
Frequency of cow's milk allergy in childhood

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Objective: The primary objective of this review is to discuss the clinical features, diagnosis, natural history, and prognosis of cow's milk allergy in early childhood and its relationship to development of inhalant allergies.

Data Sources: A review of 229 PubMed (National Library of Medicine) articles on cow's milk allergy (CMPA) for the years 1967 through 2001 was performed. In addition, references from other review articles have been included. This review represents a synthesis of these sources and the expert opinion of the author.

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

Results: The diagnosis of reproducible adverse reactions to cow's milk protein (CMP), ie, CMPA, has to be confirmed by controlled elimination and challenge procedures. The incidence of CMPA in infancy seems to be approximately 2 to 3% in developed countries. Symptoms suggestive of CMPA may be encountered in approximately 5 to 15% of infants emphasizing the importance of controlled elimination/milk challenge procedures. Reproducible clinical reactions to CMP in human milk have been reported in approximately 0.5% of breastfed infants. Most infants with CMPA develop symptoms before 1 month of age, often within 1 week after introduction of CMP-based formula. The majority has two or more symptoms from two or more organ systems. Approximately 50 to 60% have cutaneous symptoms, 50 to 60% have gastrointestinal symptoms, and approximately 20 to 30% respiratory symptoms. Symptoms may occur within 1 hour after milk intake (immediate reactions) or after 1 hour (late reactions). The prognosis of CMPA is good with a remission rate of approximately 45 to 50% at 1 year, 60 to 75% at 2 years, and 85 to 90% at 3 years. Associated adverse reactions to other foods develop in up to 50% and allergy against inhalants in 50 to 80% before puberty.

Conclusions: CMPA is the most common food allergy in early childhood with an incidence of 2 to 3% in the first year of life. The overall prognosis of CMPA in infancy is good with a remission rate of approximately 85 to 90%. In particular, gastrointestinal symptoms show a good prognosis. An early increased immunoglobulin E-response to CMP is associated with an increased risk of persistent allergy to CMP, development of adverse reactions to other foods, and development of asthma and rhinoconjunctivitis later in childhood.

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INTRODUCTION

According to a revised nomenclature for allergy,¹ reproducible adverse reactions to foods may be classified as food hypersensitivity, which may be divided into nonallergic food hypersensitivity and food allergy when immunologic mechanisms have been demonstrated (or strongly suspected). Similar to food allergy in general, cow's milk allergy may be divided into immunoglobulin (Ig)E-mediated food allergy (most common) and non-IgE-mediated food allergy, mainly type III (immune-complexes) and type IV (cell-mediated) reactions.^{2,3} Most often allergic reactions to cow's milk proteins (CMP) are IgE-mediated, causing symptoms from the skin, the gastrointestinal tract, or the respiratory tract. The gastrointestinal manifestations of food allergy may be classified as a continuum from clearly IgE-mediated to mixed reactions dominated by eosinophilic granulocytes as effector cells to clearly non-IgE-mediated reactions.³ However, most studies on "milk allergy" have not investigated the immunologic basis of the clinical symptoms. Based on clinical symptoms alone, the differentiation between IgE-mediated and

non-IgE-mediated reactions to CMP is not possible. Likewise, a diagnosis of lactose intolerance should be suspected in cases with restricted gastrointestinal symptoms, and this diagnosis should be confirmed by a lactose tolerance test. This review will concentrate on the clinical features, diagnosis, incidence, and prognosis of CMP allergy (CMPA) in childhood. Further, possible predictive factors of later inhalant allergies will be elucidated.

DIAGNOSTIC CRITERIA

As no single laboratory test or combination of tests are diagnostic of CMPA, the diagnosis of CMPA still has to be based on strict, well defined food elimination and challenge procedures including double-blind, placebo-controlled food challenges (DBPCFC) in children older than 1 to 2 years.^{4,5} In young infants, open controlled challenges have been shown to be reliable when performed under professional observation in a hospital setting.^{6,7} To avoid overdiagnosis the following minimum diagnostic criteria should be noted: 1) disappearance of symptoms after each of two dietary eliminations of cow's milk and cow's milk products; 2) recurrence of identical symptoms after one challenge; and 3) exclusion of lactose intolerance and coincidental infection (especially expected in case of monosymptomatic gastrointestinal symptoms).

