
Cow's milk allergy versus cow milk intolerance

Sami L. Bahna, MD, DrPH

Background: Although cow's milk allergy (CMA) and cow's milk intolerance (CMI) are two different terms, they are often used interchangeably, resulting in confusion both in clinical practice and in research reports.

Objective: To promote the appropriate differential use of the terms CMA and CMI.

Methods: Highlighting the differences in clinical and laboratory findings between CMA and CMI. Information was derived from reviewing the literature on these two topics, supplemented by the clinical experience of the author.

Results: CMA is an immunologically mediated reaction to cow's milk proteins that may involve the gastro-intestinal tract, skin, respiratory tract, or multiple systems, ie, systemic anaphylaxis. Its prevalence in the general population is probably 1 to 3%, being highest in infants and lowest in adults. Even though it can cause severe morbidity and even fatality, dietary elimination is associated with good prognosis. However, CMI should refer to nonimmunologic reactions to cow's milk (CM), such as disorders of digestion, absorption, or metabolism of certain CM components. The most common cause of CMI is lactase deficiency, which is mostly acquired during late childhood or adulthood. It has high racial predilection, being highest in dark-skinned populations and lowest in northern Europeans. Lactose intolerance is generally a benign condition, with symptoms limited to the gastro-intestinal tract, yet the primary acquired type lasts for a lifetime. Symptoms can be well ameliorated by reducing the intake of CM or using lactose-hydrolyzing agents.

Conclusions: Adverse reactions to CM should be differentiated into immunologic (CMA) and nonimmunologic (CMI). The latter is still a general term that comprises several conditions and requires further differentiation.

Ann Allergy Asthma Immunol 2002;89(Suppl):56-60.

INTRODUCTION

Cow's milk (CM) is one of the most commonly consumed foods worldwide. Its popularity is primarily derived from its high nutritional value, palatability, and availability. Nevertheless, its consumption can be associated with various hazards, either because of its contamination with a harmful agent or because of a disorder in the subject's digestion, absorption, metabolism, or immunologic reactivity.¹ Recurrent or chronic adverse reactions to CM are often empirically referred to as cow's milk intolerance (CMI) or cow's milk allergy (CMA). These two terms, however, differ from one another, both linguistically and scientifically, yet are often used synonymously or interchangeably, both by the public and health professionals.

Allergy has been synonymous with hypersensitivity, and denotes an immunologically mediated clinical reaction. According to the Webster's Unabridged Dictionary, *allergy* is a "condition of unusual sensitivity to a substance which, in like amounts, do not affect others." Intolerance means "inability to endure," ie, it is a general, nonspecific term. CMI is mostly caused by inadequate digestion, usually of the milk sugar lactose and occasionally of its fat. It can also be caused by certain inborn errors of metabolism relevant to specific milk constituents or their metabolites, such as in phenylketonuria

and galactosemia. Strictly speaking, aversion and psychologic reactions to milk ingestion are not true intolerances, yet are often referred to as such, at least by the public.

This presentation will focus on a comparison between CMA and lactase deficiency (LD), the most common cause of CMI worldwide.

CMA

CMA is primarily a childhood disease, with reported prevalences ranging from 0.5 to 7.5%.^{2,3} Such a wide range is attributable to differences among various studies regarding age of the study population, societal feeding habits, types of clinical manifestations included, and diagnostic criteria used. Perhaps reasonable estimates can be 1 to 3% in the general population and 3 to 5% in bottle-fed infants, with high figures in infants with family history of atopy, prematurity, or gastro-intestinal (GIT) disorders. Adult-onset CMA is rare (<1%) and is generally much milder than in infants.

CM Proteins (CMP) Allergenicity

CMP are 2.8 to 4.1 g/dL and comprise two major fractions: casein (76 to 86%) and whey (14 to 24%); the latter includes β -lactoglobulin (7 to 12%), α -lactalbumin (2 to 5%), serum albumin (0.7 to 1.3%), and serum immunoglobulins (1.4 to 2.8%).⁴ β -Lactoglobulin and casein are the most allergenic as well as the most heat-resistant. Individuals vary widely in their degree of sensitivity. There is sufficient evidence that intrauterine sensitization can occur by very minute quantities of CMP that pass from the maternal circulation across the placenta to the fetus⁵⁻⁷ or across the mammary gland to the nursing baby.⁸⁻¹⁰ In addition to ingestion, exposure to CM by

Allergy & Immunology Section, Louisiana State University School of Medicine, Shreveport, Louisiana.

