S. La Vieille, H. Eisman, R. Alizadehfar, L. Joseph, J. Morris, and M. Ben-Shoshan. 2016. Tryptase levels in children presenting with anaphylaxis: Temporal trends and associated factors. *J Allergy Clin Immunol* 137(4):1138-1142.

de Silva, D., M. Geromi, S. S. Panesar, A. Muraro, T. Werfel, K. Hoffmann-Sommergruber, G. Roberts, V. Cardona, A. E. Dubois, S. Halken, A. Host, L. K. Poulsen, R. Van Ree, B. J. Vlieg-Boerstra, I. Agache, and A. Sheikh. 2014. Acute and long-term management of food allergy: Systematic review. *Allergy* 69(2):159-167.

Decastelli, L., S. Gallina, D. Manila Bianchi, S. Fragassi, and P. Restani. 2012. Undeclared allergenic ingredients in foods from animal origin: Survey of an Italian region's food market, 2007-2009. *Food Addit Contam Part B Surveill* 5(3):160-164.

Desai, S. H., K. Jeong, J. D. Kattan, R. Lieberman, S. Wisniewski, and T. D. Green. 2015. Anaphylaxis management before and after implementation of guidelines in the pediatric emergency department. *J Allergy Clin Immunol Pract* 3(4):604-606.

Desjardins, M., A. Clarke, R. Alizadehfar, D. Grenier, H. Eisman, S. Carr, T. K. Vander Leek, L. Teperman, N. Higgins, L. Joseph, G. Shand, and M. Ben-Shoshan. 2013. Canadian allergists' and nonallergists' perception of epinephrine use and vaccination of persons with egg allergy. *J Allergy Clin Immunol Pract* 1(3):289-294.

Dhami, S., S. S. Panesar, G. Roberts, A. Muraro, M. Worm, M. B. Bilo, V. Cardona, A. E. Dubois, A. DunnGalvin, P. Eigenmann, M. Fernandez-Rivas, S. Halken, G. Lack, B. Niggemann, F. Rueff, A. F. Santos, B. Vlieg-Boerstra, Z. Q. Zolkipli, and A. Sheikh. 2014. Management of anaphylaxis: A systematic review. *Allergy* 69(2):168-175.

DunnGalvin, A., B. M. de BlokFlokstra, A. W. Burks, A. E. Dubois, and J. O. Hourihane. 2008. Food allergy QoL questionnaire for children aged 0-12 years: Content, construct, and cross-cultural validity. *Clin Exp Allergy* 38(6):977-986.

DunnGalvin, A., A. Gaffney, and J. O. Hourihane. 2009. Developmental pathways in food allergy: A new theoretical framework. *Allergy* 64(4):560-568.

Eldredge, C., and K. Schellhase. 2012. School-based management of food allergies in children. *Am Fam Physician* 86(1):16-18.

Ellis, A. K., and J. H. Day. 2007. Incidence and characteristics of biphasic anaphylaxis: A prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol* 98(1):64-69.

Ellis, B. C., and S. G. Brown. 2013. Parenteral antihistamines cause hypotension in anaphylaxis. *Emerg Med Australas* 25(1):92-93.

Ercan, H., A. Ozen, H. Karatepe, M. Berber, and R. Cengizlier. 2012. Primary school teachers' knowledge about and attitudes toward anaphylaxis. *Pediatr Allergy Immunol* 23(5): 428-432.

Eriksson, N. E., C. Moller, S. Werner, J. Magnusson, and U. Bengtsson. 2003. The hazards of kissing when you are food allergic. A survey on the occurrence of kiss-induced allergic reactions among 1139 patients with self-reported food hypersensitivity. *J Investig Allergol Clin Immunol* 13(3):149-154.

Ewan, P. W., and A. T. Clark. 2001. Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. *Lancet* 357(9250):111-115.

Factor, J. M., L. Mendelson, J. Lee, G. Nouman, and M. R. Lester. 2012. Effect of oral immunotherapy to peanut on food-specific quality of life. *Ann Allergy Asthma Immunol* 109(5):348-352.

Fiocchi, A., H. J. Schunemann, J. Brozek, P. Restani, K. Beyer, R. Troncone, A. Martelli, L. Terracciano, S. L. Bahna, F. Rance, M. Ebisawa, R. G. Heine, A. Assa'ad, H. Sampson, E. Verduci, G. R. Bouygue, C. Baena-Cagnani, W. Canonica, and R. F. Lockey. 2010. Diagnosis and Rationale for Action Against Cow's Milk Allergy (DRACMA): A summary report. *J Allergy Clin Immunol* 126(6):1119-1128.

Flammarion, S., C. Santos, D. Guimber, L. Jouannic, C. Thumerelle, F. Gottrand, and A. Deschildre. 2011. Diet and nutritional status of children with food allergies. *Pediatr Allergy Immunol* 22(2):161-165.

Fleischer, D. M., T. T. Perry, D. Atkins, R. A. Wood, A. W. Burks, S. M. Jones, A. K. Henning, D. Stablein, H. A. Sampson, and S. H. Sicherer. 2012. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics* 130(1):e25-e32.

Flinterman, A. E., A. C. Knulst, Y. Meijer, C. A. Bruijnzeel-Koomen, and S. G. Pasmans. 2006. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. *Allergy* 61(3):370-374.

Flokstra-de Blok, B. M., A. DunnGalvin, B. J. Vlieg-Boerstra, J. N. Oude Elberink, E. J. Duiverman, J. O. Hourihane, and A. E. Dubois. 2008. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. *J Allergy Clin Immunol* 122(1):139-144.

Flokstra-de Blok, B. M., A. DunnGalvin, B. J. Vlieg-Boerstra, J. N. Oude Elberink, E. J. Duiverman, J. O. Hourihane, and A. E. Dubois. 2009a. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. *Clin Exp Allergy* 39(1):127-137.

Flokstra-de Blok, B. M., G. N. van der Meulen, A. DunnGalvin, B. J. Vlieg-Boerstra, J. N. Oude Elberink, E. J. Duiverman, J. O. Hourihane, and A. E. Dubois. 2009b. Development and validation of the Food Allergy Quality of Life Questionnaire—Adult Form. *Allergy* 64(8):1209-1217.

Ford, L. S., S. L. Taylor, R. Pacenza, L. M. Niemann, D. M. Lambrecht, and S. H. Sicherer. 2010. Food allergen advisory labeling and product contamination with egg, milk, and peanut. *J Allergy Clin Immunol* 126(2):384-385.

Ford, L. S., P. J. Turner, and D. E. Campbell. 2014. Recommendations for the management of food allergies in a preschool/childcare setting and prevention of anaphylaxis. *Expert Rev Clin Immunol* 10(7):867-874.

Franxman, T. J., L. Howe, E. Teich, and M. J. Greenhawt. 2015. Oral food challenge and food allergy quality of life in caregivers of children with food allergy. *J Allergy Clin Immunol Pract* 3(1):50-56.

Furlong, T. J., J. DeSimone, and S. H. Sicherer. 2001. Peanut and tree nut allergic reactions in restaurants and other food establishments. *J Allergy Clin Immunol* 108(5):867-870.

Gendel, S. M. 2012. Comparison of international food allergen labeling regulations. *Regul Toxicol Pharmacol* 63(2):279-285.

Greenhawt, M. J., and B. P. Vickery. 2015. Allergist-reported trends in the practice of food allergen oral immunotherapy. *J Allergy Clin Immunol Pract* 3(1):33-38.

Greenhawt, M. J., A. M. Singer, and A. P. Baptist. 2009. Food allergy and food allergy attitudes among college students. *J Allergy Clin Immunol* 124(2):323-327.

Greenhawt, M., F. MacGillivray, G. Batty, M. Said, and C. Weiss. 2013. International study of risk-mitigating factors and in-flight allergic reactions to peanut and tree nut. *J Allergy Clin Immunol Pract* 1(2):186-194.

Greiwe, J. C., F. Pazheri, and B. Schroer. 2015. Nannies' knowledge, attitude, and management of food allergies of children: An online survey. *J Allergy Clin Immunol Pract* 3(1):63-67.

Groetch, M. E., L. Christie, P. A. Vargas, S. M. Jones, and S. H. Sicherer. 2010. Food allergy educational needs of pediatric dietitians: A survey by the Consortium of Food Allergy Research. *J Nutr Educ Behav* 42(4):259-264.

Groetch, M., M. Henry, M. B. Feuling, and J. Kim. 2013. Guidance for the nutrition management of gastrointestinal allergy in pediatrics. *J Allergy Clin Immunol Pract* 1(4):323-331.

Guerlain, S., A. Hugine, and L. Wang. 2010. A comparison of 4 epinephrine autoinjector delivery systems: Usability and patient preference. *Ann Allergy Asthma Immunol* 104(2):172-177.

