



Guidelines change the diagnostic process of cow milk food allergy: problem-based learning

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Purpose of review

The accurate diagnosis of food allergy and its management has been the subject of two published guidelines, the National Institute of Health Sponsored Expert Panel Guidelines and the World Allergy Organization guidelines: Diagnosis and Rationale for Action Against Cow Milk Allergy. Both guidelines have drawn attention to the unique aspects of different food allergens. They have highlighted the possible overdiagnosis and underdiagnosis of food allergy. The purpose of this review is to demonstrate the utility and application of the two published guidelines in a real-life scenario that the pediatrician or allergy/immunology specialist may be faced with.

Recent findings

This review is divided into two sections: the first section is problem-based learning, presenting a clinical scenario of a child suspected of cow milk allergy (CMA) and followed over time. At each step, the guidelines are consulted and referenced. The second section reviews recent research that demonstrates that CMA has a high prevalence, and that testing methodologies can be improved on.

Summary

Clinicians taking the approach outlined by the guidelines will be able to confirm or refute a diagnosis of CMA, all the while minimizing unnecessary tests and procedures.

Keywords

children, cow milk, food challenge, serum immunoglobulin E, skin test

INTRODUCTION

In order to assist the practicing pediatrician, internist, family practitioner and allergist/immunologist in the diagnosis and management of food allergy, two national and international organizations have assembled an expert panel and produced guidelines based on a thorough review and grading of the evidence in the literature. The two guidelines, National Institute of Health Sponsored Expert Panel Guidelines and the World Allergy Organization: Diagnosis and Rationale for Action Against Cow Milk Allergy (DRACMA), have demonstrated that testing for food allergy should only be done when indicated and can be adapted to the clinical case and the resources available. Several publications have followed the guidelines and address aspects of epidemiology of cow milk allergy (CMA) and alternate diagnostic modalities. This review is divided into two sections. The first section will utilize a case of a child diagnosed with CMA and followed over time and apply problem-based learning, highlighting and referencing the sections of the guidelines that address each part of the case. The second section

reviews the literature published after the guidelines publication in the areas of diagnosis and epidemiology of CMA.

SECTION I

When a patient comes to the office of a general practitioner, an internist, a pediatrician or an allergist/immunologist, the history of the presenting complaint of a food allergy they present is usually unique to them. The guidelines make general recommendations assuming as many scenarios as

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KEY POINTS

- CMA is a worldwide problem prevalent in all five continents.
- The diagnosis of CMA should be strongly based on all elements of medical practice, the history and probability of allergy, judicious testing and food challenges.
- Forms of CMA that do not have demonstrable IgE do not yet have established reliable tests.

have been researched in the medical literature and have been experienced by the expert panel that is assembled to write the guidelines. The following section is an attempt to demonstrate the usability of the guidelines in a real-life pediatric case of presumed CMA, followed over time.

Application of the National Institute of Health Sponsored Expert Panel Guidelines and Diagnosis and Rationale for Action Against Cow Milk Allergy guidelines to a case

A 2-year old white boy is seen in the Allergy and Immunology Clinic for a question of CMA. The child was breastfed till 13 months. At the onset of breastfeeding, mother had avoided cow milk in her diet because the older sibling had been a colicky child. The baby nevertheless developed reflux and was colicky. At 1 month of age, the mother introduced cow milk in her own diet because she thought the avoidance was not effective in preventing infantile colic. At that time, she noticed the onset of eczema. The eczema lesions were all over the body, characterized by rough skin without excoriations and with generalized itching, particularly at night. The baby was tested at 5 months of age by blood test, utilizing the pediatric panel immunoCAP (Phadia, Uppsala, Sweden) that measures serum-specific immunoglobulin E (IgE) to cow milk and other predetermined foods and environmental allergens. The immunoCAP was positive to cow milk, peanuts and cats (Table 1). Mother returned to cow milk avoidance in her diet, and added peanuts, nuts and all seed avoidance. The family removed the cat from the home. The eczema improved.

