

Milk and Soy Allergy

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- Cow's milk • Soy • Allergy • Cross-reactivity • Diagnosis
- Management • Natural history

EPIDEMIOLOGY

General population birth cohorts report a prevalence of cow's milk allergy (CMA) of 2.2% to 2.8% at 1 year of age,^{1,2} similar to the rate found in another large cohort followed for 18 to 34 months.³ Of those with CMA, about 60% have IgE-mediated CMA.⁴ A recent study from Israel by Katz and colleagues⁵ reported a much lower rate of CMA in infants (0.5%) than in 3-year-old children (0.6%).⁶ The investigators also reported a rate of 0.5% for non-IgE-mediated CMA in infants, equivalent to the rate of IgE-mediated CMA in infants.⁵ Childhood CMA is more prevalent in boys than girls.⁷ Regarding severe allergic reactions, cow's milk (CM) comprises 10% to 19% of food-induced anaphylaxis cases seen both in the field and in emergency departments in pediatric and mixed-age populations. CM is the third most common food product to cause anaphylaxis, following peanut and tree nuts.⁸⁻¹¹

In general, soy allergy is not as common as CMA, even in atopic children. Bruno and colleagues¹² found a prevalence of 1.2% in a cohort of 505 children suffering from allergic diseases and 0.4% in 243 children who had been fed soy protein formula in the first 6 months of life for supposed prevention of allergic diseases. In population-based studies, 2 European cohorts pointed to rates varying from 0.0%¹³ to 0.7%¹⁴ for children in double-blind placebo-controlled food challenge. Also, up to 10% to 14% of patients with CMA also present with soy protein allergy.¹⁵⁻¹⁷ In a study by Klemola and colleagues,¹⁶ adverse reactions to soy were seen more often in milk-allergic individuals younger than 6 months. In this study, at 2-year follow-up, sensitization to soy proteins was not higher in infants fed soy formula than in those fed extensively hydrolyzed formulas ($P = .082$; $n = 70$).¹⁸ One recent study reported

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that of 66 infants with IgE-mediated CMA, none had a proven allergy to soy, with 64 of 66 tolerating soy in their diets.⁵

Dietary exposure to milk, soy, and products containing either or both vary in different parts of the world. Traditional Asian cuisine includes less milk sources than the Western cuisine but includes several natural soy sources. Meanwhile, the consumption of soy-containing food additives (soy isolate, soy concentrate, and soy flour) is increasing in Western diets. This interesting geographic divergence may lead to a difference in the prevalence of soy and milk allergy between different populations, but this has not been confirmed.

CLINICAL MANIFESTATIONS

Patients with CMA and soy allergy present with a wide range of IgE-mediated and non-IgE-mediated clinical syndromes (**Table 1**).^{19–23} IgE-mediated reactions occur immediately or within 1 to 2 hours of ingestion, whereas non-IgE-mediated reactions generally have a delayed onset beyond 2 hours of ingestion.²⁴ Both humoral and/or cell-mediated mechanisms play a role in mixed manifestations, which may present with acute or chronic symptoms, making the causal relationship to foods more difficult to detect. Clinical symptoms of CMA commonly appear during the first months of life, usually within days or weeks after feeding with CM-based formulas have been started or may sometimes be seen in exclusively breast-fed infants.^{25,26} With such an early age of onset, symptoms of an erythematous rash or hives shortly after intake of CM (or infrequently soy) formula are suggestive of food allergy. The role of food allergy in causing flares of atopic dermatitis is less clear, although up to one-third of moderate to severe atopic dermatitis may in fact be because of CMA.^{27,28}

Table 1	
Presentation of CMA and soy allergy	
IgE Mediated	
Cutaneous	Urticaria Angioedema
Gastrointestinal	Oral itching and abdominal pain Nausea and vomiting Diarrhea
Respiratory	Rhinoconjunctivitis Wheeze and asthma exacerbation Laryngeal edema
Systemic	Anaphylaxis
Mixed IgE mediated and non-IgE mediated	
Cutaneous	Atopic dermatitis
Gastrointestinal	Eosinophilic esophagitis and gastroenteritis
Non-IgE mediated	
Gastrointestinal	Dietary protein enterocolitis/proctitis/proctocolitis Protein-losing enteropathy GER ^a Colic ^a Constipation ^a
Respiratory	Pulmonary hemosiderosis (ie, Heiner syndrome; mostly caused by milk allergy)

^a Controversial.