Gupta, R. S., J. S. Kim, E. E. Springston, B. Smith, J. A. Pongracic, X. Wang, and J. Holl. 2009. Food allergy knowledge, attitudes, and beliefs in the United States. *Ann Allergy Asthma Immunol* 103(1):43-50.

Gupta, R. S., E. E. Springston, B. Smith, J. S. Kim, J. A. Pongracic, X. Wang, and J. Holl. 2010a. Food allergy knowledge, attitudes, and beliefs of parents with food-allergic children in the United States. *Pediatr Allergy Immunol* 21(6):927-934.

Gupta, R. S., E. E. Springston, J. S. Kim, B. Smith, J. A. Pongracic, X. Wang, and J. Holl. 2010b. Food allergy knowledge, attitudes, and beliefs of primary care physicians. *Pediatrics* 125(1):126-132.

Gupta, R. S., V. Rivkina, L. DeSantiago-Cardenas, B. Smith, B. Harvey-Gintoft, and S. A. Whyte. 2014. Asthma and food allergy management in Chicago Public Schools. *Pediatrics* 134(4):729-736.

Hallett, R., L. A. Haapanen, and S. S. Teuber. 2002. Food allergies and kissing. *N Engl J Med* 346(23):1833-1834.

Harduar-Morano, L., M. R. Simon, S. Watkins, and C. Blackmore. 2010. Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida. *J Allergy Clin Immunol* 126(1):98-104.

Hefle, S. L., T. J. Furlong, L. Niemann, H. Lemon-Mule, S. Sicherer, and S. L. Taylor. 2007. Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. *J Allergy Clin Immunol* 120(1):171-176.

Herbert, L. J., and L. M. Dahlquist. 2008. Perceived history of anaphylaxis and parental overprotection, autonomy, anxiety, and depression in food allergic young adults. *J Clin Psychol Med Settings* 15(4):261-269.

Herbert, L., E. Shemesh, and B. Bender. 2016. Clinical management of psychosocial concerns related to food allergy. *J Allergy Clin Immunol Pract* 4(2):205-213; quiz 214.

Hernandez-Trujillo, V., and F. E. Simons. 2013. Prospective evaluation of an anaphylaxis education mini-handout: The AAAAI Anaphylaxis Wallet Card. *J Allergy Clin Immunol Pract* 1(2):181-185.

Hobbs, C. B., A. C. Skinner, A. W. Burks, and B. P. Vickery. 2015. Food allergies affect growth in children. *J Allergy Clin Immunol Pract* 3(1):133-134.

Hullmann, S. E., E. S. Molzon, A. R. Eddington, and L. L. Mullins. 2012. Dating anxiety in adolescents and young adults with food allergies: A comparison to healthy peers. *J Asthma & Allergy Educ* 3(4):172-177.

Isolauri, E., Y. Sutas, M. K. Salo, R. Isosomppi, and M. Kaila. 1998. Elimination diet in cow's milk allergy: Risk for impaired growth in young children. *J Pediatr* 132(6):1004-1009.

Jacobsen, R. C., S. Toy, A. J. Bonham, J. A. Salomone, 3rd, J. Ruthstrom, and M. Gratton. 2012. Anaphylaxis knowledge among paramedics: Results of a national survey. *Prehosp Emerg Care* 16(4):527-534.

Jarvinen, K. M., S. Makinen-Kiljunen, and H. Suomalainen. 1999. Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy. *J Pediatr* 135(4):506-512.

Jarvinen, K. M., S. H. Sicherer, H. A. Sampson, and A. Nowak-Wegrzyn. 2008. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. *J Allergy Clin Immunol* 122(1):133-138.

Jarvinen, K. M., G. N. Konstantinou, M. Pilapil, M. C. Arrieta, S. Noone, H. A. Sampson, J. Meddings, and A. Nowak-Wegrzyn. 2013. Intestinal permeability in children with food allergy on specific elimination diets. *Pediatr Allergy Immunol* 24(6):589-595.

Jones, C. J., C. D. Llewellyn, A. J. Frew, G. Du Toit, S. Mukhopadhyay, and H. Smith. 2015. Factors associated with good adherence to self-care behaviours amongst adolescents with food allergy. *Pediatr Allergy Immunol* 26(2):111-118.

Keet, C. A., and R. A. Wood. 2014. Emerging therapies for food allergy. *J Clin Invest* 124(5):1880-1886.

Kelleher, M. M., A. DunnGalvin, A. Sheikh, C. Cullinane, J. Fitzsimons, and J. O. Hourihane. 2013. Twenty four-hour helpline access to expert management advice for food-allergy-triggered anaphylaxis in infants, children and young people: A pragmatic, randomized controlled trial. *Allergy* 68(12):1598-1604.

Kelso, J. M. 2014. Potential food allergens in medications. *J Allergy Clin Immunol* 133(6):1509-1518; quiz 1519-1520.

Kelso, J. M., M. J. Greenhawt, J. T. Li, R. A. Nicklas, D. I. Bernstein, J. Blessing-Moore, L. Cox, D. Khan, D. M. Lang, J. Oppenheimer, J. M. Portnoy, C. R. Randolph, D. E. Schuller, S. L. Spector, S. A. Tilles, and D. Wallace. 2012. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol* 130(1):25-43.

Kelso, J. M., M. J. Greenhawt, and J. T. Li. 2013. Update on influenza vaccination of egg allergic patients. *Ann Allergy Asthma Immunol* 111(4):301-302.

Kim, J. S., and S. Sicherer. 2010. Should avoidance of foods be strict in prevention and treatment of food allergy? *Curr Opin Allergy Clin Immunol* 10(3):252-257.

Kim, J. S., A. Nowak-Wegrzyn, S. H. Sicherer, S. Noone, E. L. Moshier, and H. A. Sampson. 2011. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol* 128(1):125-131.

King, R. M., R. C. Knibb, and J. O. Hourihane. 2009. Impact of peanut allergy on quality of life, stress and anxiety in the family. *Allergy* 64(3):461-468.

Knibb, R. C., and H. Semper. 2013. Impact of suspected food allergy on emotional distress and family life of parents prior to allergy diagnosis. *Pediatr Allergy Immunol* 24(8):798-803.

Knibb, R. C., N. F. Ibrahim, G. Stiefel, R. Petley, A. J. Cummings, R. M. King, D. Keeton, L. Brown, M. Erlewyn-Lajeunesse, G. Roberts, and J. S. Lucas. 2012. The psychological impact of diagnostic food challenges to confirm the resolution of peanut or tree nut allergy. *Clin Exp Allergy* 42(3):451-459.

Kumar, S., K. Gupta, M. Das, and P. D. Dwivedi. 2013. Recent advancements in the therapeutics of food allergy. *Recent Pat Food Nutr Agric* 5(3):188-200.

Larenas-Linnemann, D., M. Blaiss, H. P. Van Bever, E. Compalati, and C. E. Baena-Cagnani. 2013. Pediatric sublingual immunotherapy efficacy: Evidence analysis, 2009-2012. *Ann Allergy Asthma Immunol* 110(6):402-415.

Lau, G. Y., N. Patel, T. Umasunthar, C. Gore, J. O. Warner, H. Hanna, K. Phillips, A. M. Zaki, M. Hodes, and R. J. Boyle. 2014. Anxiety and stress in mothers of food-allergic children. *Pediatr Allergy Immunol* 25(3):236-242.

Le, U. H., and A. W. Burks. 2014. Oral and sublingual immunotherapy for food allergy. *World Allergy Organ J* 7(1):35.

Lebovidge, J. S., H. Strauch, L. A. Kalish, and L. C. Schneider. 2009. Assessment of psychological distress among children and adolescents with food allergy. *J Allergy Clin Immunol* 124(6):1282-1288.

Lee, J. M., and D. S. Greenes. 2000. Biphasic anaphylactic reactions in pediatrics. *Pediatrics* 106(4):762-766.

Lee, T. D., G. Gimenez, G. Grishina, M. Mishoe, H. A. Sampson, and S. Bunyavanich. 2015a. Profile of a milk-allergic patient who tolerated partially hydrolyzed whey formula. *J Allergy Clin Immunol Pract* 3(1):116-118.

Lee, S., M. F. Bellolio, E. P. Hess, P. Erwin, M. H. Murad, and R. L. Campbell. 2015b. Time of onset and predictors of biphasic anaphylactic reactions: A systematic review and meta-analysis. *J Allergy Clin Immunol Pract* 3(3):408-416.

Leo, H. L., and N. M. Clark. 2012. Addressing food allergy issues within child care centers. *Curr Allergy Asthma Rep* 12(4):304-310.

