
Anaphylaxis to cow's milk and beef meat proteins

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Objective: This report summarizes a review of anaphylactic reactions to cow's milk and beef presented at a recent conference on adverse reactions to bovine proteins.

Data Sources: A review of pertinent PubMed (National Library of Medicine) articles was performed. Relevant publications were critically analyzed.

Study Selection: The expert opinion of the author was used to select the relevant data for the review.

Results: Although cow's milk has been recognized for many years as one of the leading causes of food allergy, beef has only recently been identified as a cause of immunoglobulin (Ig)E-mediated reactions. Epidemiologic data indicate that the prevalence of cow's milk allergy is approximately 1 to 2%, but no definite data are available for beef allergy. Anaphylaxis to both foods has been well characterized in childhood; however, a subset of adult patients may become reactive to cow's milk and have the characteristic features of anaphylaxis. The diagnosis is primarily based on skin prick tests and measurement of cow's milk- or beef-specific IgE antibodies. In selected patients, a standardized food challenge might be necessary to determine the diagnosis.

Conclusions: In the absence of a proactive treatment of food allergy, patients with anaphylaxis to cow's milk or beef must be instructed to avoid these foods in their diet. Although cow's milk allergy generally is associated with a good prognosis, with most young children spontaneously "outgrowing" the disease, current research is focusing on the prevention and the treatment of this condition.

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EPIDEMIOLOGIC DATA

Allergic reactions to cow's milk have been reported for many years. Although numerous food allergens have been identified over the years, cow's milk remains the first suspected nutrient when a young child has an adverse reaction to a food. Several epidemiologic studies have been designed to determine the prevalence of adverse reactions to cow's milk. The frequency of cow's milk allergy and cow's milk intolerance has been estimated to range from 1 to 7.5% in westernized countries.¹⁻⁵ Nevertheless, the perceived prevalence of reactions to cow's milk is much higher than the actual number of cases.

In a prospective study of 480 children up to 3 years of life, Bock⁶ found that 133 (28%) had symptoms attributed to the consumption of foods. Only 8% of these patients, however, had confirmed reactions reproduced by a double-blind, placebo-controlled food challenge (DBPCFC). Among the initial study population, 72 children had symptoms suspected to be provoked by milk, but symptoms could not be reproduced in 47 (65.3%) of them. In 14 (19.4%) of the 72 children, the clinical manifestations were probably attributable to cow's milk, and milk was confirmed as the allergy trigger in only 11 (15.3%). Beef was not mentioned as a potential allergen in this study population.

In another prospective study, Høst and Halken⁷ conducted a 3-year followup of 1,749 newborns for symptoms of cow's

milk allergy. The diagnosis was proven in 39 infants (2.2%), of whom two-thirds had cutaneous symptoms and one-third had respiratory symptoms. Further, although most allergic symptoms to cow's milk appear early during life, they commonly disappear before the child begins school.

In contrast to cow's milk, beef might be an underestimated culprit in food allergies. Among 184 children with atopy, Fiocchi et al⁸ reported a clinical response during open challenges with beef in 12 patients (6.5%). In a study including 113 patients with atopic dermatitis and food allergy, only two cases (1.8%) could be confirmed by a DBPCFC.⁹ In a study of children with atopic dermatitis and cow's milk allergy, Werfel et al¹⁰ reported positive results to a beef challenge in 20%. Apparently, cow's milk can be the sole food allergy in a patient, whereas sensitivity to beef is most frequently encountered in patients with multiple food allergies.

Collectively, these studies suggest that anaphylaxis to beef might be suspected primarily in patients already allergic to cow's milk who may react after consumption of partially cooked beef meat. Current studies, however, do not support the elimination of well-cooked beef from the diet of children with cow's milk allergy. The implication of beef in food allergy remains marginal in comparison to other major culprits in food allergies, such as eggs or peanuts.

ANAPHYLACTIC REACTIONS

Anaphylaxis can be defined as a life-threatening condition resulting from mast cell degranulation. It is often associated with hypersensitivity to foods. Its estimated prevalence varies widely but might be between 3.2 and 360 events in a popu-

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lation of 100,000 per year.^{11,12} Although peanuts and other nuts are often mentioned as foods leading to potentially fatal anaphylactic reactions, milk has been identified in several reports of food-induced fatalities.

In a recent study, Bock et al¹³ described 32 patients with a fatal reaction to foods, including a 3-year-old girl who received a lunch containing milk at a daycare facility. Although she was known as allergic to milk, the symptoms progressed rapidly to death. Earlier, Sampson et al¹⁴ reported another series of 13 patients with fatal or near-fatal anaphylactic reactions to foods; in this group a 9-year-old girl had a near-fatal reaction induced by milk. Relevantly, asthma is consistently considered a major risk factor for severe anaphylactic reactions to foods (Table 1).

