Allergen Data Collection - Update:
Cow's Milk *(Bos domesticus)*

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Abstract

Cow's milk allergy (CMA) can be defined as any adverse reaction mediated by immunological mechanisms to cow's milk proteins. CMA can be divided in IgE-mediated reactions (IgE-CMA) and non-IgE-mediated reactions (non-IgE-CMA) which may involve other immunoglobulins, immune complexes and cell-mediated reactions. Patients with non-IgE-CMA and digestive symptoms can present with the following well defined clinical pictures: milk- induced enterocolitis, milk- induced proctitis, milk-induced enteropathy, or eosinophilic allergic gastro-enteritis. CMA should be differentiated from cow's milk intolerance (CMI) reactions due to lactase deficiency or other non immune mediated causes which are not subject of the present review. Most CMA has its onset in the first year of life, and becomes apparent at the time of weaning from breastfeeding.
Prevalences of CMA range from 1.6% to 2.8% in randomly selected children younger than 2 years of age (elimination / challenge proven). Oral tolerance is frequently acquired in about 50 to 90% of children with CMA within the first 6 years of life. However, severe CMA may persist into adulthood. The frequency of sensitization to cow's milk in adults has recently been estimated by RAST to be 0.7% and 1.2% in Scandinavian countries.

According to the onset of symptoms after milk ingestion CMA can be classified as immediate or delayed-type. The clinical picture can vary from mild to severe, involving the skin (eczema, hives, angioedema), gastrointestinal tract (oral pruritis, colic, vomiting, diarrhea, constipation), respiratory tract (cough, stridor, wheezing), and cardiovascular system (anaphylactic shock).
No single laboratory test is diagnostic of CMA. Clinical manifestations supported by skin tests and in vitro parameters are valuable. The diagnosis is confirmed by well-defined elimination and subsequent challenge procedures. If there is evidence of anaphylaxis, challenge should be avoided. The inadvertent ingestion of small amounts of cow's milk allergens hidden in foods can result in severe life- threatening clinical reactions. Cow's milk allergens could be present in breast milk, infant formulas, milk and milk products like cheese and yogurt, as well as in "non-dairy" foods occurring as contaminants or unlabeled additives. The most effective treatment of CMA is allergen avoidance. Besides the optimal choice of breast milk, suitable milk substitutes in the nutrition of infants with CMA are soy hydrolyzed formulas, extensively casein and whey hydrolyzed formulas, and amino acid formulas. The exact frequency of sensitization to soy protein in children with CMA is still controversial. Soy allergy seems to be rare in IgE-CMA, while approximately 60% of children with milk- induced enterocolitis are sensitive to soybean. However, severe anaphylactic reactions to extensively hydrolyzed casein and partially hydrolyzed whey formulas can occur in highly sensitized infants with IgE-mediated cow's milk allergy. Due to the high homology of protein composition sheep's and goat's milk are cross-reactive in approximately 80% of subjects with CMA while mare's milk is only rarely cross-reactive with cow's milk (4% in subjects with CMA). In addition, sheep's milk may cause severe IgE-mediated allergic reactions in children not affected by CMA. IgE antibodies from children allergic to cow's milk are capable of recognizing milk proteins from mammals bred in European countries (ewe, goat, buffalo). Cross-reactivity of camel's milk proteins has not been recognized. Therefore, due to clinically important residual allergenicity in some hypoallergenic formulas and milk allergen cross-reactivity between species, clinical testing in a safe

medically-supervised environment is necessary in each cow's milk sensitive infant before use.

In infants and children the major cow' s milk allergens are casein (CAS), beta- lactoglobulin (beta-LG), and alpha- lactalbumin (alpha-LA). Caseins (alpha-, beta-, kappa-CAS) are the most important in children and adults. Other allergens involved in CMA are bovine serum albumin (BSA) and bovine immunoglobulins. Several IgE- binding epitopes of alpha-LA, beta-LG, alpha- and beta-CAS have been described. Knowledge of the immunodominant epitopes of the major allergens may be useful in identifying children who will have persistent CMA and children who are likely to outgrow CMA.
The present data collection summarizes the following topics in tabular form: prevalences of CMA, diagnostic and therapeutic features, molecular biological and allergenic properties of cow' s milk allergens, stability and hidden presence of allergens, the use of infant formulas in therapy and prevention of CMA and other atopic diseases.
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Contents

1 Prevalence of Cow's Milk Allergy

1.1 General Population

Prevalences within the author's selected populations are listed. Those that are assigned randomly selected ("unselected") with numbers more than 500 may be regarded as representative of the "general population". Inclusion criteria may involve circumstances not related to atopic predisposition according to current knowledge.