Leonard, S. A., H. A. Sampson, S. H. Sicherer, S. Noone, E. L. Moshier, J. Godbold, and A. Nowak-Wegrzyn. 2012. Dietary baked egg accelerates resolution of egg allergy in children. *J Allergy Clin Immunol* 130(2):473-480.

Leung, D. Y., H. A. Sampson, J. W. Yunginger, A. W. Burks, Jr., L. C. Schneider, C. H. Wortel, F. M. Davis, J. D. Hyun, and W. R. Shanahan, Jr. 2003. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 348(11):986-993.

Lever, R., C. MacDonald, P. Waugh, and T. Aitchison. 1998. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 9(1):13-19.

Lieberman, J. A., C. Weiss, T. J. Furlong, M. Sicherer, and S. H. Sicherer. 2010. Bullying among pediatric patients with food allergy. *Ann Allergy Asthma Immunol* 105(4):282-286.

Lieberman, P. 2005. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol* 95(3):217-226; quiz 226, 258.

Lieberman, P., R. A. Nicklas, C. Randolph, J. Oppenheimer, D. Bernstein, J. Bernstein, A. Ellis, D. B. Golden, P. Greenberger, S. Kemp, D. Khan, D. Ledford, J. Lieberman, D. Metcalfe, A. Nowak-Wegrzyn, S. Sicherer, D. Wallace, J. Blessing-Moore, D. Lang, J. M. Portnoy, D. Schuller, S. Spector, and S. A. Tilles. 2015. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol* 115(5):341-384.

Lifschitz, C. H., H. K. Hawkins, C. Guerra, and N. Byrd. 1988. Anaphylactic shock due to cow's milk protein hypersensitivity in a breast-fed infant. *J Pediatr Gastroenterol Nutr* 7(1):141-144.

Lin, R. Y., L. B. Schwartz, A. Curry, G. R. Pesola, R. J. Knight, H. S. Lee, L. Bakalchuk, C. Tenenbaum, and R. E. Westfal. 2000a. Histamine and tryptase levels in patients with acute allergic reactions: An emergency department-based study. *J Allergy Clin Immunol* 106(1 Pt 1):65-71.

Lin, R. Y., A. Curry, G. R. Pesola, R. J. Knight, H. S. Lee, L. Bakalchuk, C. Tenenbaum, and R. E. Westfal. 2000b. Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists. *Ann Emerg Med* 36(5):462-468.

Macadam, C., J. Barnett, G. Roberts, G. Stiefel, R. King, M. Erlewyn-Lajeunesse, J. A. Holloway, and J. S. Lucas. 2012. What factors affect the carriage of epinephrine auto-injectors by teenagers? *Clin Transl Allergy* 2(1):3.

MacKenzie, H., G. Roberts, D. van Laar, and T. Dean. 2010. Teenagers' experiences of living with food hypersensitivity: A qualitative study. *Pediatr Allergy Immunol* 21(4 Pt 1):595-602.

MacKenzie, H., G. Roberts, D. Van Laar, and T. Dean. 2012. A new quality of life scale for teenagers with food hypersensitivity. *Pediatr Allergy Immunol* 23(5):404-411.

Maloney, J. M., M. D. Chapman, and S. H. Sicherer. 2006. Peanut allergen exposure through saliva: Assessment and interventions to reduce exposure. *J Allergy Clin Immunol* 118(3):719-724.

Marchisotto, M. J., L. Harada, J. A. Blumenstock, L. A. Bilaver, S. Waserman, S. Sicherer, Y. Boloh, L. Regent, M. Said, S. Schnadt, K. J. Allen, A. Muraro, S. L. Taylor, and R. S. Gupta. 2016. Global perceptions of food allergy thresholds in 16 countries. *Allergy* 71(8):1081-1085.

Marrs, T., and G. Lack. 2013. Why do few food-allergic adolescents treat anaphylaxis with adrenaline?-—Reviewing a pressing issue. *Pediatr Allergy Immunol* 24(3):222-229.

Martorell Calatayud, C., A. Muriel Garcia, A. Martorell Aragones, and B. De La Hoz Caballer. 2014. Safety and efficacy profile and immunological changes associated with oral immunotherapy for IgE-mediated cow's milk allergy in children: Systematic review and meta-analysis. *J Investig Allergol Clin Immunol* 24(5):298-307.

Maslin, K., R. Meyer, L. Reeves, H. Mackenzie, A. Swain, W. Stuart-Smith, R. Loblay, M. Groetch, and C. Venter. 2014. Food allergy competencies of dietitians in the United Kingdom, Australia and United States of America. *Clin Transl Allergy* 4:37.

Maslin, K., J. Grundy, G. Glasbey, T. Dean, S. H. Arshad, K. Grimshaw, E. Oliver, G. Roberts, and C. Venter. 2016. Cows' milk exclusion diet during infancy: Is there a long-term effect on children's eating behaviour and food preferences? *Pediatr Allergy Immunol* 27(2):141-146.

Mehr, S., W. K. Liew, D. Tey, and M. L. Tang. 2009. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. *Clin Exp Allergy* 39(9):1390-1396.

Mehta, H., M. Ramesh, E. Feuille, M. Groetch, and J. Wang. 2014. Growth comparison in children with and without food allergies in 2 different demographic populations. *J Pediatr* 165(4):842-848.

Meyer, R., C. Venter, A. T. Fox, and N. Shah. 2012. Practical dietary management of protein energy malnutrition in young children with cow's milk protein allergy. *Pediatr Allergy Immunol* 23(4):307-314.

Meyer, R., C. De Koker, R. Dziubak, C. Venter, G. Dominguez-Ortega, R. Cutts, N. Yerlett, A. K. Skrapak, A. T. Fox, and N. Shah. 2014. Malnutrition in children with food allergies in the UK. *J Hum Nutr Diet* 27(3):227-235.

Monks, H., M. H. Gowland, H. MacKenzie, M. Erlewyn-Lajeunesse, R. King, J. S. Lucas, and G. Roberts. 2010. How do teenagers manage their food allergies? *Clin Exp Allergy* 40(10):1533-1540.

Monti, G., L. Marinaro, V. Libanore, A. Peltran, M. C. Muratore, and L. Silvestro. 2006. Anaphylaxis due to fish hypersensitivity in an exclusively breastfed infant. *Acta Paediatr* 95(11):1514-1515.

Morawetz, D. Y., H. Hiscock, K. J. Allen, S. Davies, and M. H. Danchin. 2014. Management of food allergy: A survey of Australian paediatricians. *J Paediatr Child Health* 50(6):432-437.

Mori, F., D. Serranti, S. Barni, N. Pucci, M. E. Rossi, M. de Martino, and E. Novembre. 2015. A kwashiorkor case due to the use of an exclusive rice milk diet to treat atopic dermatitis. *Nutr J* 14:83.

Mukaida, K., T. Kusunoki, T. Morimoto, T. Yasumi, R. Nishikomori, T. Heike, T. Fujii, and T. Nakahata. 2010. The effect of past food avoidance due to allergic symptoms on the growth of children at school age. *Allergol Int* 59(4):369-374.

Mullins, R. J. 2003. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy* 33(8):1033-1040.

Muraro, A., G. Roberts, M. Worm, M. B. Bilo, K. Brockow, M. Fernandez Rivas, A. F. Santos, Z. Q. Zolkipli, A. Bellou, K. Beyer, C. Bindslev-Jensen, V. Cardona, A. T. Clark, P. Demoly, A. E. Dubois, A. DunnGalvin, P. Eigenmann, S. Halken, L. Harada, G. Lack, M. Jutel, B. Niggemann, F. Rueff, F. Timmermans, B. J. Vlieg-Boerstra, T. Werfel, S. Dhami, S. Panesar, C. A. Akdis, and A. Sheikh. 2014a. Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 69(8):1026-1045.

Muraro, A., T. Werfel, K. Hoffmann-Sommergruber, G. Roberts, K. Beyer, C. Bindslev-Jensen, V. Cardona, A. Dubois, G. duToit, P. Eigenmann, M. Fernandez Rivas, S. Halken, L. Hickstein, A. Host, E. Knol, G. Lack, M. J. Marchisotto, B. Niggemann, B. I. Nwaru, N. G. Papadopoulos, L. K. Poulsen, A. F. Santos, I. Skypala, A. Schoepfer, R. Van Ree, C. Venter, M. Worm, B. Vlieg-Boerstra, S. Panesar, D. de Silva, K. Soares-Weiser, A. Sheikh, B. K. Ballmer-Weber, C. Nilsson, N. W. de Jong, and C. A. Akdis. 2014b. EAACI Food Allergy and Anaphylaxis Guidelines: Diagnosis and management of food allergy. *Allergy* 69(8):1008-1025.