Immediate IgE-Mediated Reactions

Immediate IgE-mediated skin reactions include hives and angioedema. Gastrointestinal manifestations include mouth and lip pruritus, abdominal pain, vomiting, and diarrhea. A variety of respiratory tract symptoms that generally involve IgE-mediated responses, including rhinorrhea and wheezing, may also be seen, although isolated asthma or rhinitis is unusual.²⁹ Occupational and household exposures involving inhalation of cooking or processing vapors containing milk droplets may cause respiratory symptoms, and casual contact by touching can cause localized urticaria.

Milk is also the third most common food responsible for fatal or near-fatal food-induced anaphylactic reactions (8%–15% cases).^{10,30–32} Although severe soy allergy reactions have been reported, they are far less common than CMA reactions. Moreover, the small number of fatal allergic reactions to soy included some patients with concomitant severe peanut allergy and/or asthma.^{33,34} Foucard and Malmheden Yman³⁵ described 4 deaths presumably caused by soy allergy in severely peanut-allergic asthmatic children with previous tolerance to soy. By contrast, Sicherer and colleagues³⁴ reported no severe allergic reactions to soy challenge in 13 years of experience with double-blind placebo-controlled food challenges. In a more recent study on allergic reactions during inpatient oral food challenges (OFCs), 7% of soy challenges were severe enough to require administration of epinephrine.³⁶ A report on patients with soy and birch pollen allergy describes 25% patients with more severe reactions, including throat or chest tightness during double-blind placebo-controlled food challenges with soy.³⁷

Mixed Reactions

Atopic dermatitis

CMA and soy allergy play a pathogenic role in a subset of patients, primarily infants and children, with atopic dermatitis. It is recommended that patients with atopic dermatitis be treated with topical medications before considering a food allergy because most cases do not seem to be caused by food allergy. However, approximately 40% of infants and young children with moderate to severe atopic dermatitis have a food allergy, with hen's eggs, CM, soy, and wheat accounting for about 90% of allergenic foods.^{6,38,39} CMA was found in 17% of children with atopic dermatitis and clinically significant IgE-mediated food hypersensitivity referred to a university-based dermatology clinic.²⁷ In a multicenter study performed in Brazil, 12 of 13 children (median age 5.4 years) with atopic eczema and IgE-mediated soy allergy confirmed by open challenges also had high levels of specific IgE for other foods, including milk, egg, wheat, and peanuts, as well as pollens (Cocco RR et al, unpublished data, 2007).

Eosinophilic gastroenteropathies

Milk and soy are among the major allergens in allergic eosinophilic esophagitis (AEE), a disorder characterized by eosinophilic inflammation of the esophagus. Symptoms are suggestive of gastroesophageal reflux (GER) but do not respond to conventional reflux therapies.¹⁹ Feeding problems, vomiting, abdominal pain, dysphagia, and food impaction may also be seen. The role of food allergy in eosinophilic gastroenteritis, which is the eosinophilic gastroenteropathy of the stomach and intestines, is less clear than in eosinophilic esophagitis. Symptoms include abdominal pain, nausea, vomiting, diarrhea, and weight loss.⁴⁰

Delayed Non-IgE-Mediated Reactions

Food protein-induced enterocolitis

Dietary protein-induced syndromes of enteropathy and enterocolitis are not IgE mediated and typically present with profuse vomiting and diarrhea within 2 to 3 hours after

ingestion of the offending allergen, causing profound dehydration and lethargy.⁴⁰ Three quarters of infants with food protein-induced enterocolitis (FPIES) appear acutely ill, and about 15% have hypotension requiring hospitalization.⁴¹ Mehr and colleagues⁴² reported that a quarter of acute FPIES episodes in young infants manifested with hypothermia less than 36°C. Patients may present with diarrhea with occult blood loss, and fecal smears reveal leukocytes and eosinophils. Chronic exposure to the offending allergen results in a less acute clinical presentation of failure to thrive and hypoalbuminemia.^{40,43} Sicherer and colleagues⁴⁴ reported that FPIES was elicited most often by CM and soy protein, with 7 of 16 patients having sensitivity to both. Similarly, Burks and colleagues⁴⁵ reported that 6 of 10 patients with FPIES reacted to both milk and soy. Our preliminary data on 76 patients with FPIES showed that CM was the trigger in 58% and soy in 47% of patients.⁴⁶ Among children with milk FPIES, 45% had soy FPIES, and among children with soy FPIES, 56% had milk FPIES.