This presentation was delivered in memory of Professor Luisa Businco as the Keynote Lecture at the Conference on Adverse Reactions to Bovine Proteins, Milan, Italy, December 13-15, 2001.

Received for publication March 10, 2002.

Accepted for publication in revised form March 22, 2002.

skin or mucous membrane contact or by inhalation can cause severe reactions in exquisitely sensitive subjects.^{11,12}

Pathogenesis and Manifestations of CMA

Hypersensitivity to CM can be mediated by any, or a combination of, the four basic types of immunologic reactions outlined by Gell and Coombs.^{4,13,14} Type I (anaphylactic or immediate) is predominantly mediated by immunoglobulin (Ig)E antibodies and seems to be the most common. Type II (cytotoxic) involves complement activation by IgG, IgM, or IgA antibodies, and is probably the least common. Type III (Arthus-type) seems to be the second most common. It requires the formation of immune complexes that comprise the antigen, its specific antibody (IgG, IgM, IgA, and occasionally IgE) and complement. Such complexes become impacted in small blood vessels causing vasculitis and perivascular inflammation. Type IV (delayed) is mediated by sensitized T lymphocytes.

Because type I reactions are the most common and best understood, they are often referred to as classic allergic reactions. The three other types are more difficult to evaluate; both clinically and in the laboratory. Hence, the popular classification of CMA manifestations into IgE-mediated and non-IgE-mediated (Table 1). Details on manifestations of non-IgE-mediated reactions are presented in other publications.^{3,4,14-17}

Diagnosis of CMA

The medical history can be useful in gathering information on the nature and course of symptoms, the feeding history, and the relationship of symptoms to milk ingestion or to other factors. The physical examination might reveal whether the presenting signs are more likely to be those of allergy or of other disorders. As none of the CMA manifestations are pathognomonic, a differential diagnosis needs to be established, depending on the information derived from the medical history and physical examination. Appropriate laboratory tests can be selected accordingly. In type I reactions, serum

total IgE level is usually elevated. To identify the specific offending allergen, skin prick testing or serum IgE antibodies are good screening tests, but neither has optimal reliability. In a series of subjects with various manifestations of CMA,¹⁸ the sensitivity (true positive test) was 44% for skin testing and 56% for radioallergosorbent test, and the specificity (true negative test) was 67% for both tests. Hence, the importance of verifying the clinical relevance of each suspected food by appropriately designed challenge tests.¹⁹ Using the Pharmacia ImmunoCAP System FEIA (Pharmacia, Uppsala, Sweden) for measuring serum food-specific IgE antibodies, it has been reported that serum CM-specific IgE concentration of 32 KU/L or greater had a diagnostic reliability of at least 95%.²⁰

Management of CMA

Treatment of CMA is basically avoidance of CM as strictly as possible. A milk-substitute for infants can be a soybean hydrolysate formula, which is tolerated by the majority of subjects, or a hypoallergenic formula (a synthesized amino acid elemental diet or an extensively hydrolyzed casein or whey formula). Unlike partially hydrolyzed formulas, allergic reactions to extensively hydrolyzed formulas are rare but do occur in exquisitely sensitive patients.²¹⁻²⁵ Goat's milk proteins strongly cross-react with CMP and would not be an appropriate substitute.²⁶ At present, there is no reliable or safe hyposensitization method for CMA.²⁷ Future studies might reveal that certain CMP peptides that are immunogenic, but nonallergenic, may be useful for effective, safe hyposensitization.

Prognosis of CMA

In young children, CMA is vastly temporary, particularly with strict milk avoidance. Tolerance has been reported in approximately one-third of cases by 1 to 2 years of age, and in approximately one-half by 3 to 4 years.²⁸ GIT manifestations tend to be outgrown faster than atopic dermatitis or asthma.^{29,30} Systemic anaphylaxis and reactions by contact or inhalation usually last for many years.

LACTOSE INTOLERANCE (LI)

Lactose is the only carbohydrate of mammalian milk and is not present in any other food. Its quantity is highest in human milk (6.2 to 7.5 g/100g) followed by bovine and goat milk (3.7 to 5.1 g/100g), low in seal and whale milk (1.8 to 2.6g/100g), and is absent in sea lion milk.³¹ Insufficient intestinal lactase enzyme secretion, relative to the quantity of lactose intake, results in lactose maldigestion, with consequent GIT symptoms.