Recently, my colleagues and I¹⁵ conducted an Internet-based survey on anaphylactic reactions to foods. The patients who participated were recontacted and questioned about the circumstances of the food-induced reactions. Among a total of 51 reactions, milk was mentioned by 12 responders (23.5%). Most of the reactions to milk (75%) had occurred at home, at school, in a daycare setting, or in a hospital. These sites would be expected to be easily secured by the provision of adequate instructions to daycare or school employees or by appropriate food handling by the parents. Of note, two patients had reactions during a hospital stay after being given milk or milk-containing products despite clear instructions to the hospital staff by the parents. Therefore, milk should be considered a food potentially leading to a substantial number of anaphylactic reactions, and special care should be exercised with milk-allergic patients.

Although allergies to cow's milk are usually seen in small children, they have also been reported in adult patients. These symptoms tend to be less frequent in this age group, and they tend to persist longer. Because such symptoms do not always suggest IgE-mediated reactions, they might be misdiagnosed for years. Stoger and Wuthrich¹⁶ characterized 34 adult patients who were allergic to milk and cheese. In most patients, the diagnosis had been made during their early adult years, and they all had positive results of skin tests with or without associated positive CAP radioallergosorbent tests (Pharmacia, Uppsala, Sweden). Most frequently, respiratory problems, rashes, and gastrointestinal symptoms were encountered. Adult patients seem to be more reactive to casein than to other milk proteins. Thus far, reactivity to beef has not been reported among adult patients.

Table 1. Major Risk Factors for Severe Anaphylactic Reactions to Foods

History of asthma
History of previous severe anaphylactic reactions
Delay in administration of epinephrine
Noncompliance with restriction diet
Adolescence
Lack of instructions to childcare or school employees for management of potential anaphylactic reactions
Self-management of anaphylactic reactions

RESPONSIBLE ANTIGENS

Antigens responsible for IgE-mediated reactivity to cow's milk have been well defined in the literature. Among the major allergens in cow's milk, several investigators have identified and characterized α -lactalbumin (14.2 kDa), β -lactoglobulin (18.3 kDa), various caseins (between 20 and 30 kDa), and bovine serum albumin (BSA) (approximately 67 kDa).¹⁷

BSA has also been identified as one of the major beef allergens. Werfel et al¹⁰ characterized 11 children with atopic dermatitis who had hypersensitivity to beef, 8 of whom were also sensitive to milk. Among these 11 patients, 3 tolerated beef in a DBPCFC but reacted after ingestion of less well-cooked beef. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of raw beef disclosed several bands corresponding to proteins and among them a band at 67 kDa corresponding to BSA. After the beef extract was heated for 2 hours at 85° C, this band disappeared. Thus, BSA seems to be a common beef and cow's milk allergen, provoking allergic reactions to raw beef in children with cow's milk allergy. Additional allergens in beef other than the band at 67 kDa corresponding to BSA were identified at 200 kDa and 60 kDa on immunoblots.¹⁸

PROBLEMS WITH AN ELIMINATION DIET

One of the major problems for patients with anaphylactic reactions to certain foods is the presence of unlabeled components of food allergens in processed foods.¹⁹ Patients with reactions to cow's milk (or their parents) are instructed to read labels and to avoid foods with labels indicating the presence of not only cow's milk but also of ingredients such as casein, whey, natural flavoring, or caramel. Nevertheless, items labeled as safe, such as kosher "dairy-free" foods, might contain a small amount of milk and thus provoke reactions.²⁰ Similarly, foods generally considered as safe, such as sorbet, may contain trace amounts of milk and lead to allergic reactions.²¹

Processing of food may also unexpectedly involve milk protein. As an example, casein might be used in the processing of salmon.²² Thus, total elimination of dietary offending agents is a challenge. Potentially severe anaphylactic reactions can be prevented only by careful scrutiny and anticipation of possible pitfalls in the daily consumption of foods.

DIAGNOSTIC PROCEDURES

The diagnosis of anaphylactic reactions to cow's milk and beef is based on tests for detection of IgE-mediated reactions to foods. Skin prick tests (SPTs) are the first-line diagnostic procedures. Although this technique might be easy to use in most patients, the interpretation might lead to false-positive results.

In 1977, Bock et al²³ reported that 3-mm or larger wheal reactions indicate a strong likelihood of clinical hypersensitivity to foods. The accuracy of SPTs was reevaluated for measurement by three different methods—interpreting as

positive a wheal greater than 3 mm, measuring the wheal by surface area, or determining the mean wheal diameter.²⁴ For milk, SPTs were found to be discriminatory with a positive cutoff level of ≥ 5 mm or 29 mm². No interpretation method was found to be superior to another. Sporik et al²⁵ found that a wheal diameter >8 mm was always associated with a positive food challenge.