Protein-induced allergic enterocolitis/proctitis/proctocolitis

Protein-induced allergic enterocolitis/proctitis/proctocolitis usually presents by 6 months of life in an otherwise well-appearing breast-fed or formula-fed infant with blood-streaked, mucous, loose stools and occasionally diarrhea.⁴⁰ CM and soy are the major causative foods. Most breast-fed infants with allergic proctocolitis respond to maternal elimination of CM proteins, although some require the additional elimination of soy⁴⁷ or conversion to extensively hydrolyzed formula. Other causes, such as viruses, may have a similar presentation.⁴⁸

GER

Although debated, symptoms of GER may be associated with CMA. However, GER is not likely to be the sole presentation of CMA or soy allergy. Underlying causes of GER, such as eosinophilic esophagitis and dietary protein-induced gastroenteropathy, should be ruled out in patients with GER symptoms and suspected CMA.

Infantile colic

The role of milk protein in infantile colic and constipation in childhood remains controversial.^{7,49–54} Improvement in colic symptoms after CM elimination or change of formula, followed by worsening of symptoms with challenge in some infants has been demonstrated.^{7,50,51} Colic and fussiness are common in early infancy but are not likely to be isolated manifestations of CMA or soy allergy.

Constipation

Also a controversial topic, CM allergy/intolerance has been suggested as a cause of constipation in infants and children, especially in those with refractory chronic constipation. In up to half of the children with refractory chronic constipation, as demonstrated by one group, symptoms were shown to be related to CM in double-blind or open food challenges.^{54,55} Biopsy findings demonstrate proctitis with eosinophil infiltration of the rectal mucosa and a reduced thickness of the rectal mucous layer,⁵⁴ as well as lymphonodular hyperplasia in the terminal ileum and colon.⁵⁵ A case report describes difficulty of spontaneous defecation mimicking Hirschsprung disease.²⁹ Other rare gastrointestinal presentations described in neonates include bilious vomiting, massive bloody stools with peripheral eosinophilia, eosinophilic infiltration in the lamina propria, and CM-specific IgE in the serum supporting the diagnosis of CMA.^{56,57} However, in a recent study, no association was found between timing of introduction of CM or soy and onset of functional constipation, although history of CMA in the first year of life was significantly associated with functional constipation in childhood.⁵⁸

Heiner syndrome

Heiner syndrome is a rare food hypersensitivity pulmonary disease that primarily affects infants. This syndrome is mostly caused by CM. The symptoms include cough, wheezing, hemoptysis, nasal congestion, dyspnea, recurrent otitis media, recurrent fever, anorexia, vomiting, colic, diarrhea, hematochezia, and failure to thrive.⁵⁹ Radiological evidence of pulmonary infiltrates and high serum titers of precipitating antibodies (IgG) to CM proteins are seen. Milk-specific IgE may be detected, and there is pulmonary hemosiderosis in some cases. Improvement of both clinical and radiological findings occurs after strict milk avoidance.⁵⁹

PATHOGENESIS

Acute (IgE-mediated) reactions to milk are caused by various milk allergens. Caseins and whey proteins account for approximately 80% and 20% of total milk protein, respectively.⁶⁰ The caseins include α_{s1} -, α_{s2} -, β -, and κ -caseins (Bos d 8) and comprise 32%, 10%, 28%, and 10% of the total protein, respectively. The most important whey allergens are α -lactalbumin (Bos d 4) and β -lactoglobulin (BLG, Bos d 5), comprising 5% and 10% of total milk protein, respectively.^{60–62} Other minor milk allergens include bovine serum albumin (BSA, Bos d 6), lactoferrin, and immunoglobulins (Bos d 7).^{17,62} Sequential IgE-binding epitopes of the major milk allergens have been identified,^{63–67} and several have been investigated for mutational analysis.^{68–70} The pathogenesis and causative allergens in non-IgE-mediated CMA and milk allergy caused by mixed IgE-mediated and non-IgE-mediated processes are less well understood.

Cooking diminishes the allergenicity of whey proteins, particularly that of BLG, presumably by denaturation of heat-labile proteins, resulting in loss of conformational epitopes.^{71,72} This diminishing of allergenicity because of cooking may explain why many CM-allergic patients tolerate extensively heated milk.⁷³ Similarly, yogurt cultures, which ferment and acidify milk, contain less intact whey protein,⁷² and therefore, individuals with CMA exclusively sensitized to whey proteins may tolerate yogurt-based dairy products.