Pathogenesis and Manifestations of LI

Lactase enzyme (β -galactosidase) in the brush border of the small intestinal mucosa hydrolyzes lactose, a disaccharide, into the readily absorbed monosaccharides glucose and galactose. Lactose that passes unhydrolyzed to the colon holds water and becomes fermented by colonic flora, with production of hydrogen, carbon dioxide, and lactic acid. Hence the symptoms can be bloating, flatulence, abdominal pain, or

Table 1. CMA Manifestations

System involved	IgE-mediated	Non-IgE-mediated
Gastrointestinal	Vomiting	Bleeding (occult, gross)
	Colic	Eosinophilic gastroenteropathy
	Diarrhea	Enterocolitis
		Protein-losing enteropathy
		Gastroesophageal reflux
Dermatologic		Constipation
	Atopic dermatitis	Contact rash
	Urticaria	Atopic dermatitis
	Angioedema	
Respiratory	Rhinitis	Chronic pulmonary disease
	Cough	(Heiner syndrome)
	Asthma	Pulmonary hemosiderosis
	Otitis media	
Systemic anaphylaxis	Most anaphylaxis	Postprandial exercise-induced

Modified from Host A, Bahna SL.³

frothy, watery diarrhea. Vomiting is uncommon. The severity of symptoms varies widely, depending on the quantity of lactose ingested relative to the intestinal lactase activity present.

Epidemiology and Types of LD

Congenital LD is very rare, seems to be inherited as an autosomal recessive trait, and in some infants may subside spontaneously.³² *Secondary LD* is common in the presence of disorders of the small intestine. After acute gastroenteritis, lactase production usually normalizes within days to a few weeks. Varying degrees of LD occur in association with milk-sensitive enteropathy, which can pose difficulty in defining the diagnosis. In such instances, symptoms would not improve unless lactose is avoided as well until mucosal regeneration occurs. In chronic GIT disease associated with LD, such as irritable bowel syndrome, improvement would be enhanced by a lactose-free diet.^{33,34} *Primary acquired or delayed-onset LD* is the most common form worldwide, seems to be inherited as an autosomal recessive disorder, presents with varying degrees of hypolactasia, and usually manifests by teenage or early adulthood. It has a marked racial predilection (Table 2), with a prevalence being highest in dark-skinned populations and lowest in Scandinavians, particularly Danes (3%).³¹

Diagnosis of LD

LD can be easily suspected in adults or older children who develop the characteristic GIT symptoms shortly after ingesting milk. It can be supported, though not necessary, by documenting the presence of stools' acidity and reducing substances. The diagnosis can be clinically settled by documenting the absence of symptoms on ingesting a lactose-free milk and their recurrence upon consuming regular CM.

Laboratory tests that confirm LD are primarily three types.³⁵ The *lactose tolerance test* involves monitoring the blood glucose level after an oral dose of lactose. The *breath hydrogen test* is both simpler and more reliable. Hydrogen produced in the colon is partially absorbed, reaches the lungs, and is excreted in the exhaled air. The rise in hydrogen concentration in a sample of exhaled air after lactose intake would reflect the degree of LD.³⁶ *Measuring the lactase activity in a jejunal mucosal biopsy* is a very sensitive

Table 3. CMA vs LI

	Cow milk allergy	Lactose intolerance
Prevalence	Low	High
Racial variation	Low	High
Common age	Infancy	Adulthood
Offender	Bovine milk proteins	Mammalian milk sugar
Mechanism	Immunologic	Enzyme deficiency
Symptoms	GI, skin, respiratory, anaphylaxis	GI only
Morbidity	Can be high	Low
Diagnosis		
Total IgE level	Usually elevated	Normal
Screening	Skin testing	Stools appearance, pH & reducing substances
In vitro tests		
Confirmation	Challenge test	Breath hydrogen
		Lactose tolerance test
		Jejunal biopsy
Treatment	Symptomatic medication	Reduce milk intake
	Avoid bovine milk	Selected substitutes
	Selected substitutes	Lactase replacement
Prognosis	Mostly self-limited	Mostly permanent
Prophylaxis	Breast-feeding	None
	Special formulas	

Modified from Bahna SL.³⁹ GI, gastro-intestinal.

method, but the enzyme content of the mucosa may vary from one site to another.³⁷ It is a rather invasive procedure and requires a special laboratory procedure; it is more suitable for research.