At 12 months of age, the infant was tested by skin prick tests to foods at an allergist office. The tests were placed using a multitest device and were recorded as 4+ to cow's milk, peanuts and almonds, 3+ to sesame seed, 2+ to hazelnuts, Brazil nuts and cashew nuts and negative to eggs, wheat, soy, fish, shell-fish and other nuts.

The child had been introduced to solids at 6 months, to soy milk at 12 months and he tolerated it and accepted it by 13 months. He is currently on table food, except for strict avoidance of cow milk, peanuts, tree nuts and seeds.

He may have had one reaction by facial swelling after they placed Cetaphil (Galderma Laboratories, Texas, USA) ultra hydrating moisturizer lotion on his face. They later found that the lotion contained macadamia nut oil. Currently, skin care consists of a moisturizer, Aquaphor (Beiersdorf AG, Hamburg, Germany), after a bath. They occasionally use hydrocortisone 1% cream on areas behind the knees. His only possible exposure to cow milk in the history is his ingestion of a cookie without any clinical reaction noted. He has had eggs without reactions.

The question that the parents have sought consultation with an allergist is whether their son has CMA and whether he can or cannot drink cow milk or eat foods containing cow milk products. In addition, since the pediatric panel immunoCAP were positive to peanuts, the parents have not introduced peanuts and tree nuts in the child's diet and have implemented strict avoidance measures of these foods for the child.

Two guidelines have been produced using an evidence-based literature search and evaluation of the evidence. The first is the National Institute of Health Sponsored Expert Panel Guidelines that have addressed the diagnosis of food allergy in North America, and the second is the World Allergy Organization guidelines that have addressed CMA in the : DRACMA guidelines [1–3].

In the following section, we will consult each of the guidelines, utilizing the elements of the case to reach a diagnosis and management strategy.

The first element of the case is that the child has a sibling with a history of infantile colic that had been ascribed to food allergy. Should this history have been an indication for testing prior to the introduction of cow milk in this child? The Expert Panel guidelines (section 5.2.3.) define a patient at high risk of reacting to highly allergenic foods such as milk, eggs and peanuts as follows: children with pre-existing severe allergic disease and/or a family history of food allergy. Another definition used in the guidelines (section 5.2.1.) for at risk is as follows: patients with biologic parents or siblings with existing or history of allergic rhinitis, asthma, atopic dermatitis or a food allergy. As none of the above places the child in an at-risk category, testing prior to the introduction of cow milk would not have been recommended.

The Expert Panel guidelines (section 5.2.3.) specifically addressed the question of whether testing is indicated prior to introduction of highly

Table 1. Skin prick test and serum-specific immunoglobulin E to foods and environmental allergens results for 2-year-old patient with the question of cow milk allergy

	Pediatric immunoCAP panel at 5 months of age in kU/L (reference range 0.34 or less)	Skin tests at 12 months of age	Selected immunoCAP at 20 months of age in kU/L (reference range 0.34 or less)
Almond		4+	28.20 (H)
Brazil nut		2+	3.53 (H)
Cashew		2+	2.96 (H)
Hazelnut			11.50 (H)
Pecan nut			<0.10
Pistachio			2.74 (H)
English walnut			0.28
Peanut	4.47 (H)		19.70 (H)
Sesame seed			9.53 (H)
Milk	1.94 (H)		18.20 (H)
Whey			18.00 (H)
Casein			1.00 (H)
Cod	<0.10		
Egg white	<0.10		
Soybean	<0.10		
Wheat	<0.10		
<i>Alternaria tenuis</i>	<0.10		
American cockroach	<0.10		
Cat dander	4.82 (H)		
Dog dander	<0.10		
<i>Dermatophagoides pteronyssinus</i>	<0.10		
<i>Dermatophagoides farinae</i>	<0.10		

H, high. The tests at 5 months of age are derived from the pediatric immunoCAP panel. The tests at 19 months of age are individually selected by our clinic. Although not discussed in the National Institute of Health Expert Panel guidelines or in the World Allergy Organization: Diagnosis and Rational for Action Against Cow Milk guidelines, measuring serum IgE to the specific cow milk proteins may increase the sensitivity of the results. It also may assist in predicting whether the child will clinically tolerate baked milk as some of the cow milk proteins may be degraded by heat.

allergenic foods in the general population and recommends against it. Although it suggested that testing be considered in a high-risk population, it specified that the testing would be a complete evaluation that includes an oral food challenge.