The specificity of soy allergens is variable and complex. As many as 28 different soy proteins were recognized as being able to bind IgE in soy-allergic patients.^{74,75} However, only a few of these proteins are considered major allergens, defined as those to which more than 50% of tested population reacted.⁷⁶ In this context, only the birch pollen-related allergens, Gly m 3 (a profilin) and Gly m 4 (a PR-10 protein), in addition to soybean hull proteins, Gly m 1 and Gly m 2 (see later), have been officially accepted as soybean allergens by the International Union of Immunological Societies Allergen Sub-Committee (<http://www.allergen.org?Allergen.aspx>). Several other soy proteins have been characterized, including storage proteins (β -conglycinin and glycinin, named Gly m 5 and Gly m 6, respectively),^{77–79} the thiol protease Gly m Bd 30 k (possibly a major soybean allergen),^{80–82} the soybean Kunitz trypsin inhibitor,^{83–85} and the 2S albumin soy protein.⁸⁵ The 2 soybean major storage proteins, β -conglycinin and glycinin, are 7S and 11S globulins and account for about 30% and 40% of the total seed proteins, respectively. Sensitization to both of these allergens has been shown to be a potential indicator for severe allergic reactions to soy.⁸⁶ Specific linear IgE-binding epitopes on some soy allergens have been identified,^{78,81} and mutational analysis is underway.⁸²

Soybeans are also aeroallergens, although the pathology and allergen reactivity profiles are different for ingestion versus inhalation, whereby soy hull antigens (Gly m 1 and Gly m 2), not present in soy protein isolates, seem to dominate.⁸⁷ The

hydrophobic soybean hull proteins Gly m 1 and Gly m 2 have been described to be relevant in respiratory soy allergy, which is acquired through inhalation of soy proteins.⁸⁸

Soy allergy may also develop secondary to initial sensitization to birch pollen and resulting cross-reactivity (see later). A retrospective analysis of specific IgE to foods and inhalants from 273 children by The German Multi-Centre Allergy Study revealed that IgE sensitization to soy in infancy is relatively uncommon and mostly primary (generated by food ingestion). On the other hand, IgE sensitization is more frequent at school age because of cross-reacting pollen antigens via inhalation.⁸⁹

CROSS-REACTIVITY

Mammals that are phylogenetically related have quite similar milk protein expression.⁹⁰ As an example, significant amino acid sequence homology and resulting high rate of clinical cross-reactivity render sheep or goat milk inappropriate feeding alternatives for most CM-allergic individuals.^{91,92} However, some patients with primary goat's or sheep's milk allergy may tolerate CM and vice versa.^{93,94} Some patients with CMA may tolerate milk from other mammals, such as camels, pigs, reindeer, horses, and donkeys.^{92,95–100} Clinical allergy to human milk has been shown in one case report, and sensitization to human milk with immediate-type skin reaction has been reported in another one, although confirmatory clinical data are missing and the clinical significance is largely unknown.^{101,102} The authors identified IgE-reactive human epitopes that were cross-reactive with bovine milk and human milk epitopes that were non-cross-reactive using peptides representing the known IgE-binding regions of bovine milk proteins and the corresponding highly similar peptides on human milk.¹⁰³ Cross-reactivity between different mammalian milks has been reviewed in detail elsewhere.¹⁰⁴

Serum albumin is thought to be involved in cosensitization to milk and beef, reported in 13% to 20% of children with CMA.¹⁰⁵ Clinical cross-reactivity may be more pronounced with less well-cooked meat. In another study, 7 of 8 patients with persistent CMA who were sensitized to CM, BSA, and animal dander recognized serum albumin in different raw, but not heated, meats (beef, lamb, deer, and pork) and epithelia (dog, cat, and cow).¹⁰⁶

Cosensitization to soy is common in patients with CMA, but clinical coallergy due to cross-sensitization based on cross-reactive proteins between milk and soy is not.⁶² In one study, cosensitization without clinical reactivity to soy milk was noted in 17% of patients with CMA.¹⁰⁷ Several other studies suggest that most individuals with CMA tolerate soy or soy formula, and reactions in those who do not tolerate soy are non-IgE-mediated (see "Epidemiology"). The soy protein component that cross-reacts with casein has been identified as the A5-B3 glycinin molecule, although findings have not been reproduced.¹⁰⁸