In solely breastfed infants, elimination and challenge procedures should be performed via regulation of the mother's

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intake of cow's milk. A well defined, standardized challenge schedule should be followed, including description of time intervals between increasing amounts of cow's milk and total amount of cow's milk before reaction.⁷ In unusual or not so well known manifestations of CMPA such as allergic eosinophilic esophagitis and allergic proctitis (inflammation of the rectum) with constipation, the challenge schedule may have to be modified to register the relevant symptoms. In older children and adults, DBPCFC will often be necessary to exclude psychologic or other reactions.^{4,6} However, in patients with delayed reactions, DBPCFC will often not be practical. Therefore, a negative DBPCFC should always be followed by an open, controlled challenge including normal amounts of intake of cow's milk. For practical purposes, the challenge recommendations given by Niggemann et al⁶ are useful.

INCIDENCE

Before 1950 the incidence of CMPA during the first year of life was reported to be low, approximately 0.1 to 0.3%.⁸ Since then, varying estimates of the incidence (1.8 to 7.5%) have been reported, mainly reflecting differences in diagnostic criteria and study design⁹⁻¹⁵ (Table 1). Symptoms suggestive of CMPA have been reported in 5 to 15% of infants.^{7,13,14} However, when controlled elimination/challenge procedures were used, a diagnosis of CMPA was only confirmed in approximately 1 of 3 of the infants resulting in an incidence of CMPA of approximately 2 to 5%. Reproducible clinical reactions to CMP in human milk have been reported in approximately 0.5% of breastfed infants.^{11,14} CMPA is the most common confirmed food protein allergy in early infancy with an incidence in the first year of life of approximately 2 to 3% in well conducted prospective studies compared with an incidence of 0.8% of allergy to peanut, 0.8% to soy, 0.6% to egg, and an incidence of 0.2% to wheat.¹³ Similarly, adverse reactions to cow's milk is the most frequent parentally perceived adverse reaction to food reported with a point prevalence of 7.5% at 12 months, 5.0% at 24 months, and a cumulative incidence of 11.6% in a large Norwegian birth cohort of 3,623 infants followed from 0 to 2 years by questionnaires at 6-month intervals.¹⁶ Such figures emphasize the

importance of proper diagnostic procedure to avoid overdiagnosis and overtreatment.

CLINICAL FEATURES

Most infants with CMPA develop symptoms before 1 month of age, often within 1 week after introduction of cow's milk-based formula. The majority have two or more symptoms with symptoms from two or more organ systems. Approximately 50 to 70% have cutaneous symptoms, 50 to 60% gastrointestinal symptoms, and 20 to 30% have respiratory symptoms.⁷ In exclusively breastfed infants with CMPA, severe atopic eczema is a predominant symptom. The onset of CMPA after 1 year is extremely rare.^{7,13} Clinical features of CMPA in children are listed in Table 2.

Symptoms may occur within a few minutes to 1 hour after milk exposure (immediate reactions; mostly IgE-mediated) or after 1 hour (late reactions), and in some cases after several

Table 2. Clinical Features of Cow's Milk Allergy in Children

Cutaneous reactions

IgE-mediated:

- Atopic dermatitis
- Urticaria, acute, or chronic (rare)
- Angioedema

Non-IgE-mediated:

- Contact rash
- Atopic dermatitis (some forms?)

Gastrointestinal reactions

IgE-mediated:

- Oral allergy syndrome (local reactions)
 - Nausea/vomiting
 - Colic
 - Diarrhoea
- #### Non-IgE-mediated:
- Enterocolitis syndrome
 - Colitis
 - Eosinophilic gastroenteritis
 - Transient enteropathy (mimicking celiac disease)
 - Protein-losing enteropathy

Respiratory reactions

IgE-mediated:

- Rhinoconjunctivitis
- Asthma (wheeze, cough)
- Laryngeal edema
- Otitis media with effusion (secondary to allergic rhinitis and eustachian tube dysfunction or an allergic reaction in the middle ear?)