Country / Subjects	Sensitivity / Allergy to	References
Australia, Melbourne 620 unselected children (age of <2 years)	cow's milk 2.0%	Hill et al. 1997, 1999
Brazil, Campinas 114 newborns at term	cow's milk 1.8% (prospective follow-up)	Lopez et al. 1999
Canada 3000 unselected children (private practice)	cow's milk 0.3% (case history)	Collins-Williams 1956
Canada 787 unselected children (<3 years of age)	cow's milk 7.5% (2 open challenges)	Gerrard et al. 1973
Denmark, Odense a) 1749 unselected newborns b) 52% exclusively brest-fed infants	a) cow's milk 2.2% b) cow's milk 1.0% (elimination/challenge)	Host et al. 1988 Host & Halken 1990
Estonia 251 consecutive born infants	cow's milk 1.2%, 0.8% (SPT) at 6 and 12 months	Julge et al. 1997
Estonia, Tartu 237 consecutive born infants (1993-94)	cow's milk 12, 21%, 26%, and 23% at 0.5, 1, 2, and 5 years of age (beta-LG specific RAST >/= class 1) cow's milk 1.7%, 0.9%, and 0% at 0.5, 1, and 2 years of age (SPT)	Julge et al. 2001
Finland unselected children (<6 months of age)	cow's milk 1.3-1.9% (with intestinal form only: 0.06%)	Kuitunen et al. 1985
Finland, Helsinki 866 children from well-baby clinic (1-6 years of age)	cow's milk 2-5% (open challenge)	Kajosaari 1982
Finland, Helsinki 6209 infants followed prospectively from birth	cow's milk 1.9% (challenge at a mean age of 6.7 months)	Saarinen & Savilahti 2000
France a) 33110 persons who answered a questionnaire addressed to a representative sample of the French population (age of <61 years) b) 1121 persons with food allergies selected from group a) received a second questionnaire (study period 1997-98)	a) food allergy 3.2% b) cow's milk 8% (0.26% in group a) (2 phase survey, questionnaires)	Kanny et al. 2001
Germany 1235 unselected preschool children (5-6 years)	cow's milk 3.9% (SPT)	Schäfer et al. 1999
Germany, Augsburg 1537 subjects between 25 and 74 years of age (study period from 1997 to 1998)	cow's milk 3.8% (SPT) cow's milk 2.3% (corresponding frequency estimates for the representative study base, n=4178)	Schäfer et al. 2001
Iceland, Reykjavik 502 unselected adults	cow's milk 1.2% (RAST)	Gislason et al. 1999

Japan 1336 children in nusery school < 6 years of age (12.6% reported symptoms of immediate-type food allergy)	cow's milk 4.0% (questionnaire)	Iikura et al. 1999
Netherlands, Maastricht 1158 unselected newborns (followed prospectively from birth to 1 year of age)	cow's milk 2.8% (elimination / challenge tests)	Schrander et al. 1993b
Norway, Oslo 2721 unselected children (population-based cohort) a) point prevalence at age of 2.5 years b) cumulative prevalence at age of 2 years c) prevalence of CMA in children without parents perceived reactions to milk, but perceived reaction to other food (egg) and d) prevalence of CMA in children with no perceived reaction to any food, but reported chronic conditions which could be due to food	a) cow's milk 1.1%* b) cow's milk 3.2% c) cow's milk 0.2% d) cow's milk 1.8% (parentally perceived reactions followed by stepwise diagnostic procedure including diet trials at home, SPT, and open challenge and DBPCFC)	Eggesbø et al. 2001 * according to authors underestimate, as unrecognized reactions were detected
Spain, Valencia 1663 unselected newborns (follow-up to 1 year of age)	cow's milk 0.36% (clinical history, SPT, RAST)	Sanz Ortega et al. 2001
Sweden 1397 unselected adults (20-44 years of age)	cow's milk 1.0% (RAST, questionaire)	Björnsson et al. 1996
Sweden, Linköping healthy girls at birth and mean age of 3, 8, 25, and 48 months (n=57-86, all Rh negative)	cow's milk 0%, 4.6%, 9.0%, 0%, 1.2% (RAST)	Hattevig et al. 1984
Sweden, Malmö 1079 unselected children (age at onset 2-44 weeks)	cow's milk in 1.9% (elimination / challenge tests)	Jakobsson & Lindberg 1979
Sweden, Uppsala 414 unselected adults	cow's milk 0.7% (RAST)	Gislason et al. 1999
Turkey, Adana 1348 unselected children (age 15 weeks)	cow's milk in 1.6% (elimination / challenge tests)	Altintas et al. 1995
UK 16420 randomly selected adults (age of >15 years)	cow's milk 0.71% (interview survey, questionnaire)	Emmett et al. 1999
UK, Isle of Wight 609 unselected newborns	cow's milk 2.5% (case history)	Hide & Guyer 1983
UK, Isle of Wight unselected children (birth cohort of 1456 consecutively born children)	a) cow's milk 4.1% (SPT) b) cow's milk appr. 1.5% (SPT at age of 4 years, n=981)	a) Dean 1997 b) Arshad et al. 2001
USA appr. 1000 unselected infants (private practice)	cow's milk appr. 7% (case history)	Clein 1951
USA 403 unselected infants (well-baby clinic)	cow's milk 1% (history, skin test)	Bachman & Dees 1957
USA 299 unselected newborns	cow's milk 1% (history, skin test)	Mueller et al. 1963
USA, Ann Arbor, MI 66598 children from randomly selected public elementary schools	cow's milk 1.4% (questionnaire, school completed)	Rhim & Morris 2001
USA, Denver, CO 480 unselected children (age of 0 to 3 years)	cow's milk 2.2% (challenge tests)	Bock 1987