Clinical cross-reactivity between peanut and soy, both legumes, is extremely rare, despite the high degree of cross-sensitization based on IgE binding and skin tests.^{109,110} Green and colleagues¹¹¹ found that 7% of 140 peanut-allergic patients were allergic to soy as determined from a combination of history taking, serum food-specific IgE level tests, skin prick tests (SPTs), and OFCs. Consistent with this, Bernhisel-Broadbent and Sampson¹¹² performed open or double-blind placebo-controlled food challenges in 69 highly atopic children with at least 1 positive skin test result to a legume and found that 6.5% of the peanut-allergic children reacted to soy. In their study, among the 43% of patients with a positive skin test result for soy, only 11.5% were soy reactive.¹¹² Another study found that 6% of individuals with positive soy skin test results reacted to soy.¹¹³

Soy proteins can also elicit allergic oropharyngeal or systemic reactions in adult patients sensitized to major birch pollen allergen Bet v 1. This reaction results from cross-reactivity to pathogenesis-related protein (PR-10) from soy, designated as the allergen starvation-associated message 22 or, more recently, as Gly m 4.^{37,114} Relevant studies in children are lacking, although the same phenomenon is seen in the clinical setting. The content of Gly m 4 in soy food products strongly depends on the degree of food processing.³⁷ A prevalence of 10% of soy allergy was reported among Central European patients sensitized to birch pollen, which was caused by IgE cross-reactivity between the major birch pollen allergen, Bet v 1, and its homologous protein in soy, Gly m 4.³⁷

DIAGNOSIS

The diagnosis of CMA or soy allergy is based on the clinical history; allergy testing, when it is available (diagnostic tests for non-IgE-mediated manifestations are limited); and, if needed, a diagnostic trial including elimination of the suspected food, challenge, and reelimination. In breast-fed infants, CM/soy protein is restricted in the maternal diet, and in formula-fed infants, either extensively hydrolyzed or amino acid-based infant formula may be used.¹¹⁵ If there is no improvement on a milk or soy avoidance diet, the food in question may not be responsible for the symptoms. Alternatively, the diet may not have been restricted enough and additional foods may be considered suspicious.

The double-blind placebo-controlled food challenge is the gold standard for the diagnosis of food allergy. Numerous efforts have been made to standardize these challenges, which are time consuming and expensive endeavors and induce severe and potential life-threatening allergic reactions. OFCs should be approached cautiously even in children with sensitization to CM without a history of clinical reactions who have undergone a long-term (median 2.3 years in one study) elimination of CM because the challenge has a potential to elicit severe immediate allergic reactions to CM.¹¹⁶ The indications and conduct of controlled OFCs in children with suspected food-related symptoms have been reviewed recently.¹¹⁷

IgE-Mediated Reactions

Although SPT and specific IgE testing may reveal sensitization to a food allergen, this sensitivity may not translate to clinical symptoms in up to half of the sensitized population.^{118,119} However, in the context of a convincing reaction to ingestion of milk or soy protein and the presence of milk-specific or soy-specific IgE, a diagnosis of CMA or soy allergy is likely. In the setting of a convincing history but negative tests or sensitization in the presence of an unconvincing history, an oral milk or soy challenge may be needed. In infants, skin tests may not be as useful in ruling out CMA because detectable levels of milk-specific IgE are less frequent.¹²⁰ Higher concentrations of CM-specific IgE and larger skin test wheals generally correlate with an increased likelihood of a reaction on ingestion. However, these values are not predictive of the nature or severity of reaction to milk and are based on few clinical studies in selected populations.

Several studies have investigated the relationship between the specific IgE levels and SPT wheal size and CM and the outcome of milk double-blind placebo-controlled food challenges to identify cutoff values above which there is a high likelihood of a positive OFC (**Table 2**).^{121–127} Such cutoff values could eliminate the need for a challenge. A CM-specific IgE level of 15 kU_A/L using the ImmunoCAP (Phadia, Uppsala, Sweden) assay is 95% predictive of a clinical reaction to milk ingestion.¹²² A level of

	Age (y)	95% PPV	Methods
CM-specific IgE			
Sampson, ¹²² 2001	—	15 kU _A /L	CAP System FEIA ^a
Garcia-Ara et al, ¹²³ 2001	<1	5 kU _A /L	CAP System FEIA ^a
van der Gugten et al, ¹²⁵ 2008	<2.5	7.5 kU _A /L	CAP System FEIA ^a
SPT			
Hill et al, ¹²⁴ 2004	<2	100% PPV: 6-mm wheal	CM allergen extract
	All children	100% PPV: 8-mm wheal	
Verstege et al, ¹²⁶ 2005	—	12.5-mm wheal or 2.7 SI ^b	Fresh CM
Calvani et al, ¹²⁷ 2007	—	15-mm wheal	Fresh CM

^a Phadia, Uppsala, Sweden.