Muraro, A., A. E. Dubois, A. DunnGalvin, J. O. Hourihane, N. W. de Jong, R. Meyer, S. S. Panesar, G. Roberts, S. Salvilla, A. Sheikh, A. Worth, and B. M. Flokstra-de Blok. 2014c. EAACI Food Allergy and Anaphylaxis Guidelines. Food allergy health-related quality of life measures. *Allergy* 69(7):845-853.

Muraro, A., I. Agache, A. Clark, A. Sheikh, G. Roberts, C. A. Akdis, L. M. Borrego, J. Higgs, J. O. Hourihane, P. Jorgensen, A. Mazon, D. Parmigiani, M. Said, S. Schnadt, H. van Os-Medendorp, B. J. Vlieg-Boerstra, and M. Wickman. 2014d. EAACI Food Allergy and Anaphylaxis Guidelines: Managing patients with food allergy in the community. *Allergy* 69(8):1046-1057.

Nachshon, L., M. R. Goldberg, N. Schwartz, T. Sinai, R. Amitzur-Levy, A. Elizur, E. Eisenberg, and Y. Katz. 2014. Decreased bone mineral density in young adult IgE-mediated cow's milk-allergic patients. *J Allergy Clin Immunol* 134(5):1108-1113.

Nermes, M., S. Salminen, and E. Isolauri. 2013. Is there a role for probiotics in the prevention or treatment of food allergy? *Curr Allergy Asthma Rep* 13(6):622-630.

Noimark, L., J. Wales, G. Du Toit, C. Pastacaldi, D. Haddad, J. Gardner, W. Hyer, G. Vance, C. Townshend, M. Alfaham, P. D. Arkwright, R. Rao, S. Kapoor, A. Summerfield, J. O. Warner, and G. Roberts. 2012. The use of adrenaline autoinjectors by children and teenagers. *Clin Exp Allergy* 42(2):284-292.

Nowak-Wegrzyn, A., and H. A. Sampson. 2011. Future therapies for food allergies. *J Allergy Clin Immunol* 127(3):558-573; quiz 574-555.

Nowak-Wegrzyn, A., K. A. Bloom, S. H. Sicherer, W. G. Shreffler, S. Noone, N. Wanich, and H. A. Sampson. 2008. Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol* 122(2):342-347.

Nurmatov, U., G. Devereux, A. Worth, L. Healy, and A. Sheikh. 2014a. Effectiveness and safety of orally administered immunotherapy for food allergies: A systematic review and meta-analysis. *Br J Nutr* 111(1):12-22.

Nurmatov, U. B., E. Rhatigan, F. E. Simons, and A. Sheikh. 2014b. H2-antihistamines for the treatment of anaphylaxis with and without shock: A systematic review. *Ann Allergy Asthma Immunol* 112(2):126-131.

Oren, E., A. Banerji, S. Clark, and C. A. Camargo, Jr. 2007. Food-induced anaphylaxis and repeated epinephrine treatments. *Ann Allergy Asthma Immunol* 99(5):429-432.

Otani, I. M., P. Begin, C. Kearney, T. L. Dominguez, A. Mehrotra, L. R. Bacal, S. Wilson, and K. Nadeau. 2014. Multiple-allergen oral immunotherapy improves quality of life in caregivers of food-allergic pediatric subjects. *Allergy Asthma Clin Immunol* 10(1):25.

Oyoshi, M. K., H. C. Oettgen, T. A. Chatila, R. S. Geha, and P. J. Bryce. 2014. Food allergy: Insights into etiology, prevention, and treatment provided by murine models. *J Allergy Clin Immunol* 133(2):309-317.

Pajno, G. B., L. Cox, L. Caminiti, V. Ramistella, and G. Crisafulli. 2014. Oral immunotherapy for treatment of immunoglobulin e-mediated food allergy: The transition to clinical practice. *Pediatr Allergy Immunol Pulmonol* 27(2):42-50.

Perry, T. T., M. K. Conover-Walker, A. Pomes, M. D. Chapman, and R. A. Wood. 2004. Distribution of peanut allergen in the environment. *J Allergy Clin Immunol* 113(5):973-976.

Polloni, L., F. Lazzarotto, A. Toniolo, G. Ducolin, and A. Muraro. 2013. What do school personnel know, think and feel about food allergies? *Clin Transl Allergy* 3(1):39.

Powers, J., M. D. Bergren, and L. Finnegan. 2007. Comparison of school food allergy emergency plans to the Food Allergy and Anaphylaxis Network's standard plan. *J Sch Nurs* 23(5):252-258.

Pumphrey, R. S. 2000. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 30(8):1144-1150.

Pumphrey, R. S. 2003. Fatal posture in anaphylactic shock. *J Allergy Clin Immunol* 112(2):451-452.

Pumphrey, R. S., and M. H. Gowland. 2007. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol* 119(4):1018-1019.

Quercia, O., G. Zoccatelli, G. F. Stefanini, G. Mistrello, S. Amato, M. Bolla, F. Emiliani, and R. Asero. 2012. Allergy to beer in LTP-sensitized patients: Beers are not all the same. *Allergy* 67(9):1186-1189.

Reeves, L., R. Meyer, J. Holloway, and C. Venter. 2015. The development and implementation of a training package for dietitians on cow's milk protein allergy in infants and children based on UK RCPCH competencies for food allergies—A pilot study. *Clin Transl Allergy* 5(1):4.

Resnick, E. S., M. M. Pieretti, J. Maloney, S. Noone, A. Munoz-Furlong, and S. H. Sicherer. 2010. Development of a questionnaire to measure quality of life in adolescents with food allergy: The FAQL-teen. *Ann Allergy Asthma Immunol* 105(5):364-368.

Roberts, G., N. Golder, and G. Lack. 2002. Bronchial challenges with aerosolized food in asthmatic, food-allergic children. *Allergy* 57(8):713-717.

Robertson, O. N., J. O. Hourihane, B. C. Remington, J. L. Baumert, and S. L. Taylor. 2013. Survey of peanut levels in selected Irish food products bearing peanut allergen advisory labels. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 30(9):1467-1472.

Robinson, J. M., and M. Ficca. 2012. Managing the student with severe food allergies. *J Sch Nurs* 28(3):187-194.

Rolland, J. M., E. Apostolou, M. P. de Leon, C. S. Stockley, and R. E. O'Hehir. 2008. Specific and sensitive enzyme-linked immunosorbent assays for analysis of residual allergenic food proteins in commercial bottled wine fined with egg white, milk, and nongrape-derived tannins. *J Agric Food Chem* 56(2):349-354.

Rosen, J., S. Albin, and S. H. Sicherer. 2014. Creation and validation of web-based food allergy audiovisual educational materials for caregivers. *Allergy Asthma Proc* 35(2):178-184.

Roy, K. M., and M. C. Roberts. 2011. Peanut allergy in children: Relationships to health-related quality of life, anxiety, and parental stress. *Clin Pediatr (Phila)* 50(11):1045-1051.

Runge, J. W., J. C. Martinez, E. M. Caravati, S. G. Williamson, and S. C. Hartsell. 1992. Histamine antagonists in the treatment of acute allergic reactions. *Ann Emerg Med* 21(3):237-242.

Sahiner, U. M., S. T. Yavuz, B. Buyuktiryaki, O. Cavkaytar, E. A. Yilmaz, A. Tuncer, and C. Sackesen. 2014. Serum basal tryptase may be a good marker for predicting the risk of anaphylaxis in children with food allergy. *Allergy* 69(2):265-268.

Sala-Cunill, A., V. Cardona, M. Labrador-Horrillo, O. Luengo, O. Esteso, T. Garriga, M. Vicario, and M. Guilarte. 2013. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. *Int Arch Allergy Immunol* 160(2):192-199.

Salvilla, S. A., A. E. Dubois, B. M. Flokstra-de Blok, S. S. Panesar, A. Worth, S. Patel, A. Muraro, S. Halken, K. Hoffmann-Sommergruber, A. DunnGalvin, J. O. Hourihane, L. Regent, N. W. de Jong, G. Roberts, and A. Sheikh. 2014. Disease-specific health-related quality of life instruments for IgE-mediated food allergy. *Allergy* 69(7):834-844.

Sampson, H. A., L. Mendelson, and J. P. Rosen. 1992. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 327(6):380-384.

Sampson, M. A., A. Munoz-Furlong, and S. H. Sicherer. 2006a. Risk-taking and coping strategies of adolescents and young adults with food allergy. *J Allergy Clin Immunol* 117(6):1440-1445.