1.2 Subjects with Atopic or Other Diseases

Country / Subjects	Sensitivity / Allergy to	References
Finland, Oulu 57, 43, and 42 children with atopic dermatits	cow's milk 12%, 9.3%, and 7.1% in patients < 1 year, 1-3 years, and 3-15 years of age (SPT)	Hannuksela 1987
Finland, Tampere 113 infants with atopic eczema (age of 2-24 months)	cow's milk 48% (oral challenge)	Kekki et al. 1997
France 81 cases of anaphylactic shock to food (from 1991-1992)	cow's milk 6.5%	Moneret-Vautrin & Kanny 1995
France 80 cases of food- related anaphylaxis (from 1993-97)	cow's milk 6.3% (reported to CICBAA databank)	European Commission 1998
France 45 children with severe food allergies enrolled in a personalized care project in schools	11% cow's milk (SBPCFC or DBPCFC)	Moneret-Vautrin et al. 2001
France, Pierre Benite a) 580 patients with adverse reactions to food b) 60 cases of anaphylaxis (study period 1984-92)	a) cow's milk 18% b) cow's milk 3.3%	Andre et al. 1994
France, Nancy and Toulouse 544 food allergic children	cow's milk 13%, goat's milk 0.55% (food challenge)	Rance et al. 1999b
France, Toulouse 142 food allergic children	cow's milk 9.2 % (labial food challenge)	Rance & Dutau 1997
France, Toulouse 378 food allergic children	cow's milk 12% (food challenge)	Rance et al. 1999a
Germany,Berlin 107 children with atopic dermatitis (and suspicion of food allergy)	cow's milk 51% (n=92, DBPCFC)	Niggemann et al. 1999b
Germany,Bonn 150 food allergic children (egg white, milk, cod fish, wheat, peanut and/or soybean)	cow's milk 52.0% (RAST)	Liappis & Starke 1999
Italy, Bari 134 patients with atopic dermatitis	cow's milk 13% (case history), 21% (RAST)	Bonifazi et al. 1978
Italy, Florence 54 episodes of food-dependent anaphylaxis in 44 children (age of 1 month to 16 years) (from 1994-1996)	cow's milk 22% goat's milk 4%	Novembre et al. 1998
Italy, Milan 202 with chronic urticaria and suspected food allergy	cow's milk 1.0% (DBPCFC)	Pigatto & Valsecchi 2000
Italy, Palermo 204 children (median age of 6.3 months) with gastroesophageal reflux	cow's milk 9.3% (history) cow's milk 46% (RAST, SPT, eosinophils) cow's milk 42% (challenge test)	Iacono et al. 1996
Italy, Rome 371 children with food allergy	cow's milk 54% (RAST)	Giampietro et al. 1992
Japan, Gifu / Nabu children with asthma and/or atopic dermatitis from a) Gifu (n = 167) and b) Nanbu (n = 146)	cow's milk a) 8.1% (Nanbu), b) 19% (Gifu) (RAST)	Agata et al. 1994