The child has a history of eczema. Would this history be an indication to test the child prior to the introduction of cow milk? The Expert Panel guidelines (section 5.2.4.) suggested that children less than 5 years of age with moderate-to-severe atopic dermatitis be considered for food allergy evaluation for the common food allergens, if at least one of the following conditions is met: the child has persistent atopic dermatitis, despite optimized management and topical therapy, or that the child has a reliable history of an immediate reaction after ingestion of a food. So, although the child had eczema, he did not have any of the indications for testing prior to the introduction of cow milk per the guidelines.

Despite the above, the child comes to the allergy clinic with the testing already done. The next step is to evaluate the interpretation of the tests.

The DRACMA guidelines (section 9), as do the Expert Panel guidelines, discuss the three methods of diagnosis of food allergy, namely the skin prick tests, the serum food-specific IgE and the oral food challenge. The Expert Panel guidelines (section 4.2.1.) indicate that the medical history taken with a complete set of very specific questions is useful for identifying food allergens that may be responsible for IgE-mediated reactions, but warn that it lacks sufficient sensitivity or specificity to definitively make a diagnosis. The DRACMA guidelines utilize the history to establish the pretest probability against which the need to perform the other two tests, the skin prick tests and the serum food-specific IgE prior to an oral food challenge, is weighed and decided upon. Neither guideline addresses the evaluation of food allergy in the absence of a clinical

history. DRACMA has calculated from studies that from a mostly used cutoff value of 3 mm or more wheal diameter, the sensitivity of skin prick tests to cow milk is 0.67 [confidence interval (CI): 0.64–0.70] and the specificity is 0.74 (95% CI: 0.72–0.77) and concluded that in low, average or high pretest probability, in settings in which oral food challenge is done routinely, there is no need to perform a skin prick test. The Expert Panel guidelines (section 4.2.2.1.) recommended to perform skin tests to assist in the identification of foods that may be provoking IgE-mediated food allergic reactions, but the skin prick test alone cannot be diagnostic of food allergy. The statement applies well to this case.

Considering the serum IgE specific to cow milk, the Expert Panel guidelines has made the same statement it made regarding skin tests that the serum-specific IgE can assist in the identification of foods that may be provoking food allergy, but alone cannot be diagnostic of food allergy. Furthermore, the Expert Panel guidelines laid out the studies that have shown that the various analytical methods commercially available do not give comparable results. The DRACMA guidelines suggest utilizing the serum-specific IgE to cow milk based on the availability of the oral food challenge. In situations in which the oral food challenge is routinely performed, it obviates the need for measuring the serum-specific IgE. However, where a more prudent approach is taken, the test may help avoid an oral food challenge and allow the introduction of the food if the pretest probability is low and the serum-specific IgE is less than 0.35 IU/l. On the other hand, where the pretest probability is high, a threshold of more than 0.35 IU/l may avoid a food challenge and recommend avoidance of the food. In both circumstances, there is a risk of false negatives and false positives that is in the range of 2–5% and 6–10%, respectively.

Our last consideration is the combination of both tests, the skin prick test and the serum-specific IgE. The Expert Panel guidelines addressed the combination of both tests and the atopy patch test (which is not a diagnostic consideration in this case) and recommended not using the combination of tests. The DRACMA guidelines reviewed the combination of skin tests and serum-specific IgE and found a paucity of studies that are comparable and that provide the answer to the question. The DRACMA guidelines finds that the tests are 28% discordant and that applying the same logic of utilizing the pretest probability to the need to perform an oral food challenge, there will still be a chance of misclassification based on just the two tests in the range of 1–3%.

Finally, the Expert Panel guidelines strongly advocate for the oral food challenge (section 4.2.2.8) as ruling out a food allergy or making the diagnosis of a food allergy, but only in the circumstances in which the challenge elicits objective symptoms. The type of challenge, double-blinded placebo-controlled or open can be designed based on the circumstances. The DRACMA guidelines also advocate for the oral food challenge, but do take into consideration the practical aspects of the availability, or lack of, of these tests in various medical delivery systems. Therefore, DRACMA recommends factoring the pretest probability in the decision to perform or not to perform the oral food challenge.