Non-IgE-mediated:

- Pulmonary hemosiderosis (Heiners syndrome, rare)

Other reactions

Systemic anaphylaxis

- Food-dependent, exercise-induced asthma/anaphylaxis

Unknown mechanisms:

- Anemia (not attributable to colitis)
- Arthritis (rare)
- Henoch Schönlein purpura (type III ?, rare)
- Irritability/sleeplessness?
- Migraine (rare)

Table 1. Incidence of Cow's Milk Allergy during the First Year of Life—Prospective Studies

Authors, year	Incidence
Halpern et al, 1973 ⁹	20/1,084 (1.8%)
Gerrard et al, 1973 ¹⁰	59/787 (7.5%)
Jakobsson & Lindberg, 1979 ¹¹	10/1,079 (1.9%)
Hide & Guyer, 1983 ¹²	15/609 (2.5%)
Bock, 1987 ¹³	25/480 (5.2%)
	11/480 (2.2%)*
Høst et al, 1988 ¹⁴	39/1,749 (2.2%)
Schrander et al, 1993 ¹⁵	25/1,158 (2.3%)

* Diagnosed by DBPCFC.

Table 3. Prognosis of Cow's Milk Allergy in Prospective Unselected Series

Study	Number	Recovery	Other FA/I	Inhalant allergy
Jakobsson et al, 1979	20	60% at 2 y	60%	
Bock, 1987	25	84% at 3 y		
Høst et al, 1990	39	87% at 3 y	54%	28%
Høst et al, 1996	39	92% at 10 y	18%	48%

FA/I, food allergy/intolerance.

days. Most often, the late reactions are non-IgE-mediated. Anaphylaxis attributable to CMP was reported in 9% of infants with CMPA in one study.¹⁷ Based on clinical and immunologic types of reactions, some authors have classified patients into three groups: immediate onset reactors, intermediate reactors, and late reactors.¹⁸⁻²¹ However, patterns of reactivity may vary because of different exposure levels and different time intervals between exposures. Recently, organ-specific manifestations of cow's milk allergy such as gastroesophageal reflux, allergic eosinophilic gastroenteritis, and constipation as a manifestation of allergic eosinophilic proctitis have become of increased scientific interest.^{3,22,23} There is some controversy on the underlying mechanism for constipation caused by CMPA,²⁰ but in selected patients with CMPA, allergic eosinophilic colitis has been demonstrated.²³

Gastrointestinal hypersensitivity to foods including cow's milk represents a pattern depending on the age of the individual (infants to children), the anatomical sites (esophagus, ventricle, small intestine, colon, and rectum), and the continuum of reactivity from IgE-mediated reactions to non-IgE-mediated reactions.^{2,3} It is beyond the scope of this review to discuss these gastrointestinal reactions to CMP in further detail. There is some evidence that otitis media with effusion in a subset of patients may be caused by allergy in the middle ear because of CMPA.²⁴

PROGNOSIS

Only a few reports have focused on the clinical course in prospective observational studies of primarily unselected infants.^{11,13,25} In these studies the overall prognosis of CMPA was good with a total recovery of 45 to 56% at 1 year, 60 to

77% at 2 years, 84 to 87% at 3 years, and approximately 90 to 95% at 5 and 10 years (Table 3). Other investigators have reported on the prognosis of CMPA in selected groups of infants (Table 4).²⁶⁻³⁴ A very high recovery rate of 100% in children with CMP gastroenteropathy under the age of 2 years old has been reported.²⁶ In a long-term followup study of 206 infants with CMPA, a recovery rate of approximately 98% was found at 15 years.²⁷ In other studies with a shorter followup period, varying recovery rates between 33 and 87% have been found. These varying results probably reflect differences in composition of the materials, study design, diagnostic criteria, age at entry into the studies, and the duration of followup period. With increasing age at inclusion, a lower proportion of still intolerant children will develop tolerance to CMP. Further, some studies have demonstrated that infants with high IgE levels to CMP have a lower rate of recovery than infants with non-IgE-mediated reactions.⁷

Adverse reactions to other foods have been reported in 31 to 75% of children with CMPA (Tables 3 and 4). The most frequent reactions are against egg, soy, peanut, citrus, fish, and cereals.⁷ Interestingly, up to 10% of children with CMPA may also react to bovine protein in bovine meat.³⁵ The varying frequencies of associated food allergy mainly reflect different eating habits including age at introduction of certain foods.

