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# Milk and Soy Allergy

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## SYNOPSIS

Cow's milk allergy (CMA) affects 2% to 3% of young children and presents with a wide range of immunoglobulin E (IgE-) and non-IgE-mediated clinical syndromes, which have a significant economic and lifestyle impact. Definitive diagnosis is based on a supervised oral food challenge (OFC), but convincing clinical history, skin prick testing, and measurement of cow's milk (CM)-specific IgE can aid in the diagnosis of IgE-mediated CMA and occasionally eliminate the need for OFCs. It is logical that a review of CMA would be linked to a review of soy allergy, as soy formula is often an alternative source of nutrition for infants who do not tolerate cow's milk. The close resemblance between the proteins from soy and other related plants like peanut, and the resulting cross-reactivity and lack of predictive values for clinical reactivity, often make the diagnosis of soy allergy far more challenging. This review examines the epidemiology, pathogenesis, clinical features, natural history and diagnosis of cow's milk and soy allergy. Cross-reactivity and management of milk allergy are also discussed.

### Keywords

cow's milk; soy; bovine; allergy; cross-reactivity; diagnosis; management; natural history; pediatric; children

## EPIDEMIOLOGY

General population birth cohorts report a CMA prevalence 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% are due to IgE-mediated CMA.[4] In a recent study from Israel by Katz et al reported a much lower rate of CMA in infants (0.5%), [5] comparable to the

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0.6% rate reported in 3-year-old children.[6] They also reported a rate of 0.5% for non-IgE mediated CMA, in infants, equivalent to their rate of IgE-mediated CMA.[5] Childhood CMA is more prevalent in boys than girls.[7] In regards to severe allergic reactions, cow's milk comprises 10 to 19% of food-induced anaphylaxis cases seen both in the field and in emergency departments in pediatric and mixed age populations. It 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 et al 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.[12] In population-based studies, two European cohorts pointed to rates varying from zero[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 et al, adverse reactions to soy were seen more often in those milk-allergic individuals less than 6 months of age.[16] In that study, at follow up 2 years later, sensitization to soy proteins was not higher in infants fed soy formula compared to those fed extensively hydrolyzed formulas ($p=0.082$; $n=70$). [18] One recent study reported that of 66 infants with IgE-mediated CMA, none had a proven allergy to soy, with 64/66 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 kitchen, but 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 geographical 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- and non-IgE-mediated clinical syndromes (Table 1).[19–23] IgE-mediated reactions occur immediately or within 1–2 hours of ingestion, whereas non-IgE-mediated reactions generally have a delayed onset beyond two 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 breastfed infants.[25,26] With such an early age of onset, symptoms of an erythematous rash or hives shortly after 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 due to CMA.[27,28]

### 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, though 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% to 15% of cases).[10,30–32] Although severe soy allergy

reactions have been reported, they are far less common than those to CM. Moreover, the small number of fatal allergic reactions to soy included some patients with concomitant severe peanut allergy and/or asthma[33][34], and Foucard et al. described 4 deaths presumably due to soy allergy in severely peanut-allergic, asthmatic children with previous tolerance to soy.[35] By contrast, Sicherer et al reported no severe allergic reactions to soy challenge in 13 years of experience with double-blind placebo-controlled food challenges.[34] In a more recent study on allergic reactions during in-patient OFCs, 7% of soy challenges were severe enough to require administration of epinephrine.[36] Finally, a report on patients with soy and birch pollen allergy describes 25% 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 prior to considering a food allergy, since the majority of cases do not seem to be caused by it. 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).

**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 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 (FPIES)—**Dietary protein-induced syndromes of enteropathy and enterocolitis are not IgE-mediated, and typically present with profuse vomiting and diarrhea within 2–3 hours after ingestion of the offending allergen, causing profound dehydration and lethargy.[40] Three quarters of infants with FPIES appear acutely ill, and about 15% have hypotension requiring hospitalization.[41] Mehr et al reported that one quarter of acute FPIES episodes in young infants manifested with hypothermia less than 36°C.[42] The diarrhea may have occult blood, 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 et al reported that FPIES was elicited most often by CM and soy protein, with 7 of 16 patients having sensitivity to both.[44] Similarly, Burks et al reported that 6 of 10 patients with FPIES reacted to both milk and soy.[45] Our preliminary data on 76 patients with FPIES showed 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*** usually presents by 6 months of life in an otherwise well-appearing breastfed or formula-fed infant with blood-streaked, mucousy, loose stools and occasionally diarrhea.[40] CM and soy are the major causative foods. The majority of breastfed infants with allergic proctocolitis respond to maternal elimination of CM proteins, although some require the additional elimination of soy[47] or conversion to extensively hydrolyzed formula. Other causes, such as viruses, may have a similar presentation.[48]

**Gastroesophageal reflux (GER)—**Although debated, symptoms in GER may be associated with CMA. However, gastroesophageal reflux is not likely to be the sole presentation of CM 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 CM or soy allergy.