In the case presented and in the absence of a reliable method to establish a pretest probability, an oral food challenge was recommended. The parents requested to repeat the serum IgE to cow milk prior to the challenge. The results returned higher than before and in the range that would suggest a clinical reaction on an open challenge (Table 1). According to DRACMA, oral food challenges are to be utilized where available. According to the Expert Panel guidelines, an oral food challenge is the definitive diagnosis. As our clinic has experience in the performance of an oral food challenge to cow's milk in children, we recommended performing the procedure as a definitive diagnostic test. Due to the skin test and the serum-specific IgE results, the parents were reluctant to perform a challenge using plain cow milk, but opted for a challenge using the baked cow milk methodology [4]. An open challenge was performed in the office with baked cow milk in a muffin. The child consumed the muffin without any immediate side-effect, except for a small area of erythema on the upper lip that appeared an hour after the conclusion of the challenge. This was considered an objective finding, but rather clinically nonsignificant. The child was sent home on a regimen of consuming one or two muffins per day, with plans to perform an oral food challenge to plain cow milk in the future if the child continues to tolerate the baked milk and when the parents become comfortable with the procedure. According to both guidelines, repeat skin tests or serum-specific IgE would not be recommended in this setting, given the low pretest probability of a reaction.

SECTION II

In this section, the authors have reviewed the medical literature following the publication of the Expert Panel and DRACMA guidelines in the area of diagnosis and epidemiology of CMA and provide a summary and commentaries.

ADVANCES IN EPIDEMIOLOGY OF COW MILK ALLERGY AND THE CHALLENGES FACED

The review by Sackesen *et al.* [5] addressed geographical trends in CMA in children or adults based on the opinion of experts from Australia, Asia, North America, Latin America, the middle East and Europe who had gathered in a 2-day meeting in order to present various regional approaches to CMA. The experts found that even though there seems to be uniformity in the diagnosis and treatment of CMA, the diagnostic approach to CMA shows variations among different regions. Common concerns were inadequate applications of challenge tests for the diagnosis and inadequate supply of the cow's milk substitute formulae. The review calls for collaboration of the national and international scientific communities in order to produce and update practical guidelines for CMA.

A review by the Expert Panel that specifically addressed the pediatric population highlights the need to establish the diagnosis of food allergy by reliable methods, specifically that there is no curative therapy. A diagnosis of food allergy leads to the elimination of foods from the diet as the only avoidance measure, and knowing that dietary eliminations might endanger the health of children, the diagnosis should be made reliably [6].

Three epidemiologic studies were published, one from the USA, one from Finland and one from Australia [7,8,9].

In the USA, food allergy prevalence, determined by survey methodology, was 8% (95% CI: 7.6–8.3). Among children with food allergy, 38.7% had a history of severe reactions, and 30.4% had multiple food allergies. Prevalence according to allergen among food-allergic children was highest for peanuts [25.2% (95% CI: 23.3–27.1)], followed by milk [21.1% (95% CI: 19.4–22.8)] and shellfish [17.2% (95% CI: 15.6–18.9)]. In Australia, infants who had a positive skin test, defined as a wheal size of 1 mm or more to one or more foods (raw egg, peanut, sesame, shellfish or cow's milk) underwent oral food challenges to raw egg, peanut or sesame. Amongst 2848 infants, the prevalence of any sensitization to peanut was 8.9% (95% CI, 7.9–10.0); raw egg white, 16.5% (95% CI, 15.1–17.9); sesame, 2.5% (95% CI, 2.0–3.1); cow's milk, 5.6% (95% CI, 3.2–8.0) and shellfish, 0.9% (95% CI, 0.6–1.5). The prevalence of challenge-proven peanut allergy was 3% (95% CI, 2.4–3.8); raw egg allergy, 8.9% (95% CI, 7.8–10.0) and sesame allergy, 0.8% (95% CI, 0.5–1.1). Oral food challenges to cow's milk and shellfish were not performed. They concluded that more than 10% of 1-year-old infants had challenge-proven IgE-mediated food allergy to one of the