Development of allergy against inhalant allergens occurs mostly in infants with high levels of specific IgE to CMP. In these infants, inhalant allergy particularly develops against substances to which the children have been exposed from early infancy, ie, house-dust mites, cat, and dog.⁷ In a long-term followup study,²⁷ inhalant allergy was reported in up to

Table 4. Prognosis of Cow's Milk Allergy in Prospective Selected Series of Infants

Study	Number	Followup period	Recovery	Other FA/I	Inhalant allergy
Clein, 1958	206	0-15 y	98%		80%
Kuitunen et al, 1975	54*	0-2 y	100%		
Hill et al, 1979	17	0-3 y	71%	41%	
Dannaeus et al, 1979	47	0.5-4.7	87%		
Hill et al, 1989	47	0.5-3.25 y	38%		
Bishop et al, 1990	97	>5 y	78%	75%	40% asthma
James et al, 1992	29	3-6 y	38%		
Hill et al, 1993	98	2-4 y	33%		
Sprinkelman, 1999	93	0-7 y		31%	31% asthma 19% rhinitis

* CMP gastroenteropathy.

FA/I, food allergy/intolerance.

80% of children with CMPA before they had reached the age of puberty. More recent studies have confirmed these findings.^{7,25,28} In a Danish prospective study,²³ followup investigation at the age of 10 years showed a cumulated incidence of adverse reactions to other foods in 54%, and 18% were still intolerant to other foods at 10 years. Asthma and/or rhinoconjunctivitis had developed in approximately 50%. Only three children (8%) were still intolerant to CMPA at 5 and 10 years. Children with IgE-mediated reactions had an increased risk of persisting adverse reactions to other foods, asthma and rhinoconjunctivitis.^{7,25}

CONCLUSION

The incidence of CMPA in infancy seems to be approximately 2 to 3% in developed countries. Symptoms suggestive of CMPA are seen in approximately 5 to 15% of infants, but in approximately 2 of 3 of these instances a cause-effect relationship between cow's milk and symptoms can be disproven by proper elimination/milk challenge procedures. CMPA develops in early infancy, rarely after 12 months of age. The onset of disease is in most cases closely related to the time of introduction of cow's milk products. The majority have two or more symptoms from two or more organ systems, 50 to 70% have cutaneous symptoms, 50 to 60% gastrointestinal symptoms, and approximately 20 to 30% respiratory symptoms. The gastrointestinal manifestations of food allergy reflect a continuum from clearly IgE-mediated to mixed reactions dominated by eosinophilic granulocytes as effector cells to clearly non-IgE-mediated reactions. The overall prognosis of CMPA in infancy is good with an overall remission rate of approximately 85 to 90% at 3 years and a remission of 100% of gastrointestinal symptoms. However, an early increased IgE response to CMP is associated with an increased risk of persisting allergy to CMP, development of associated reactions to other foods, especially egg, and development of asthma and rhinoconjunctivitis later in childhood.

Early development of IgE-mediated CMP is predictive of subsequent development of allergy to environmental inhalant allergens and should lead to undertaking preventive measures.