Recent studies showed that the addition of atopy patch tests increased the sensitivity of SPTs in the diagnosis of IgE-mediated food allergy, especially in patients with atopic dermatitis.^{26–28} Milk specific IgE concentrations can also be measured to predict the presence of allergy. In patients with atopic dermatitis, a prospective study showed an excellent performance of the Pharmacia CAP System fluorescence enzyme immunoassay for predicting clinical reactivity with values >15 kU_A/L.²⁹ Nonetheless, false-positive and, in a lower number, false-negative test results might still lead to an erroneous diagnosis; thus, a DBPCFC is considered the gold standard diagnostic technique for any food hypersensitivity.³⁰ This procedure, however, is contraindicated if the patient previously had severe anaphylactic reactions to the suspected food.

Overall, either SPTs or specific IgE studies might be used first for the diagnosis of anaphylaxis to cow's milk or beef meat. In most cases, a definite diagnosis will rely on a positive test result in conjunction with a suggestive history. In only a few patients will a standardized food challenge need to be implemented to determine the diagnosis.

PATIENT PROGNOSIS

Several investigators have noted that patients with cow's milk hypersensitivity have a good prognosis, in that the clinical sensitivity disappears in most of them. Høst and Halken⁷ reported recovery from cow's milk allergy in 56% of children by 1 year of age, in 77% by 2 years of age, and in 87% by 3 years of age. The natural history of beef allergy, however, is less well defined.

Several studies have been designed to identify predictors of the outcome of milk allergy. In children whose milk sensitivity disappeared, James and Sampson³¹ found a decreased ratio of casein-specific IgE/IgG₁ and IgE/IgG₄. In a group of patients with persisting cow's milk allergy beyond 9 years of age, the concentration of milk and casein-specific IgE was higher in comparison to that in a group of children who achieved tolerance of cow's milk before the age of 3 years.³² Other works have attempted to identify specific binding epitopes in an effort to predict the outcome of milk allergy. Different IgE-binding epitopes on β -casein and on κ -casein were recognized in serum samples from patients with persistent milk allergy but not in samples from patients who achieved milk tolerance.³³

These studies suggest that high levels of specific IgE to casein and the presence of antibodies to specific epitopes of caseins predispose to prolonged sensitivity to milk. In the future, in vitro tests to identify patients at risk for prolonged hypersensitivity to cow's milk might be available.

Table 2. Potential Treatments for IgE-Mediated Reactions to Foods

Systemic immunotherapy with modified allergens
Peptide immunotherapy
Oral immunotherapy with effective immunogenic vectors
DNA vaccines
Immunotherapy with Th1/Th3 or Tr1-promoting vectors coupled to antigens
Cytokine modulation
Blocking of homing receptors or chemokine receptors by specific antibodies
Pharmacotherapy with immunomodulating agents
Genetic modification of allergenic foods

FUTURE PERSPECTIVES

Although a proactive cure of food allergy is not yet available, studies are currently attempting to characterize the pathogenesis of food allergy more completely and to identify potential strategies for the treatment of food allergy (Table 2). A murine model of IgE-mediated cow's milk allergy has recently been established.³⁴ Young C3H/HeJ mice are sensitized by gastric administration of cow's milk plus cholera toxin as a mucosal adjuvant. The presence of sensitization can be determined by high levels of specific IgE to cow's milk as well as by T cell reactivity in gut-associated mucosal structures. After oral challenges with cow's milk, these mice have anaphylactic symptoms similar to those observed in humans. Recently, my associates and I³⁵ adapted this model to investigate the tolerogenic effect of carrageenan, a high-molecular-weight polysaccharide. Mice treated with carrageenan before oral sensitization had no clinical reaction on challenge to cow's milk. Further, the reactivity of mesenteric lymph node and spleen cells was significantly decreased in carrageenan-pretreated mice. This mouse model of anaphylaxis to food might facilitate future identification of proactive therapeutic options for food allergy.

Cow's milk and, more recently, beef proteins are known culprits for food-induced anaphylaxis. Symptoms can lead to severe, and even life-threatening, reactions. Thus far, such reactions can be prevented only by careful avoidance of food containing these proteins, a caution that should be emphasized to the patients and their parents. Because current studies are attempting to find a cure for anaphylactic food allergy, effective treatment might be available in the near future.

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REFERENCES

1. Collins-Williams C. The incidence of milk allergy in pediatric practice. *J Pediatr* 1956;48:39–47.
2. Gerrard JW, MacKenzie JW, Goluboff N, et al. Cow's milk allergy: prevalence and manifestations in an unselected series of newborns. *Acta Paediatr Scand Suppl* 1973;234:1–21.