Sampson, H. A., A. Munoz-Furlong, R. L. Campbell, N. F. Adkinson, Jr., S. A. Bock, A. Branum, S. G. Brown, C. A. Camargo, Jr., R. Cydulka, S. J. Galli, J. Gidudu, R. S. Gruchalla, A. D. Harlor, Jr., D. L. Hepner, L. M. Lewis, P. L. Lieberman, D. D. Metcalfe, R. O'Connor, A. Muraro, A. Rudman, C. Schmitt, D. Scherrer, F. E. Simons, S. Thomas, J. P. Wood, and W. W. Decker. 2006b. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 117(2):391-397.

Sampson, H. A., S. Aceves, S. A. Bock, J. James, S. Jones, D. Lang, K. Nadeau, A. Nowak-Wegrzyn, J. Oppenheimer, T. T. Perry, C. Randolph, S. H. Sicherer, R. A. Simon, B. P. Vickery, and R. Wood. 2014. Food allergy: A practice parameter update—2014. *J Allergy Clin Immunol* 134(5):1016-1025.

Sasaki, K., S. Sugiura, T. Matsui, T. Nakagawa, J. Nakata, N. Kando, and K. Ito. 2015. A workshop with practical training for anaphylaxis management improves the self-efficacy of school personnel. *Allergol Int* 64(2):156-160.

Sato, S., N. Yanagida, K. Ogura, T. Asaumi, Y. Okada, Y. Koike, K. Iikura, A. Syukuya, and M. Ebisawa. 2014. Immunotherapy in food allergy: Towards new strategies. *Asian Pac J Allergy Immunol* 32(3):195-202.

Schneider, L. C., R. Rachid, J. LeBovidge, E. Blood, M. Mittal, and D. T. Umetsu. 2013. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol* 132(6):1368-1374.

Senti, G., and T. M. Kundig. 2016. Novel delivery routes for allergy immunotherapy: Intralymphatic, epicutaneous, and intradermal. *Immunol Allergy Clin North Am* 36(1):25-37.

Shah, S. S., C. L. Parker, and C. M. Davis. 2013. Improvement of teacher food allergy knowledge in socioeconomically diverse schools after educational intervention. *Clin Pediatr (Phila)* 52(9):812-820.

Shanahan, L., N. Zucker, W. E. Copeland, E. J. Costello, and A. Angold. 2014. Are children and adolescents with food allergies at increased risk for psychopathology? *J Psychosom Res* 77(6):468-473.

Sharma, A., T. Prematta, and T. Fausnight. 2012. A pediatric food allergy support group can improve parent and physician communication: Results of a parent survey. *J Allergy (Cairo)* 2012:168053.

Sheetz, A. H., P. G. Goldman, K. Millett, J. C. Franks, C. L. McIntyre, C. R. Carroll, D. Gorak, C. S. Harrison, and M. A. Carrick. 2004. Guidelines for managing life-threatening food allergies in Massachusetts schools. *J Sch Health* 74(5):155-160.

Sheikh, A., V. ten Broek, S. G. Brown, and F. E. Simons. 2007. H1-antihistamines for the treatment of anaphylaxis with and without shock. *Cochrane Database Syst Rev*(1):CD006160.

Sheikh, A., F. E. Simons, V. Barbour, and A. Worth. 2012a. Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community. *Cochrane Database Syst Rev* 8:CD008935.

Sheikh, A., U. Nurmatov, I. Venderbosch, and E. Bischoff. 2012b. Oral immunotherapy for the treatment of peanut allergy: Systematic review of six case series studies. *Prim Care Respir J* 21(1):41-49.

Shemesh, E., R. A. Annunziato, M. A. Ambrose, N. L. Ravid, C. Mullarkey, M. Rubes, K. Chuang, M. Sicherer, and S. H. Sicherer. 2013. Child and parental reports of bullying in a consecutive sample of children with food allergy. *Pediatrics* 131(1):e10-e17.

Shemesh, E., B. J. Lewis, M. Rubes, M. A. Ambrose, M. K. Cahill, C. Knight, S. H. Sicherer, and R. A. Annunziato. 2015. Mental health screening outcomes in a pediatric specialty care setting. *J Pediatr* 168:193.

Sicherer, S. H. 2001. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 108(6):881-890.

Sicherer, S. H., T. J. Furlong, J. DeSimone, and H. A. Sampson. 1999. Self-reported allergic reactions to peanut on commercial airliners. *J Allergy Clin Immunol* 104(1):186-189.

Sicherer, S. H., J. A. Forman, and S. A. Noone. 2000. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. *Pediatrics* 105(2):359-362.

Sicherer, S. H., F. E. Simons, and the Section on Allergy and Immunology. 2007. Self-injectable epinephrine for first-aid management of anaphylaxis. *Pediatrics* 119(3):638-646.

Sicherer, S. H., T. Mahr, and the Section on Allergy and Immunology. 2010. Management of food allergy in the school setting. *Pediatrics* 126(6):1232-1239.

Sicherer, S. H., P. A. Vargas, M. E. Groetch, L. Christie, S. K. Carlisle, S. Noone, and S. M. Jones. 2012. Development and validation of educational materials for food allergy. *J Pediatr* 160(4):651-656.

Sicherer, S. H., R. A. Wood, B. P. Vickery, T. T. Perry, S. M. Jones, D. Y. Leung, B. Blackwell, P. Dawson, A. W. Burks, R. Lindblad, and H. A. Sampson. 2016. Impact of allergic reactions on food-specific IgE concentrations and skin test results. *J Allergy Clin Immunol Pract* 4(2):239-245.

Simons, F. E., L. R. Ardusso, M. B. Bilo, V. Cardona, M. Ebisawa, Y. M. El-Gamal, P. Lieberman, R. F. Lockey, A. Muraro, G. Roberts, M. Sanchez-Borges, A. Sheikh, L. P. Shek, D. V. Wallace, and M. Worm. 2014. International consensus on (ICON) anaphylaxis. *World Allergy Organ J* 7(1):9.

Simons, F. E., M. Ebisawa, M. Sanchez-Borges, B. Y. Thong, M. Worm, L. K. Tanno, R. F. Lockey, Y. M. El-Gamal, S. G. Brown, H. S. Park, and A. Sheikh. 2015. 2015 Update of the evidence base: World Allergy Organization anaphylaxis guidelines. *World Allergy Organ J* 8(1):32.

Simonte, S. J., S. Ma, S. Mofidi, and S. H. Sicherer. 2003. Relevance of casual contact with peanut butter in children with peanut allergy. *J Allergy Clin Immunol* 112(1):180-182.

Soller, L., J. Hourihane, and A. DunnGalvin. 2014. The impact of oral food challenge tests on food allergy health-related quality of life. *Allergy* 69(9):1255-1257.

Sova, C., M. B. Feuling, M. Baumler, L. Gleason, J. S. Tam, H. Zafra, and P. S. Goday. 2013. Systematic review of nutrient intake and growth in children with multiple IgE-mediated food allergies. *Nutr Clin Pract* 28(6):669-675.

Springston, E. E., B. Smith, J. Shulruff, J. Pongracic, J. Holl, and R. S. Gupta. 2010. Variations in quality of life among caregivers of food allergic children. *Ann Allergy Asthma Immunol* 105(4):287-294.

Sun, J., X. Hui, W. Ying, D. Liu, and X. Wang. 2014. Efficacy of allergen-specific immunotherapy for peanut allergy: A meta-analysis of randomized controlled trials. *Allergy Asthma Proc* 35(2):171-177.

Tey, D., S. C. Dharmage, M. N. Robinson, K. J. Allen, L. C. Gurrin, and M. L. Tang. 2012. Frequent baked egg ingestion was not associated with change in rate of decline in egg skin prick test in children with challenge confirmed egg allergy. *Clin Exp Allergy* 42(12):1782-1790.

Tiainen, J. M., O. M. Nuutinen, and M. P. Kalavainen. 1995. Diet and nutritional status in children with cow's milk allergy. *Eur J Clin Nutr* 49(8):605-612.

Tripathi, A., S. P. Commins, P. W. Heymann, and T. A. Platts-Mills. 2015. Diagnostic and experimental food challenges in patients with nonimmediate reactions to food. *J Allergy Clin Immunol* 135(4):985-987.

Turner, P. J., J. Southern, N. J. Andrews, E. Miller, and M. Erlewyn-Lajeunesse. 2015. Safety of live attenuated influenza vaccine in atopic children with egg allergy. *J Allergy Clin Immunol* 136(2):376-381.

Vale, S., J. Smith, M. Said, R. J. Mullins, and R. Loh. 2015. ASCIA guidelines for prevention of anaphylaxis in schools, pre-schools and childcare: 2015 update. *J Paediatr Child Health* 51(10):949-954.

van der Velde, J. L., B. M. Flokstra-de Blok, H. de Groot, J. N. Oude-Elberink, M. Kerkhof, E. J. Duiverman, and A. E. Dubois. 2012. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. *J Allergy Clin Immunol* 130(5):1136-1143.

van Os-Medendorp, H., I. van Leent-de Wit, M. de Bruin-Weller, and A. Knulst. 2015. Usage and users of online self-management programs for adult patients with atopic dermatitis and food allergy: An explorative study. *JMIR Res Protoc* 4(2):e57.