REFERENCES

- Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813–824.
- Metcalfe DD, Sampson HA. Workshop on experimental methodology for clinical studies of adverse reactions to foods and food additives. *J Allergy Clin Immunol* 1990;86:421–442.
- Sampson HA, Anderson JA. Summary and recommendations: Classification of gastrointestinal manifestations due to immunological reactions to foods in infants and young children. *J Pediatr Gastroenterol Nutr* 2000;30:S87–S94.
- Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988;82:986–997.
- 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.
- Niggemann B, Wahn U, Sampson HA. Proposals for standardization of oral food challenge tests in infants and children. *Pediatr Allergy Immunol* 1994;5:11–13.
- Høst A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. *Pediatr Allergy Immunol* 1994;5(Suppl):1–36.
- Vendel S. Cow's milk idiosyncrasy in infants. *Acta Paediatr Scand* 1948;35:1–37.
- Halpern SR, Sellars WA, Johnson RB, et al. Development of childhood allergy in infants fed breast, soy, or cow milk. *J Allergy Clin Immunol* 1973;51:139–151.
- Gerrard JW, Mackenzie JW, Goluboff N, et al. Cow's milk allergy. Prevalence and manifestations in an unselected series of newborn. *Acta Paediatr Scand* 1973;234:1–21.
- Jacobsson O, Lindberg T. A prospective study of cow's milk protein intolerance in Swedish infants. *Acta Paediatr Scand* 1979;68:853–859.
- Hide DW, Guyer BM. Cow's milk intolerance in Isle of Wight infants. *Br J Clin Pract* 1983;37:285–287.
- 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.
- Høst A, Husby S, Østerballe 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, characterization of bovine milk protein in human milk. *Acta Paediatr Scand* 1988;77:663–670.
- Schrander JJ, Bogart JH, Forget PP, et al. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. *Eur J Pediatr* 1993;152:640–644.
- Eggesbo M, Botten G, Halvorsen R, Magnus P. The prevalence of CMP/CMPI in young children: the validity of parentally perceived reactions in a population-based study. *Allergy* 2001;56:393–402.
- Goldman AS, Anderson DW Jr, Sellars WA, et al. Milk allergy. I. Oral challenge with milk and isolated milk proteins in allergic children. *Pediatrics* 1963;32:425–443.
- Hill DJ, Ball G, Hosking CS. Clinical manifestations of cow's milk allergy in childhood. I. Association with in vitro cellular immune responses. *Clin Allergy* 1988;18:469–479.
- Hill DJ, Firer MA, Shelton MJ, Hosking CS. Manifestations of milk allergy in infancy: clinical and immunological findings. *J Pediatr* 1986;109:270–276.
- Hill DJ, Ford RP, Shelton MH, Hosking CS. A study of 100 infants and young children with cow's milk allergy. *Clin Rev Allergy* 1984;2:125–142.
- Hill DJ, Duke AM, Hosking CS, Hudson IL. Clinical manifestations of cow's milk allergy in childhood. II. The diagnostic value of skin tests and RAST. *Clin Allergy* 1988;18:481–490.
- Iacono G, Cavataio F, Montalto G, et al. Intolerance of cow's milk and chronic constipation in children. *N Engl J Med* 1998;339:1100–1104.
- Daher S, Tahan S, Solé D, et al. Cow's milk protein intolerance and chronic constipation in children. *Pediatr Allergy Immunol* 2001;12:339–342.
- Hurst DS, Venge P. Evidence of eosinophil, neutrophil, and mast-cell mediators in the effusion of OME patients with and without atopy. *Allergy* 2000;55:435–441.
- Høst A, Halken S. A prospective study of cow milk allergy in

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- Danish infants during the first 3 years of life. Clinical course to clinical and immunological type of hypersensitivity reaction. *Allergy* 1990;45:587-596.
26. Kuitunen P, Visakorpi JK, Savilathi E, Pelkonen P. Malabsorption syndrome with cow's milk intolerance. Clinical findings and course in 54 cases. *Arch Dis Child* 1975;50:351-356.
27. Clein NW. Cow's milk allergy in infants and children. *Int Arch Allergy* 1958;13:245-256.
28. Hill DJ, Davidson GP, Cameron DJ, Barnet GL. The spectrum of cow's milk allergy in childhood: clinical, gastrointestinal and immunological studies. *Acta Paediatr Scand* 1979;68:847-852.
29. Dannaeus A, Johansson SG. A follow-up study of infants with adverse reactions to cow's milk. I. Serum IgE, skin test reactions and RAST in relation to clinical course. *Acta Paediatr Scand* 1979;68:377-382.
30. Hill DJ, Firer MA, Ball G, Hosking CS. Recovery from milk allergy in early childhood. Antibody studies. *J Pediatr* 1989;114:761-766.
31. Bishop JM, Hill J, Hosking CS. Natural history of cow milk allergy. Clinical outcome. *J Pediatr* 1990;116:862-867.
32. James JM, Sampson HA. Immunologic changes associated with the development of tolerance in children with cow milk allergy. *J Pediatr* 1992;121:371-377.
33. Hill DJ, Firer MA, Ball G, Hosking CS. Natural history of cow's milk allergy in children: immunological outcome over 2 years. *Clin Exp Allergy* 1993;23:124-131.
34. Sprickelman AB. Cow's milk protein allergy or intolerance: a prospective follow-up study [thesis]. University of Groningen, The Netherlands, 1999.
35. Werfel SJ, Cooke SK, Sampson HA. Clinical reactivity to beef in children allergic to cow's milk. *J Allergy Clin Immunol* 1997;99:293-300.¹

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