**Constipation—**Also a controversial topic, CMA/intolerance has been suggested as a cause of constipation in infants and children, especially in those with refractory chronic constipation. In up to one half of 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] Biopsies demonstrate proctitis with eosinophil infiltration of the rectal mucosa and a reduced thickness of the rectal mucus 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 positive serum CM-specific IgE supporting the diagnosis of CMA.[56,57] However, in a recent study, no association was found between timing of introduction of CM or soy with 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—**This syndrome is a rare food hypersensitivity pulmonary disease that primarily affects infants. It 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] Radiologic 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 radiologic findings occurs after strict milk avoidance.[59]

## PATHOGENESIS

Acute (IgE-mediated) reactions to milk are due to various milk allergens. Caseins and whey proteins account for approximately 80% and 20% of total milk protein, respectively.[60] The caseins include $\alpha_{s1}$-, $\alpha_{s2}$-, 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 (ALA, Bos d 4) and β-lactoglobulin (BLG, Bos d 5), comprising 5% and 10% of total milk protein.[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 due to mixed IgE- 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 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 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 below) 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 30k (possibly a major soybean allergen),[80–82] the soybean Kunitz trypsin inhibitor,[83–85] and 2S albumin soy protein.[85] The two 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 those 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, where 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, acquired through inhalation of soy proteins.[88]

Soy allergy may also develop secondary to initial sensitization to birch pollen and resulting cross-reactivity (see below). 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, it is more frequent at school age due to 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 reported in another one, although confirmatory clinical data are missing and the clinical significance largely unknown.[101,102] We identified IgE-reactive human epitopes that were cross-reactive with bovine milk and human

milk epitopes that were non-cross-reactive utilizing 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 co-sensitization 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, bovine serum albumin, 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]

Co-sensitization to soy is common in patients with CMA, but clinical co-allergy due to cross-sensitization based upon cross-reactive proteins between milk and soy is not.[62] In one study, co-sensitization without clinical reactivity to soy milk was noted in 17 % of patients with CMA.[107] Several other studies suggest that the majority of subjects 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 et al found that 7% of 140 peanut-allergic patients were allergic to soy as determined from a combination of history, serum food-specific IgE levels, skin prick testing, and OFCs.[111] Consistent with this, Bernhisel-Broadbent & Sampson[112] performed open or double-blind placebo-controlled food challenges in 69 highly atopic children with at least one positive skin test to a legume, and found 6.5% of the peanut-allergic children reacted to soy. In their study, among the 43% of patients with a positive skin test for soy, only 11.5% were soy-reactive.[112] Another study found that 6% of soy skin test positive subjects 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 results from cross-reactivity to pathogenesis-related protein (PR-10) from soy, designated as the allergen starvation-associated message (SAM) 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 10% prevalence of soy allergy was reported among Central European patients sensitized to birch pollen, 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 upon 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 re-elimination. In breastfed 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 have the potential to induce severe and potentially life-threatening allergic reactions. Oral food challenges should be approached cautiously 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 cow's milk, since 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 has been recently reviewed[117], and are reviewed elsewhere in this issue of the Pediatric Clinics of North America.

## IgE-mediated reactions

Although skin prick test (SPT) and specific IgE testing may reveal sensitization to a food allergen, this 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 as 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 upon ingestion. Unfortunately, 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 to CM and the outcome of milk double-blind placebo-controlled food challenges to identify cut-off values above which there is a high likelihood of a positive oral food challenge (Table 2).[121–127] Such cut-off values could eliminate the need for a challenge. A CM-specific IgE level of 15 $kU_A/L$ using the ImmunoCAP assay is 95% predictive of a clinical reaction to milk ingestion.[122] A level of 5 $kU_A/L$ in children less than 2 years of age 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 two years of age and under and 8 mm in children over two is 95% predictive of a clinical reaction.[124] The limiting factor is that positive predictive values (PPV) have been performed on highly selected pediatric populations and may not be applied to less selected patient populations. [128] Furthermore, it is important to note that the predictive values for clinical reactivity associated with food-specific IgE levels determined by ImmunoCAP (Phadia, Uppsala, Sweden) 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 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 may provide additional information in these cases, though there are currently no standardized reagents, application methods, or guidelines for interpretation for atopy patch

testing (APT). Currently, this type of testing cannot be recommended outside of research settings.

The diagnosis of AEE is based on clinical presentation and biopsy with ≥15 eosinophils/high power field after aggressive therapy with anti-gastroesophageal reflux medications, and the disappearance of eosinophils following an appropriate elimination diet.[133] Some experts use SPT and APT to guide elimination diets,[134] while 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 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 would be supported by a gastric juice analysis with >10 leukocytes/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 above, APT has been suggested as an addition to the work-up 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 to 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] They 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 a number of 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 which 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 due to 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 subjects with anaphylaxis to soy, but in only 55% (6/11) of subjects with moderate and 33% (4/12) of subjects with mild soy-related symptoms.[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, due to the ubiquitous nature of milk proteins, or misdiagnosed as egg allergy as 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 subjects reacting to soy milk due to use of

common production lines. Tolerance of soy oil and soy lecithin does not exclude the possibility of soy allergy because they are tolerated by the majority of patients with soy allergy.[150]