common allergenic foods of infancy. In Finland, the study included a questionnaire survey and a retrospective collection of food allergy test results, skin prick tests, IgE antibodies or open food challenges from the patient records of the entire study population. The findings in 961 children showed that by the age of 4 years, the cumulative incidence of food allergy for the common food allergens, milk, egg and cereals was 17% and that testing was performed on these foods in 90% of children who reportedly had a physician-diagnosed food allergy. The study raises the question of the financial burden of food allergy testing based on current testing practices.

ADVANCES IN THE AREA OF DIAGNOSTICS FOR COW MILK ALLERGY AND OTHER SYNDROMES ASSOCIATED WITH COW MILK INGESTION

DunnGalvin *et al.* [10[¶]] sought to develop and validate a model to predict food challenge outcome by using routinely collected data in a diverse sample of children considered suitable for a food challenge. They developed allergen-specific models for peanut, egg and milk and examined the predictive ability of six clinical factors: skin prick test, serum-specific IgE, total IgE minus serum-specific IgE, symptoms, sex and age in the model. They found that 97% of cases were accurately predicted as positive and 94% as negative by their model that showed an advantage in clinical prediction compared with serum-specific IgE alone, skin prick test alone and serum-specific IgE and skin prick test (92 accuracy versus 57 and 81%, respectively). The actual algorithm seems to be protected by intellectual property and has not been made available for clinical use yet.

Hamilton *et al.* [11] published work that attempted to define factors that could be used to translate IMMULITE-measured IgE (Siemens Healthcare Diagnostics Inc., NY, USA) antibody levels for chicken egg white, cow's milk and peanut into immunoCAP-comparable quantities that could then be correlated with published levels that have been generated with the immunoCAP system, including 135 samples for CMA. They found that antibody levels from both assays were highly correlated $r(2) = 0.93$ for milk. Empirically determined IMMULITE/immunoCAP ratios (mean ± 1 SD) were 2.33 ± 1.0 kU/l for milk and that the IgE antibody levels for individuals who either passed or failed a food challenge were not significantly different between the assay methods.

In the area of nonimmediate CMA, Hochwallner *et al.* [12] examined whether patients suffering from

non-IgE-mediated cow's milk protein intolerance can be distinguished from persons without cow's milk protein intolerance based on serological measurement of IgG and IgA specific for purified cow's milk antigens utilizing purified recombinant α S1-casein, α S2-casein, β -casein, κ -casein, α -lactalbumin and β -lactoglobulin in patients with IgE-mediated CMA, with non-IgE-mediated cow's milk protein intolerance, with gastrointestinal symptoms not associated with cow's milk ingestion and in control persons without gastrointestinal problems. They found that only patients with CMA had IgE antibodies to cow's milk and that they mounted the highest IgG(1) and IgG(4) antibody levels to α S1-casein, α S2-casein, β -casein, κ -casein and α -lactalbumin and that IgG subclass or IgA reactivity to cow's milk allergens cannot distinguish cow's milk protein intolerant patients from persons without cow's milk protein intolerance.

On the contrary, Kimura *et al.* [13] examined the use of a lymphocyte stimulation test in formula-fed infants who develop intestinal CMA. Intestinal CMA refers to infants who develop gastrointestinal symptoms, mostly vomiting, diarrhea and blood in the stools that are ascribed to the ingestion of cow milk. Those infants commonly do not have demonstrable IgE to cow milk in their serum or skin tests. They found that 86.1% of patients with intestinal cow's milk allergy tested positive to κ -casein that suggests that this could be a useful diagnostic test for the disorder.

CONCLUSION

In conclusion, the published guidelines, as they become more widely adopted and applied in clinical practice and in research, will definitely improve the diagnostic ability for CMA for the patients and the general population. It remains imperative that the diagnostic modalities be improved upon to yield a higher degree of specificity while they remain feasible, safe and economically possible for all populations.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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