3. Hide DW, Guyer BM. Cows milk intolerance in Isle of Wight infants. *Br J Clin Pract* 1983;37:285-287.
4. Host A, Husby S, Osterballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants. Incidence, pathogenetic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk. *Acta Paediatr Scand* 1988;77:663-670.
5. Verkasalo M, Kuitunen P, Savilahti E, Tiilikainen A. Changing pattern of cow's milk intolerance: an analysis of the occurrence and clinical course in the 60s and mid-70s. *Acta Paediatr Scand* 1981;70:289-295.
6. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79:683-688.
7. Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life: clinical course in relation to clinical and immunological type of hypersensitivity reaction. *Allergy* 1990;45:587-596.
8. Fiocchi A, Restani P, Riva E, et al. Meat allergy: I-Specific IgE to BSA and OSA in atopic, beef sensitive children. *J Am Coll Nutr* 1995;14:239-244.
9. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985;107:669-675.
10. Werfel SJ, Cooke SK, Sampson HA. Clinical reactivity to beef in children allergic to cow's milk. *J Allergy Clin Immunol* 1997;99:293-300.
11. Stewart AG, Ewan PW. The incidence, aetiology and management of anaphylaxis presenting to an accident and emergency department. *Q J Med* 1996;89:859-864.
12. Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. *Mayo Clin Proc* 1994;69:16-23.
13. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-193.
14. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-384.
15. Eigenmann PA, Pastore FD, Zamora SA. An Internet-based survey of anaphylactic reactions to foods. *Allergy* 2001;56:540-543.
16. Stoger P, Wuthrich B. Type I allergy to cow milk proteins in adults: a retrospective study of 34 adult milk- and cheese-allergic patients. *Int Arch Allergy Immunol* 1993;102:399-407.
17. Wal JM. Cow's milk allergens. *Allergy* 1998;53:1013-1022.
18. Han GD, Matsuno M, Ito G, et al. Meat allergy: investigation of potential allergenic proteins in beef. *Biosci Biotechnol Biochem* 2000;64:1887-1895.
19. Steinman HA. "Hidden" allergens in foods. *J Allergy Clin Immunol* 1996;98:241-250.
20. Jones RT, Squillace DL, Yunginger JW. Anaphylaxis in a milk-allergic child after ingestion of milk-contaminated kosher-pareve-labeled "dairy-free" dessert. *Ann Allergy* 1992;68:223-227.
21. Laoprasert N, Wallen ND, Jones RT, et al. Anaphylaxis in a milk-allergic child following ingestion of lemon sorbet containing trace quantities of milk. *J Food Prot* 1998;61:1522-1524.
22. Koppelman SJ, Wensing M, de Jong GA, Knulst AC. Anaphylaxis caused by the unexpected presence of casein in salmon. *Lancet* 1999;354:2136.
23. Bock SA, Buckley J, Holst A, May CD. Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. *Clin Allergy* 1977;7:375-383.
24. Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1998;9:186-191.
25. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;30:1540-1546.
26. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996;97:9-15.
27. Roehr CC, Reibel S, Ziegert M, et al. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;107:548-553.
28. Saarinen KM, Suomalainen H, Savilahti E. Diagnostic value of skin-prick and patch tests and serum eosinophil cationic protein and cow's milk-specific IgE in infants with cow's milk allergy. *Clin Exp Allergy* 2001;31:423-429.
29. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-896.
30. Sicherer SH. Food allergy: when and how to perform oral food challenges. *Pediatr Allergy Immunol* 1999;10:226-234.
31. James JM, Sampson HA. Immunologic changes associated with the development of tolerance in children with cow milk allergy. *J Pediatr* 1992;121:371-377.
32. Sicherer SH, Sampson HA. Cow's milk protein-specific IgE concentrations in two age groups of milk-allergic children and in children achieving clinical tolerance. *Clin Exp Allergy* 1999;29:507-512.
33. Chatchatee P, Jarvinen KM, Bardina L, et al. Identification of IgE- and IgG-binding epitopes on $\alpha(s1)$ -casein: differences in patients with persistent and transient cow's milk allergy. *J Allergy Clin Immunol* 2001;107:379-383.
34. Li XM, Schofield BH, Huang CK, et al. A murine model of IgE-mediated cow's milk hypersensitivity. *J Allergy Clin Immunol* 1999;103:206-214.
35. Frossard CP, Hauser C, Eigenmann PA. Oral carrageenan induces antigen-dependent oral tolerance: prevention of anaphylaxis and induction of lymphocyte anergy in a murine model of food allergy. *Pediatr Res* 2001;49:417-422.

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