Versluis, A., A. C. Knulst, A. G. Kruizinga, A. Michelsen, G. F. Houben, J. L. Baumert, and H. van Os-Medendorp. 2015. Frequency, severity and causes of unexpected allergic reactions to food: A systematic literature review. *Clin Exp Allergy* 45(2):347-367.

Vieira, M. C., M. B. Morais, J. V. Spolidoro, M. S. Toporovski, A. L. Cardoso, G. T. Araujo, V. Nudelman, and M. C. Fonseca. 2010. A survey on clinical presentation and nutritional status of infants with suspected cow' milk allergy. *BMC Pediatr* 10:25.

Wahl, A., H. Stephens, M. Ruffo, and A. L. Jones. 2015. The evaluation of a food allergy and epinephrine autoinjector training program for personnel who care for children in schools and community settings. *J Sch Nurs* 31(2):91-98.

Wainstein, B. K., S. Kashef, M. Ziegler, D. Jelley, and J. B. Ziegler. 2007. Frequency and significance of immediate contact reactions to peanut in peanut-sensitive children. *Clin Exp Allergy* 37(6):839-845.

Wang, J., M. C. Young, and A. Nowak-Wegrzyn. 2014. International survey of knowledge of food-induced anaphylaxis. *Pediatr Allergy Immunol* 25(7):644-650.

Ward, C. E., and M. J. Greenhawt. 2015. Treatment of allergic reactions and quality of life among caregivers of food-allergic children. *Ann Allergy Asthma Immunol* 114(4):312-318.

Warren, C. M., R. S. Gupta, M. W. Sohn, E. H. Oh, N. Lal, C. F. Garfield, D. Caruso, X. Wang, and J. A. Pongracic. 2015. Differences in empowerment and quality of life among parents of children with food allergy. *Ann Allergy Asthma Immunol* 114(2):117-125.

Wassenberg, J., M. M. Cochard, A. Dunngalvin, P. Ballabeni, B. M. Flokstra-de Blok, C. J. Newman, M. Hofer, and P. A. Eigenmann. 2012. Parent perceived quality of life is age-dependent in children with food allergy. *Pediatr Allergy Immunol* 23(5):412-419.

Weiss, C., A. Munoz-Furlong, T. J. Furlong, and J. Arbit. 2004. Impact of food allergies on school nursing practice. *J Sch Nurs* 20(5):268-278.

White, L., J. Aubin, C. Bradford, C. Alix, L. Hughes, and W. Phipatanakul. 2015. Effectiveness of a computer module to augment the training of school staff in the management of students with food allergies. *Ann Allergy Asthma Immunol* 114(3):254-255.

Wongkaewpothong, P., P. Pacharn, C. Sripramong, S. Boonchoo, S. Piboonpocanun, N. Visitsunthorn, P. Vichyanond, and O. Jirapongsananuruk. 2014. The utility of serum tryptase in the diagnosis of food-induced anaphylaxis. *Allergy Asthma Immunol Res* 6(4):304-309.

Wood, R. A., J. S. Kim, R. Lindblad, K. Nadeau, A. K. Henning, P. Dawson, M. Plaut, and H. A. Sampson. 2015. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. *J Allergy Clin Immunol* 137(4):1103-1110.

Worth, A., U. Nurmatov, and A. Sheikh. 2010. Key components of anaphylaxis management plans: Consensus findings from a national electronic Delphi study. *JRSM Short Rep* 1(5):42.

Yeung, J. P., L. A. Kloda, J. McDevitt, M. Ben-Shoshan, and R. Alizadehfar. 2012. Oral immunotherapy for milk allergy. *Cochrane Database Syst Rev* 11:CD009542.

Young, M. C., A. Munoz-Furlong, and S. H. Sicherer. 2009. Management of food allergies in schools: A perspective for allergists. *J Allergy Clin Immunol* 124(2):175-182; quiz 183-184.

Yu, J. E., A. Kumar, C. Bruhn, S. S. Teuber, and S. H. Sicherer. 2008. Development of a food allergy education resource for primary care physicians. *BMC Med Educ* 8:45.

Zijlstra, W. T., A. E. Flinterman, L. Soeters, A. C. Knulst, G. Sinnema, M. P. L'Hoir, and S. G. Pasmans. 2010. Parental anxiety before and after food challenges in children with suspected peanut and hazelnut allergy. *Pediatr Allergy Immunol* 21(2 Pt 2):e439-e445.

Zurzolo, G., J. Koplin, M. Mathai, S. Taylor, D. Tey, and K. Allen. 2013. Foods with precautionary allergen labeling in Australia rarely contain detectable allergen. *J Allergy Clin Immunol Pract* 1(4):401-403.

7

Management of Packaged Foods

Consumers with a food allergy, like the general population, rely on packaged foods as a key component of their diet. Therefore, the packaged foods industry is an essential stakeholder if consumers with food allergies are to succeed in their prevention approaches and be safe. For this reason, the labeling of allergenic foods is an important public health intervention that assists consumers in avoiding potentially allergenic foods.

The food supply chain from production to consumption is complex (see Figure 7-1). Packaged foods are made and assembled primarily in commercial food processing facilities but also in restaurants, retail grocery stores, and other retail outlets. Commercial food processing facilities range from very large companies that may make dozens of different products within a single facility to very small companies that tend to make a narrower range of products but also often use shared facilities. In addition, food processing equipment is frequently shared to make different products. Furthermore, a packaged food may contain several dozen ingredients that may be obtained from a range of suppliers who likewise may have upstream suppliers. Finally, the farms and other suppliers that are sources of these ingredients (e.g., oceans, mines) are also often diversified and often share harvesting equipment, transportation vehicles, and storage facilities.

Allergens, then, can enter foods from many sources along the food chain, intentionally or unintentionally, through cross-contact[1] in farms,

[1] Cross-contact is the inadvertent introduction of allergenic food residues into a product. It is generally the result of environmental exposure during processing or handling, which may occur when multiple foods are produced in the same facility, when the same processing line

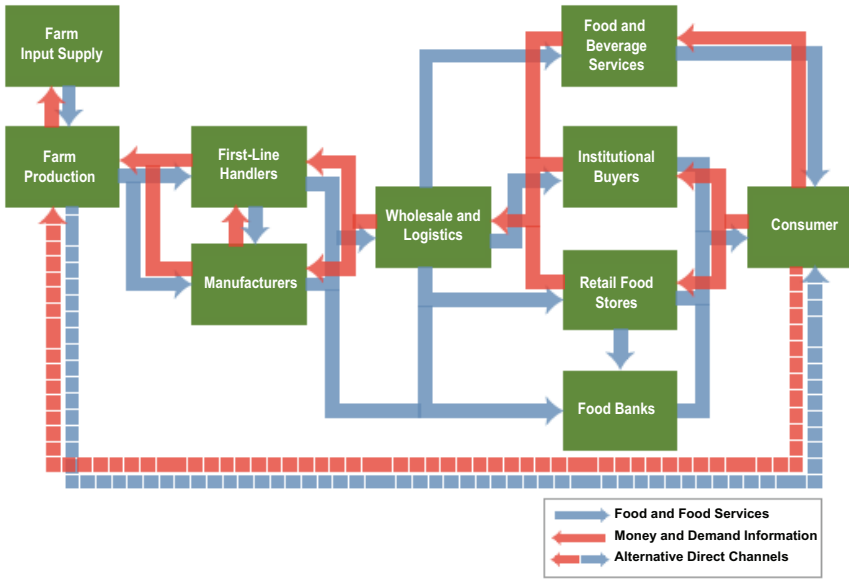

FIGURE 7-1 Conceptual model of a food supply chain. Elements or actors in this supply chain in one area (e.g., region or country) also have interactions (e.g., international trade) with actors in other areas.
SOURCE: IOM and NRC, 2015.

storage, distribution and manufacturing facilities, food service establishments, or the home. The food industry, of course, wishes to prevent the possibility that a consumer with a food allergy will experience an adverse reaction after consuming a packaged food product. In reality, achieving this goal at all times is challenging. From the food industry perspective, three general approaches can be used to minimize the risk of a reaction from an allergenic food: (1) eliminate potential allergens or specific allergens from products; (2) list the allergen on the product label as an ingredient, when it is intentionally added as such; and (3) implement strict allergen control plans (ACPs) to minimize allergen contamination and use advisory labels (precautionary allergen labeling, or PAL) to inform the consumer about the risk when necessary. The Food and Drug Administration (FDA) Food Safety

is used to produce allergenic and nonallergenic food as the result of ineffective cleaning, the generation of dust or aerosols containing an allergen, or other causes (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/ucm106890.htm#q19 [accessed January 5, 2017]).