^b SI, ratio of allergen-induced wheal diameter to histamine-induced wheal diameter.

5 kU_A/L in children younger than 2 years is similarly predictive of a reaction.¹²³ Similar analyses have been performed for skin testing using a commercial CM extract; a wheal diameter of 6 mm in children who are 2 years or younger and 8 mm in children older than 2 years is 95% predictive of a clinical reaction.¹²⁴ The limiting factor is that positive predictive values (PPVs) have been obtained from highly selected pediatric populations and may not be applied to less-selected patient populations.¹²⁸ Furthermore, the predictive values for clinical reactivity associated with food-specific IgE levels determined by ImmunoCAP should not be applied to results from other laboratory assays.¹²⁹

Regarding soy allergy, the performance of specific IgE levels for predicting clinical reactivity is poorer.^{121,122,130} Several studies point out the dissociation between high levels of specific IgE to soy proteins and low rates of clinical symptoms confirmed by means of double-blind placebo-controlled food challenges.^{113,131,132} A soybean IgE level of 65 kU_A/L or higher has a high specificity (99%) but only 86% PPV in predicting clinical allergy.¹²²

Non-IgE-Mediated Reactions

IgE tests are not helpful if the symptoms do not suggest an IgE-mediated reaction, such as delayed gastrointestinal reactions and some cases of atopic dermatitis. Atopy patch testing (APT) may provide additional information in these cases, although there are currently no standardized reagents, application methods, or guidelines for interpretation of APT. At present, this type of testing cannot be recommended outside research settings.

The diagnosis of AEE is based on clinical presentation and biopsy with 15 or more eosinophils per high-power field after aggressive therapy with anti-GER medications and the disappearance of eosinophils after an appropriate elimination diet.¹³³ Some experts use SPT and APT to guide elimination diets,¹³⁴ whereas others empirically remove common foods allergens such as CM, soy, egg, wheat, peanuts, and tree nuts.¹³⁵ In one study, although the combination of SPT and APT correctly identified an appropriate diet in about 70% of the population with resolution of the symptoms and biopsies (the remaining 30% required an elemental diet), the negative predictive value (NPV) for milk APT was unacceptably low.¹³⁶

In FPIES, IgE-based allergy testing is commonly negative, and a presumptive diagnosis is made based on a typical presentation, resolution of symptoms on elimination diets, and exclusion of other causes. In a small cohort of 19 infants with FPIES most commonly to CM and soy, APT was found to have a PPV of 75% and a NPV of 100%.¹³⁷ Another study suggested that a diagnosis for CM protein-induced enterocolitis is supported by a gastric juice analysis with more than 10 leukocytes per high-power field, when vomiting or lethargy after an OFC is not apparent or is difficult to interpret.¹³⁸

Experimental Tools for Diagnosis

As mentioned earlier, APT has been suggested as an addition to the workup for children with suspected CMA, although results are conflicting.^{134,136,137,139–147} The most recent studies found no additional value of APT when compared with specific IgE measurement in the diagnosis of CMA or soy allergy.^{145,146}

Most recently, protein microarrays using purified natural CM allergen components have been introduced to the diagnostic armamentarium of milk allergy.¹⁴⁸ These microarrays showed performance characteristics comparable to the current diagnostic tests with the advantages of using small blood volumes (ideal for small children) and multiplex detection of responses to several proteins. Peptide microarray immunoassay is a novel method that can be used to analyze IgE and IgG4 binding to sequential epitopes on individual milk allergens and has been shown to differentiate between tolerant and milk-reactive patients.⁶⁷ Further studies are needed to validate its utility in clinical practice.