## NATURAL HISTORY

Children with CMA should be monitored for development of tolerance, since most will 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 due to 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 et al 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 10 years.[155] By age 6 years, peak soy-specific IgE level less than 10 kUA/L was predictive of >50% chance of outgrowing allergy, but peak level more than 50 kUA/L suggested <20% chance of tolerance development. 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. Authors 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. Notably, the prevalence of soy sensitization progressively increased with age from 2% at age 2 years to 7% at 10 years in the German Multi-Centre Allergy Study, which followed 1314 children from birth to age 13.[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 subjects with FPIES shows that the majority of 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 of any food allergy is complete avoidance of the culprit food. Elimination of milk can pose nutritional concerns, since milk is an important source of fat and protein in early childhood. Also, eliminating milk from the diet can be difficult due to the ubiquitous nature of CM protein in candy, custard, pudding, sherbet, luncheon meats, hot dogs, sausages, margarine, salad dressing, breaded foods, and more. It may be found in some milk, cream, and butter substitutes, even those labeled “non-dairy”. CM may contaminate shrimp, as 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 (i.e., inadvertent exposure to the allergenic food by contamination of 'safe' foods with small amounts of the culprit food) can happen anywhere food is served, and due to shared utensils, counters contaminated with dairy product and shared grills. Furthermore, 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, evidence [159] 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 subjects to continue to eat milk or soy in more processed forms (e.g. in baked goods) than what triggered their reaction(s) (e.g. straight milk, ice cream, soy milk or soy beans) if they have eaten these forms regularly and in the recent past, although it is unclear whether exposure in this form in the diet will induce, prevent, or delay 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 less than 12 months of age, extensively hydrolyzed casein or whey protein formulas are commonly tolerated, but occasionally amino acid-based formulas are indicated. For older subjects 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 less than 6 months of age[160] 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 ESPGHAN and an Australian expert panel consider transition to soy infant formula after 6 months of age,[161] while the AAP recommends the use of soy infant formula prior to 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 breastfeeding 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 cow milk protein-induced enteropathy or enterocolitis, soy protein-based formulas are not indicated and CM hydrolyzed protein formulas should instead be used for these infants. Finally, 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. They are discussed in detail elsewhere in this series.

## CONCLUSION

CMA affects 2–3% and soy allergy about 0.4% of young children. They present with a wide range of IgE- and non-IgE-mediated clinical syndromes. Diagnosis is based on a supervised OFC, but convincing clinical history and measurement of cow's milk-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 like 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 co-sensitization 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 above 6 months of age. They 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 due to a high prevalence of concomitant soy allergy. Natural history is favorable for the majority of milk- and soy-allergic children, although recovery may take several years in the majority of them.

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## Table 1

Presentation of cow's milk and soy allergy.

| | |
|---|---|
| **IgE-mediated** | |
| Cutaneous | Urticaria<br>Angioedema |
| Gastrointestinal | Oral itching and abdominal pain<br>Nausea and vomiting<br>Diarrhea |
| Respiratory | Rhinoconjunctivitis<br>Wheeze and asthma exacerbation<br>Laryngeal edema |
| Systemic | Anaphylaxis |
| **Mixed IgE- and non-IgE mediated** | |
| Cutaneous | Atopic dermatitis |
| Gastrointestinal | Eosinophilic esophagitis and gastroenteritis |
| **Non-IgE mediated** | |
| Gastrointestinal | Dietary protein enterocolitis/proctitis/proctocolitis<br>Protein-losing enteropathy<br>Gastroesophageal reflux*<br>Colic*<br>Constipation* |
| Respiratory | Pulmonary hemosiderosis (i.e. Heiner syndrome) (mostly caused by milk allergy) |

* controversial

## Table 2

Cut-off values based on 95% positive predicted values (PPV) for cow's milk (CM)-specific IgE and skin prick test (SPT) in children with cow's milk allergy (CMA).

| | Age | 95% PPV | Methods |
|---|---|---|---|
| **CM-specific IgE** | | | |
| Sampson 2001[122] | | 15 $kU_A/L$ | CAP System FEIA[#] |
| Garcia-Ara et al 2001[123] | <1 year | 5 $kU_A/L$ | CAP System FEIA[#] |
| Van der Gugten et al 2008[125] | < 2.5 years | 7.5 $kU_A/L$ | CAP System FEIA[#] |
| **SPT** | | | |
| Hill et al 2004[124] | < 2 years<br>All children | 100% PPV: 6 mm wheal<br>100% PPV: 8 mm wheal | CM allergen extract |
| Verstege et al 2005[126] | | 12.5 mm wheal or 2.7 SI[*] | Fresh CM |
| Calvani et al 2007[127] | | 15 mm wheal | Fresh CM |

[*] SI, ratio of allergen-induced wheal diameter to histamine-induced wheal diameter

[#] Phadia, Uppsala, Sweden