Modernization Act[2] (FSMA) identifies allergens as a hazard that is reasonably likely to occur in food manufacturing operations and requires that food manufacturing develop ACPs, In so doing, the FSMA acknowledges the importance of food allergy as a public health priority for the packaged food industry. This chapter includes a brief description of ACPs in Box 7-1 but does not attempt to review them in depth even though the development of effective ACPs has an impact on both labeling and PAL.

Likewise, although the committee recognizes that processing can affect the allergenicity of foods either by reducing the amount of the allergenic protein or by altering the protein in some manner, the chapter does not examine the effects of processing in depth. The main focus of this chapter is on labeling and PAL because of the obvious importance of these approaches to the consumer.

Although this chapter focuses on the food manufacturing industry, it is important to note that in addition to packaged foods, foods are consumed in many other forms and venues (e.g., homes, restaurants, other retail food establishments, places of worship, camps, recreational facilities). A few of these situations are addressed in Chapter 8. Following a review of the current labeling practices in packaged foods, the chapter describes a labeling approach based on risk and makes recommendations to that effect. Research needs are also included. The Annex to this chapter delves into data inputs needed for a risk-based approach and their limitations.

ELIMINATING ALLERGENS FROM PACKAGED FOODS

As noted above, one approach to managing food allergen hazards within food manufacturing operations is to eliminate one or more allergens from the group of products being manufactured in shared facilities. Within the product development groups in some major food companies, a so-called allergen-gating process has been implemented as a best practice. This process is intended to question and, if desirable or possible, eliminate specific allergenic foods (or ingredients derived from those foods) from a new food product under development. Allergen-gating can take several forms. For example, a food company might question the development of a new product containing a peanut butter component because the manufacturing of that new product might introduce peanut into a manufacturing facility that presently does not include peanuts. In another example, a milk ingredient might be considered as a relatively minor part of a new product formulation. The decision to include the milk ingredient could be questioned and the product might be formulated without the milk ingredient if that change has no impact on product quality. Finally, in a third varia-

[2] Public Law 353, 111th Cong., 2d sess. (January 4, 2011).

BOX 7-1
Allergen Control Plans in the Packaged Foods Industry

To protect consumers with food allergy, food manufacturing companies need to implement comprehensive allergen control plans (ACPs). For products regulated by the U.S. Department of Agriculture (USDA), in addition to good manufacturing practices, food companies have been required since 2005 to have hazard analysis and critical control points (HACCP[a]) written plans. Presumably, companies have considered food allergens as a hazard in their HACCP plans or prerequisite programs.[b] In addition, over the past two decades and together with the increasing recognition of the public health importance of food allergy, many, but not all, companies that manufacture Food and Drug Administration (FDA)-regulated foods have developed and implemented comprehensive ACPs. ACPs began to be adopted from the mid-1990s (Deibel et al., 1997) and were rather widely adopted in the United States by the mid-2000s (Taylor et al., 2006). This industry-led initiative will become a requirement when the FDA Preventive Controls for Human Foods Rule, part of the 2010 Food Safety Modernization Act (FSMA), is implemented late in 2016. The Preventive Control for Human Foods Rule established food allergens as a hazard that is reasonably likely to occur within food processing facilities. Thus, as the rule becomes fully implemented by the FDA, food companies will be expected to hone their ACPs.

The following are the ideal steps in a comprehensive ACP. The development of an ACP starts with a facility hazard and risk assessment done by the food manufacturer. The first step is the identification of the hazard, which would be all sources of allergenic foods. This assessment starts with an assessment of all raw materials to identify those that are allergenic foods or ingredients derived from allergenic foods. Any allergenic raw materials must then be segregated in receiving, storage, and handling that occurs ahead of processing. Ingredient suppliers are expected to have adequate ACPs and are periodically audited for compliance. Segregation must then be maintained through processing, packaging, and labeling of the finished food product. During processing and packaging, segregation

tion of this approach, a food company might decide to harmonize certain ingredients across all products made on shared equipment. For example, if a food company made 30 different cake mixes on shared equipment and 27 of those cake mixes contained milk ingredients, they could decide to add milk to the other three formulations. Consumers have been known to protest harmonization efforts because this decision can eliminate popular food products from the diets of consumers with specific food allergies. Each of these "allergen-gating" decisions would be advantageous to the company because it would avoid additional costs and reduce the complexity of the company's ACP.

With the enhanced awareness of food allergies among consumers,

can be accomplished by separation in either space or time. With separation in space, allergen-containing formulations can be processed on separate lines or even in separate facilities from other formulations that do not contain the specific allergen. Dedicated facilities or dedicated equipment are used in feasible situations. With separation in time, the scheduling of different formulations with varying allergen content is managed. For example, a wheat-containing product might be run first, followed by wheat plus milk, and finished with wheat plus milk plus peanut. After the most complex formulation, the shared equipment is cleaned to remove allergen residues. The critical control points[c] within the manufacturing operation are identified and monitored to prevent unintentional cross-contact. The cleaning of shared equipment and facilities is a critical component of the ACP because allergen residues must be removed after the manufacturing of an allergenic food product. With the scale of food processing equipment, allergen cleaning can be daunting in some situations. Understandably, the control of allergens in processing facilities and along the food chain is extremely complex and beyond the scope of this document. However, the essence of ACPs can be reviewed in several documents including an on-line brochure (www.http://farrp.unl.edu/allergen-control-food-industry [accessed January 5, 2017]).

[a] Hazard analysis and critical control points (HACCP) is a systematic management approach to food safety from biological, chemical, and physical hazards in production processes. It includes tools to reduce these risks to a safe level and it focuses on prevention at all stages of the food chain and processes rather than on inspection of the finish product. The Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) require mandatory HACCP programs for juice, seafood, and meat as an effective approach to food safety and protecting public health.

[b] Prerequisite programs are practices and conditions needed before and during the implementation of HACCP, such as Good Manufacturing Practices or Pest Control Programs, and which are essential for food safety

[c] Critical control point (CCP) is a point in the food manufacturing operation where the failure of a standard operating procedure (SOP) could cause harm to consumers and to the business, or even loss of the business.

marketing interest has grown in the development of "free-from" foods. Dairy-free[3] and gluten-free products have been marketed for years, but their availability and popularity with consumers has increased greatly recently. Now, some foods are marketed as peanut-free, peanut- and tree nut–free (nut-free), and allergen-free, which typically means the absence of all of the eight most allergenic foods and food groups (milk, egg, peanut, tree nuts, wheat, soybean, fish, and crustacean shellfish).

Of course, producing allergen-free food precludes the need to develop and implement ACPs if done in a facility dedicated to allergen-free food

[3] It should be noted that dairy-free and nondairy foods may contain caseins, the major allergenic proteins in cow milk.

manufacturing. However, the chief reason for the expanding commercial interest in "free-from" foods is the opportunity to exploit a profitable niche market. In such cases, the involved food companies must exercise extreme vigilance to assure that their suppliers do not have the allergens of interest in any of the ingredients and perhaps even in their facilities. Although some companies do make "free-from" products in facilities where the allergens of interest are also present in other formulations, great care must be taken to assure that no cross-contact occurs under those circumstances.

LABELING OF FOOD ALLERGENS

As described above, the label on a food package is a tool that ideally should alert consumers of the presence of specific allergens so they can make informed decisions about the level of risk they are willing to take. Two types of labeling exist and they serve two distinct purposes: (1) mandatory labeling, used when the allergen is intentionally added as an ingredient; and (2) voluntary labeling, used when the allergen may inadvertently be in the food as a result of cross-contact. Even when ACPs (see Box 7-1) are strictly followed, errors occur that might result in the presence of low levels of the allergen in the formulated food (i.e., residue). This is shown in part by the number of food recalls that are due to undeclared allergens in food products (see Box 7-2). Such unintentional allergens, when the possible cross-contact is predictable, can be identified on the labels of packaged foods using PAL statements, such as "May Contain X." Although PAL statements on packaged food are voluntary, the FDA has indicated that they should be truthful and not misleading.

The food industry, however, lacks the ability to conduct allergen risk assessments to determine threshold doses and safe levels. As a result of the uncertainties regarding limits necessary to avoid cross-contact as well as unacceptable risks that could result in litigation, PAL statements have proliferated. They are now applied to a wide range of products, including products that likely pose little risk to consumers with a food allergy. Another result of this uncertainty is that the majority of food recalls in the United States are now due to undeclared food allergens (see Box 7-2). Recalls, however, can happen for numerous reasons and are not limited to cross-contact. Important lessons can be learned from product recalls if information is shared about root causes, preventive and corrective actions that are implemented to prevent recurrences, and consumer complaints.