An allergenic source, such as soybeans, may contain several allergenic proteins or allergenic components. The component-resolved diagnosis (CRD) is a method that provides a detailed analysis of the sensitization profile in individual patients.¹⁴⁹ CRD may be especially useful to differentiate specific IgE binding that is clinically relevant or associated with more severe reactions from that caused by IgE cross-reactivity and milder or no reactions. Evaluation of patients with soy allergy from Switzerland, Denmark, and Italy identified that IgE binding to Gly m 5 or Gly m 6 was found in 86% (6/7) of individuals with anaphylaxis to soy but in only 55% (6/11) and 33% (4/12) of individuals with moderate and mild soy-related symptoms, respectively.⁸⁶

Diagnostic Pitfalls

Digestion, various processing methods (heating, cooking), and fermentation may influence the amount of relevant allergen in a final food product. Thus, tolerance of milk or soy in processed foods may not exclude allergy in forms such as liquid CM, soy milk, or ice cream. Furthermore, CM may be initially missed as a potential allergen because of the ubiquitous nature of milk proteins or misdiagnosis as egg allergy because egg proteins are commonly present in the same foods. Milk should also be considered as a possible contaminant in infants reacting to mixed jarred baby foods and in individuals reacting to soy milk because of use of common production lines. Tolerance of soy oil and soy lecithin does not exclude the possibility of soy allergy because these soy products are tolerated by most patients with soy allergy.¹⁵⁰

NATURAL HISTORY

Children with CMA should be monitored for development of tolerance because most outgrow their allergy in childhood. Non-IgE-mediated CMA has a better prognosis and tends to resolve more quickly than IgE-mediated CMA. An earlier report indicated that most children with IgE-mediated CMA became tolerant by 3 years of age.² However,

a more recent study argued that IgE-mediated CMA is more persistent, with only 64% of children developing tolerance by 12 years of age.¹⁵¹ It is unclear whether these differing results are because of population differences or a change in the natural history of milk allergy. Several prognostic indicators for the development of tolerance include lower initial level of milk-specific IgE,¹⁵¹ faster rate of decline of milk-specific IgE level over time,¹⁵² lack of specific IgE to a set of specific sequential epitopes on milk allergens,¹⁵³ and absence of concomitant allergic rhinitis or asthma.^{151,154}

Regarding soy allergy, most people become tolerant over time, although as with CMA, it may take longer than previously thought. Savage and colleagues¹⁵⁵ retrospectively described the natural history of 133 patients allergic to soy (88% with concomitant peanut allergy) with a variety of clinical reactions and found that approximately 50% of the children outgrew their allergy by age 7 years and 69% by age 10 years. By age 6 years, peak soy-specific IgE level less than 10 kU_A/L was predictive of more than 50% chance of outgrowing allergy, but peak level more than 50 kU_A/L suggested a chance of tolerance development of more than 20%. Although soy allergy is commonly considered to have an early onset, the study identified a subset of patients with late-onset soy allergy whose symptoms started after tolerating soy on a regular basis in their diet. The investigators suggested that such late-onset soy allergy may be related to either birch pollen cross-reactivity or persistent peanut allergy, as indicated by a very high peanut-specific IgE levels at their last follow-up. The prevalence of soy sensitization progressively increased with age from 2% at 2 years to 7% at 10 years in the German Multi-Centre Allergy Study, which followed 1314 children from birth to age 13 years.⁸⁹

FPIES responds well to dietary elimination of the offending food, with tolerance usually developing within 3 years of life,⁴¹ although rate of tolerance development varies between studies and populations. Occasionally, FPIES may persist into the teenage years. Earlier reports suggested that within 2 years, 60% of milk and 20% of soy-induced FPIES resolves.⁴⁴ Our preliminary data on 76 individuals with FPIES show that most patients with milk FPIES become tolerant by 3 to 4 years, but the natural history was not as favorable for soy.⁴⁶ However, a recent study by Korean investigators on 23 infants with milk FPIES reported that 64% tolerated milk at 10 months and 92% tolerated soy at 10 months.¹⁵⁶

MANAGEMENT

Avoidance

The mainstay of therapy for any food allergy is complete avoidance of the culprit food. Elimination of milk can pose nutritional concerns because milk is an important source of fat and protein in early childhood. Also, eliminating milk from the diet can be difficult because of the ubiquitous nature of CM protein in candy, custard, pudding, sherbet, luncheon meats, hot dogs, sausages, margarine, salad dressing, breaded foods, and more. CM protein may be found in some milk, cream, and butter substitutes, even in those labeled nondairy. CM may contaminate shrimp because some establishments store shrimp in milk to avoid the development of a fishy odor. In addition, breads and pastries may be brushed with milk. Exposure to food allergens via cross-contact (ie, inadvertent exposure to the allergenic food by contamination of "safe" foods with small amounts of the culprit food) can happen anywhere the food is served and because of shared utensils, counters contaminated with dairy product, and shared grills. Furthermore, up to 10% to 40% of products with advisory labeling, such as "may contain milk," have indeed been shown to contain milk.^{157,158}

Soy lecithins are commonly used in the food industry as emulsifiers. Concerns about reactivity with soy lecithin and soy oil by soy-allergic patients exist based on

the likelihood of contamination with soy proteins. However, evidence¹⁵⁹ and clinical experience suggest that proteins present in both soy lecithin and oil have little allergenicity.