It is worth noting that laboratory tests may detect LD in subjects who ingest milk without symptoms. Such a state may be referred to as "lactose maldigestion" rather than LI. In a study on healthy Chinese children 3 to 13 year of age, clinical LI was demonstrated in only one-third of those with LD.³⁸

Management of LI

In any particular individual, LI can be usually controlled by reducing the lactose intake to a quantity that does not cause significant symptoms. Except in the rare cases of congenital LD, total avoidance of lactose is unnecessary. Infants can be fed a lactose-free formula such as a soybean formula or a milk-base formula with prehydrolyzed lactose. In cases of secondary LD, patients need to avoid lactose for one to a few weeks after recovery of the primary GIT disease. Although the primary delayed-onset LD usually lasts for a lifetime, most patients can tolerate varying quantities of milk or certain milk products.^{31,39} β -Galactosidase enzyme produced by live *Lactobacillus* in fresh (nonheated) yogurt and aged cheeses makes these foods well tolerated by the majority of patients.^{40,41}

Patients who would like to consume larger quantities of milk can take a lactase preparation orally just before or with milk ingestion, or by adding the enzyme to milk a few hours before. Commercial lactase preparations (Lactaid, McNeil, Fort Washington, PA) are available in tablet or liquid forms. Available also in the supermarkets in the United States, and

Table 2. Prevalence of Primary Acquired Delayed-Onset LD in Adults of Various Racial Groups

Highest prevalence (70–100%):

Eskimos, Orientals, American Indians, African-Americans

High prevalence (50–70%):

Middle Eastern, most Africans, most South Americans, Mexicans, Asian Indians

Moderate prevalence (25–50%):

Caucasian Americans, Australian nonaboriginals, Germans

Lowest prevalence (3–15%):

Scandinavians

Data extracted from Scrimshaw NS, Murray EB.³¹

probably in many other countries, are CM preparations with varying reduced lactose content (0 to 30% of the original).

CONCLUSION

CMA is an immunologic reaction that may affect one or more body systems, and can be life-threatening. However, CMI is a general term that may comprise a variety of adverse reactions to CM, the most common of which is LI. The interchangeable use of the terms CMI and CMI should be minimized, as they refer to two different clinical problems (Table 3). It would be prudent to reserve the term CMI to nonimmunologic adverse reactions to CM, such as maldigestion or abnormal metabolism of certain milk components. Psychologic reactions and aversion may be empirically included as well. CMI may be also used as an initial working diagnosis for a milk-related symptom until a more specific diagnosis is settled.