The mandatory ingredient labeling of packaged foods is a government regulatory issue. Despite the fact that PAL is voluntary, its widespread use invites regulatory limitations. If government chooses to move forward, it would have to answer several questions, such as: What allergens should be labeled? What criteria to identify allergens should appear on a label?

BOX 7-2
Packaged Food Recalls

Beginning in the early 1990s, the Food and Drug Administration (FDA) began to recognize that food allergies were a public health priority for the United States. The FDA recognized that the ingredient label on packaged food products provided essential information to consumers following avoidance diets. Food industry awareness of the importance of accuracy in the labeling of food allergens in food ingredient labeling emerged simultaneously. As a result, recalls of packaged food products with undeclared allergens began to occur at an increasing rate. By 1999, 36 percent of all FDA recalls in the United States were associated with undeclared allergens (Vierk et al., 2002). More recently, undeclared allergens became the leading cause for Reportable Food Registry (RFR) reports to the FDA (Gendel, 2014). Many of these RFR reports led to product recalls. Undeclared allergens also have become one of the leading causes of meat and poultry product recalls occurring under the auspices of the USDA's Food Safety and Inspection Service (FSIS). Undeclared allergens also have become a leading cause of food product recalls in Canada (Zarkadas et al., 1999).

These recalls reveal that, despite the allergen control efforts of the food industry, errors do continue to occur that potentially can affect the health of consumers with a food allergy. Several root causes are involved in these product recalls, including placement of a product in the wrong package, inappropriate labeling terminology (e.g., casein not identified as from milk), failure to carry forward information from an ingredient to the final product, cross-contact occurring within the manufacturing facility, and mislabeling of an ingredient by a supplier (Gendel, 2014). In some cases, food manufacturers recognize their error and initiate recalls before consumer complaints have been received; in some of these situations, the level of undeclared allergen in the product may be insufficient to pose a hazard. In other cases, regulatory inspections can reveal labeling issues that result in recalls, especially in the case of FSIS, where continuous federal inspection occurs. The percentage of product recalls that are initiated as a result of consumer complaints of allergic reactions is unclear. Product recalls clearly indicate that there is room for improvement in allergen control within the food processing industry.

Although the discussion below is centered on the United States, policies in other countries are also described to illustrate the global diversity in the criteria used and lists of major allergens. For the packaged food industry, labeling is a matter of compliance with regulatory requirements, including the variable requirements of different countries. As more allergens are added to the priority lists, the complexity of ACPs increases for the food industry.

Which Allergens Need to Be Labeled?

A Historical Perspective

Many countries have implemented laws, regulations, or standards specifically governing food allergen labeling for a list of priority allergenic foods. The foods on such lists vary around the world due to several factors, including differing eating habits and differing criteria to select the priority allergenic foods (see Table 7-1). Likewise, the regulatory framework for the labeling of allergenic foods differs from country to country (Gendel, 2012), which can affect individuals as they travel between countries.

Increased attention to the labeling of allergenic foods emerged within the Codex Alimentarius Commission (CAC)[4] in 1993, when a working paper on food allergens was developed by the Nordic countries. This working paper led to the creation of a Food and Agricultural Organization of the United Nations (FAO) Technical Consultation in 1995 that was charged with developing a list of priority foods that cause food allergies and sensitivities. Ultimately, the priority foods list promulgated by the FAO Technical Consultation was adopted by CAC in 1999 and continues to serve as guidance to all countries (individual countries have the option to adopt this list or to modify the list as they might choose).

Part of the background discussion that occurred within the 1995 FAO Technical Consultation has been reported by Taylor and Baumert (2015). They reported that, in 1995, the amount of published information available to the FAO Technical Consultation concerning the comparative prevalence of allergies to specific foods was limited largely to pediatric populations, with virtually no information on the prevalence of food allergy among adults. Comparative prevalence was the main criterion of the FAO Technical Consultation, although the differential severity of certain allergenic foods also was recognized as a criterion. In 1999, a revised CAC priority was released. As a consequence of data gaps, expert judgment was used, in part, to develop this list. The 1999 CAC priority list included milk, egg, fish, crustacean shellfish, peanut, soybean, tree nuts, cereal grain sources of gluten, and sulfites. Several of these items were added because the FAO Technical Consultation also considered celiac disease, intolerances, and sensitivity reactions in addition to immunoglobulin E (IgE)-mediated food allergies in its deliberations. For example, gluten was included because of its association with celiac disease. Sulfites were added because of the documented severity of sulfite-induced asthma.

Following this, a Task Force of the International Life Sciences Institute-

[4] Codex Alimentarius Commission is an organization formed jointly by the Food and Agricultural Organization (FAO) and the World Health Organization (WHO) to develop food standards and guidelines that would be recognized worldwide.

TABLE 7-1 Priority Allergenic Food Lists

Food	Codex Alimentarius Commission	USA	European Union	Australia/ New Zealand	Canada	Japan
Milk	X	X	X	X	X	X
Egg	X	X	X	X	X	X
Fish	X	X	X	X	X	
Crustacea	X	X	X	X	X	X[a]
Tree nuts[b]	X	X	X	X	X	
Peanut	X	X	X	X	X	X
Wheat	X	X	X	X	X	X[a]
Soybean	X	X	X	X	X	
Gluten	X		X	X	X	
Sesame seed			X	X	X	
Molluscs			X		X	
Mustard			X		X	
Celery			X			
Lupine			X			
Buckwheat						X
Other						X[a]

[a] Japan: Shrimp and crab are the only crustacea on the list. Grains include wheat and buckwheat but not other cereal sources of gluten. Other includes foods that are not required, but are on a recommended labeling list include salmon, salmon roe, mackerel, abalone, squid, beef, pork, chicken, soybean, walnut, orange, kiwi, banana, peach, apple, yam, matsutake mushroom, and gelatin.

[b] See Box 7-3.

SOURCE: Taylor and Baumert, 2015.

Europe (ILSI-EU) conducted a more thorough assessment of foods that warranted placement on a list of priority allergenic foods (Bousquet et al., 1998). The criteria used by the ILSI-EU group included published evidence of severe or fatal anaphylactic reactions. The ILSI-EU Task Force recommended a priority food allergens list that included milk, egg, fish, crustacean shellfish, peanut, soy, tree nuts, wheat, and sesame seed. Other groups within ILSI-EU have continued to develop criteria for the selection of allergenic foods of public health importance and have recently recommended that the criteria should encompass consideration of prevalence, severity and potency[5] (Bjorksten et al., 2008; Houben et al., 2016; van Bilsen et al., 2011).

In the United States, the priority list of allergenic foods was established by the Congress with the passage of the Food Allergen Labeling and Consumer Protection Act[6,7] (FALCPA) of 2004. The FALCPA list mirrored the 1999 CAC list except that the FALCPA list did not address celiac disease and therefore did not recognize cereal sources of gluten as major allergenic foods.

In the European Union (EU), the first priority list of allergenic foods was established by EC Directive 2003/89[8] as a result of deliberations within the EU Parliament. The initial EU list included the eight foods or food groups from the CAC list, but also included sesame seed, mustard, and celery.[9] In addition to allergenic foods, the EU list also includes cereal sources of gluten and sulfites. Subsequently, the EU priority list of allergenic foods was updated by EC Directive 2007/68[10] and included the addition of molluscan shellfish and lupine to the EU list based on the opinion of the European Food Safety Authority (EFSA) Panel Scientific Panel on Dietetic Products, Nutrition, and Allergies (EFSA, 2005, 2006). The decision to include lupine appeared to be based on the recognition that some peanut-allergic individuals will experience allergic reactions on ingestion of lupine due to the presence of cross-reacting allergens in these two legumes.

---

[5] Prevalence is defined as the percentage of the general population who have a clinically confirmed allergic reaction to a specific food. Severity is defined as the frequency of occurrence of fatal or life-threatening allergic reactions to a specific food. Potency is defined as the minimal eliciting dose or threshold dose needed to provoke objective symptoms among individuals allergic to a specific food.

[6] For an analysis on Food Allergen Labeling and Consumer Protection Act see Derr, 2006.

[7] Public Law 282, 108th Cong., 2d sess. (August 2, 2004).

[8] See http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32003L0089 (accessed July 3, 2016).

[9] "Celery" in the EU priority list of food allergens refers to "celery root." Celery root and celery stalk are marketed as foods derived from different varieties of *Apium graveolens*. Allergy to celery root is frequent in some European countries but not in the United States.

[10] See http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1467581123948&uri=CELEX:32007L0068 (accessed July 3, 2016).