Many individuals with CMA can tolerate extensively heated or baked forms of milk or small amounts of soy protein as an ingredient. However, the only currently available diagnostic test to determine which individuals can tolerate such products (unless it is currently in their diet) is an OFC. During oral challenge to extensively heated milk, severe reactions can occur, and extreme caution is advised. It can be argued that it is reasonable to allow individuals to continue to eat milk or soy in more processed forms (eg, in baked goods) than what triggered their reactions (eg, straight milk, ice cream, soy milk, or soybeans) if they have eaten these forms regularly and in the recent past, although it is unclear whether exposure in this form in the diet induces, prevents, or delays the development of tolerance. It is advisable that these patients avoid more intermediate forms of cooked or processed milk or soy, such as pudding, yogurt, or soy flour, and that anyone who has reacted to such intermediate forms avoid all forms of milk.

Substitutes

In children younger than 12 months, extensively hydrolyzed casein or whey protein formulas are commonly tolerated but occasionally amino acid–based formulas are indicated. For older individuals avoiding milk, calcium supplementation is recommended. Because of the small risk of allergic reactions to soy in milk-allergic individuals, soy protein–based formulas are not indicated in the management of IgE-mediated milk allergy in those younger than 6 months¹⁶⁰ or documented CM protein–induced enteropathy or enterocolitis. The Nutrition Committees of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the American Academy of Pediatrics (AAP) differ regarding the use of soy infant formula in the treatment of infants with CMA.^{15,161} The guidelines published by the ESPGHAN and an Australian expert panel consider transition to soy infant formula after 6 months of age,¹⁶¹ whereas the AAP recommends the use of soy infant formula before the use of an extensive hydrolysate in the treatment of CMA, regardless of age, with the consideration of extensively hydrolyzed formula.¹⁵ Soy infant formula remains a valid option to feed term infants if breast-feeding is not possible and if CM formula is not tolerated.¹⁶² However, because of the reported high frequency of sensitivity to both CM and soy antigens in infants with documented CM protein–induced enteropathy or enterocolitis, soy protein–based formulas are not indicated, and instead, CM hydrolyzed protein formulas should be used for these infants. The routine use of isolated soy protein–based formula has no proven value in the prevention of atopic disease in healthy or high-risk infants.¹⁵

Oral Immunotherapy

There is a growing evidence of the efficacy of oral immunotherapy with milk protein in the treatment of milk allergy. According to the current knowledge, such therapies induce desensitization as opposed to long-term tolerance and are currently investigational. These therapies are discussed in detail elsewhere in this issue.

SUMMARY

CMA affects 2% to 3% and soy allergy about 0.4% of young children. These allergies present with a wide range of IgE-mediated and non-IgE-mediated clinical syndromes. Diagnosis is based on a supervised OFC, but convincing clinical history taking and

measurement of CM-specific IgE can aid in the diagnosis of IgE-mediated CMA and occasionally eliminate the need for OFCs. The close resemblance and resultant cross-reactivity between proteins from soy and other related plants such as peanut and the lack of predictive values for clinical reactivity often make the diagnosis of soy allergy far more challenging. Furthermore, diagnostic tests for non-IgE-mediated manifestations are lacking. Avoidance of the culprit food protein is the mainstay of therapy, although there is a growing body of evidence on the efficacy of investigational new therapies such as oral or sublingual immunotherapy. Despite concerns regarding cosensitization or allergy to soy in CM-allergic subjects, soy-based formulas continue to be a management option for CM-allergic infants with IgE-mediated reactions, especially those older than 6 months. These formulas are not suitable for prevention of milk allergy or as a treatment of milk-induced enterocolitis, for which extensively hydrolyzed CM-based formulae are recommended because of a high prevalence of concomitant soy allergy. Natural history is favorable for most milk- and soy-allergic children, although recovery may take several years in most of them.

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