REFERENCES

1. Freed DL. Health Hazards of Milk. London: Bailliere Tindell, 1984.
2. 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.
3. Host A, Bahna SL. Cow's milk allergy. In: Frieri M, Kettlehut B, editors. Food Hypersensitivity and Adverse Reactions: A Practical Guide for Diagnosis and Management. New York: Marcel Dekker, 1999:99-111.
4. Bahna SL, Heiner DC. Allergies to Milk. New York: Grune, Stratton, 1980.
5. Businco L, Marchetti F, Pellegrini G, Perlini R. Predictive value of cord blood IgE levels in "at-risk" newborn babies and influence of type of feeding. *Clin Allergy* 1983;13:503-508.
6. Delespesse G, Sarfati M, Lang G, Sehon AH. Prenatal and neonatal synthesis of IgE. *Monogr Allergy* 1983;18:83-95.
7. Gerrard JW, Perelmutter L. IgE-mediated allergy to peanut, cow's milk, and egg in children with special reference to maternal diet. *Ann Allergy* 1986;56:351-354.
8. Gerrard JW, Shenassa M. Food allergy: two common types as seen in breast fed and formula fed babies. *Ann Allergy* 1985;50:375-379.
9. Host A, Husby S, Osterballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants. *Acta Paediatr Scand* 1988;77:663-670.
10. Machtinger S, Moss R. Cow's milk allergy in breast-fed infants: the role of allergen and maternal secretory IgA antibody. *J Allergy Clin Immunol* 1986;77:341-347.
11. Bahna SL. Unusual presentations of food allergy. *Ann Allergy Asthma Immunol* 2001;86:414-420.
12. Tan BM, Sher MR, Good RA, Bahna SL. Severe food allergies by skin contact. *Ann Allergy Asthma Immunol* 2001;86:583-586.
13. Bahna SL, Gandhi MD. Milk hypersensitivity. I. Pathogenesis and symptomatology. *Ann Allergy* 1983;50:218-223.
14. Bahna SL. Pathogenesis of milk hypersensitivity. *Immunol Today* 1985;6:153-154.
15. Bahna SL. Milk allergy in infancy. *Ann Allergy* 1987;59:131-136.
16. Bahna SL. Diagnostic tests for food allergy. *Clin Rev Allergy* 1988;6:259-284.
17. Metcalfe DD, Sampson HA, Simon RA, editors. Food Allergy: Adverse Reactions to Foods and Food Additives, 2nd ed. Boston: Blackwell Scientific Publications, 1997.
18. Bahna SL, Gandhi MD. Reliability of skin testing and RAST in food allergy diagnosis. In: Chandra RK, editor. Food Allergy. St John's, Newfoundland, Canada: Nutrition Research Foundation, 1987:139-147.
19. Bahna SL. Food challenge procedures in research and in clinical practice. *Pediatr Allergy Immunol* 1995;6(Suppl):49-53.
20. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-896.
21. Businco L, Cantani A, Longhi MA, Giampietro PG. Anaphylactic reactions to a cow's milk whey protein hydrolysate (Alfa-Re, Nestle) in infants with cow's milk allergy. *Ann Allergy* 1989;62:333-335.
22. Saylor JD, Bahna SL. Anaphylaxis to casein hydrolysate formula. *J Pediatr* 1991;118:71-74.
23. Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM. Safety of casein hydrolysate formula in children with cow milk allergy. *J Pediatr* 1991;118:520-525.
24. Rugo E, Wahl R, Wahn U. How allergenic are hypoallergenic infant formulae? *Clin Exp Allergy* 1992;22:635-639.
25. Ragno V, Giampietro P, Bruno G, Businco L. Allergenicity of milk protein hydrolysate formulae in children with cow's milk allergy. *Eur J Pediatr* 1993;152:760-762.
26. Bellioni-Businco B, Paganelli R, Lucenti P, et al. Allergenicity of goat's milk in children with cow's milk allergy. *J Allergy Clin Immunol* 1999;103:1191-1194.
27. Bahna SL. Oral desensitization with cow's milk in IgE-mediated cow's milk allergy: Contra! In: Wuthrich B, Ortolani C, editors. Highlights in Food Allergy. Monographs in Allergy. Vol 32. Basel, Switzerland: Karger, 1996:233-235.
28. Bishop W, Hill D, Hosking C. Natural history of cow milk allergy: clinical outcome. *J Pediatr* 1990;116:862-867.
29. Lothe L, Lindberg T, Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics* 1982;70:7-10.
30. Businco L, Benincori N, Cantani A, et al. Chronic diarrhea due to cow's milk allergy. A 4- to 10-year follow-up study. *Ann Allergy* 1985;55:844-847.
31. Scrimshaw NS, Murray EB. The acceptability of milk and milk products in populations with a high prevalence of lactose intolerance. *Am J Clin Nutr* 1988;48(Suppl):1079-1159.
32. Sunshine P, Kretschmer N. Studies of small intestine during development. III. Infantile diarrhea associated with intolerance to disaccharides. *Pediatrics* 1964;34:38-50.
33. Bohmer CJ, Tuynman HA. The effect of a lactose-restricted diet in patients with a positive lactose tolerance test, earlier diagnosed as irritable bowel syndrome: a 5-year follow-up study. *Eur J Gastroenterol Hepatol* 2001;13:941-944.
34. Vernia P, Di Camillo M, Marinaro V. Lactose malabsorption, irritable bowel syndrome and self-reported milk intolerance. *Dig Liver Dis* 2001;33:234-239.
35. Owens FJ Sr. Alimentary tract gas and lactose intolerance. In: Achkar E, Farmer RG, Fleshler B. Clinical Gastroenterology, 2nd ed. Philadelphia: Lea, Febiger, 1992:25-32.
36. Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med* 1995;333:1-4.

-
37. Newcomer AD, McGill DB. Distribution of disaccharidase activity in the small bowel of normal and lactase-deficient subjects. *Gastroenterology* 1966;51:481-488.
38. Yang Y, He M, Cui H, et al. The prevalence of lactase deficiency and lactose intolerance in Chinese children of different ages. *Chin Med J* 2000;113:1129-1132.
39. Bahna SL. Is it milk allergy or lactose intolerance? *Immunol Allergy Clin North Am* 1996;16:187-198.
40. Riskalla SW, Luo J, Kabir M, et al. Chronic consumption of fresh but not heated yogurt improves breath hydrogen status and short chain fatty acid profiles: a controlled study in healthy men with or without lactose maldigestion. *Am J Clin Nutr* 2000;72:1474-1479.
41. Pelletier X, Laure-Boussuge S, Donazzolo Y. Hydrogen excretion upon ingestion of dairy products in lactose-intolerant male subjects: importance of the live flora. *Eur J Clin Nutr* 2001;55:5109-5112.
- Requests for reprints should be addressed to:*
Sami L. Bahna, MD
Allergy & Immunology Section
Department of Pediatrics
LSU School of Medicine
1501 Kings Highway
Shreveport, LA 71130-3932
E-mail: sbahna@lsuhsc.edu
-