Japan, Kochi 200 patients with atopic dermatitis and suspected food allergy	cow's milk 52% (food challenge)	Ogura et al. 2001
Japan, Tokyo 39 children with positive food challenge	cow's milk 28% (food challenge)	Iwasaki et al. 1994
Malaysia, Kuala Lumpur 148 adults with symptoms of nasal congestion and rhinorrhea	cow's milk 12% (SPT)	Gendeh et al. 2000
Netherlands 131 cases of food- induced anaphylaxis (from 1993-1997)	cow's milk 8.4% (survey, reported to the TNO Nutrition and Food Research Institute)	European Commission 1998
Netherlands, Rotterdam 91 patients with atopic dermatitis	cow's milk 47% (SAFT)	Oranje et al. 1992
Poland 163 food allergic infants	cow's milk 64% (RAST)	Hofman 1994
Poland, Warshaw 153 hospitalized infants with respiratory symptoms	cow' milk 21%	Maciejewski et al. 1995
Singapore 124 children with food-induced anaphylaxis	cow's milk and/or egg 11%	Goh et al. 1999
South Africa, Cape Town 112 children with atopic dermatitis (age of 5 months to 13 years)	cow's milk 20% (reported by parents)	Steinman & Potter 1994
Spain, Madrid 355 food allergic children	cow's milk 25% (SPT, RAST)	Crespo et al. 1995
Spain, Pamplona 74 patients with atopic dermatitis	cow's milk 37% (SPT, RAST, Histamine Release)	Resano et al. 1998
Sweden a) 61 cases and b) 55 cases of food- induced anaphylaxis (from 1994-1996)	a) cow's milk 20% (reported to the National Food Administration) b) cow's milk 5.5% (Hospital Reports)	European Commission 1998
Switzerland, Geneva 74 children with atopic dermatitis (age of 6 months to 16 years, median 2.5 years)	cow's milk 19% (SPT) cow's milk 15% (history, RAST, and challenge)	Eigenmann & Calza 2000
Switzerland, Zurich 402 food allergic adults (study period 1978-87)	cow's milk 16% (cheese only 6.2%, milk only 3.5%)	Wüthrich 1993
Switzerland, Zurich 383 food allergic patients (study period 1990-94)	cow's milk 11% cheese 5.7%	Etesamifar & Wüthrich 1998
Thailand 100 asthmatic children	milk 2% (SPT)	Kongpanichkul et al. 1997
Turkey, Erdine 50 asthmatic children (age of 1.5 to 6 years) with specific serum IgE to foods (egg white, milk, codfish, wheat, peanut and/or soybean)	cow's milk 18% (SPT)	Yazicioglu et al. 1999
UK, London 100 patients with food intolerance	cow's milk 46%, cheese only 5% (repeated challenge)	Lessof et al. 1980
UK, Manchester 172 patients expierenced anaphylactic reactions to foods (from 1994-1996)	cow's milk 1.7% (suspected cause of patients' worst reaction)	Pumphrey & Stanworth 1996

USA, Baltimore, MD 196 food-allergic patients with atopic dermatitis	cow's milk 50% (n=109, DBPCFC)	Sampson & Ho 1997
USA, Baltimore, MD 11 beef-allergic patients (DBPCFC)	cow's milk 73% (DBPCFC)	Werfel et al. 1997a
USA, Baltimore, MD 63 patients with atopic dermatitis (age of 6 months to 20 years)	cow's milk 11% (history, RAST, and challenge)	Eigenmann et al. 1998
USA, Boston, MA 279 adults with exercise- induced anaphylaxis (study period 1980-98)	cow's milk 4% (reported trigger)	Shadick et al. 1999
USA, Denver, CO a) 74 age of <3 years b) 111 age of 3-19 years	a) cow's milk 57% (DBPCFC) b) cow's milk 14% (DBPCFC)	Bock & Atkins 1990
USA, Durham, NC a) 113 food allergic children with atopic dermatitis b) 63 DBPCFC positive children of a)	a) cow's milk 23% (SPT) b) cow's milk 17% (DBPCFC)	Sampson & McCaskill 1985
USA, Little Rock, AR 165 patients with atopic dermatitis	cow's milk 19% (SPT) from which 50% were DBPCFC-positive	Burks et al. 1998
USA, New Haven, CT 98 infants and children with multiple gastrointestinal allergies	soy and milk 62% milk and gluten 3%	Gryboski & Kocoshis 1980
USA, New Haven, CT 38 children with ulcerative colitis (age of <10 years)	cow's milk 13% (history)	Gryboski 1993
USA, OH 148 respiratory-allergic children with reproduced symptoms after food challenge	cow's milk 29%	Ogle et al. 1980

1.3 Prevalence of Associated Allergies

Country / Subjects	Sensitivity / Allergy to	References
Australia, Parkville 42 children with CMA (followed for 2 years)	egg 67%, peanut 55% (challenge test)	Hill et al. 1994
Finland, Helsinki 19 children with CMA	soybean 32%	Paganus et al. 1992
France, Gif Sur Yvette / Paris 58 patients with CMA and specific IgE to bovine CAS	sheep's milk: ovine CAS 98% (RAST) goat's milk: caprine CAS 93% (RAST) rat's milk CAS 59% (RAST) rabbit's milk CAS 57% (RAST)	Bernard et al. 1999

Germany, Augsburg 59 subjects sensitized to cow's milk in SPT (25-74 years of age) (study period from 1997 to 1998)	**Foods**	**SPT**	**Aeroallergens**	**SPT**	Schäfer et al. 2001
	egg	57%	grass pollen	75%	
	peanut	17%	birch pollen	76%	
	pork	40%	rye pollen	80%	
	mackerel	56%	mugwort	73%	
	celery	15%	Alternaria	63%	
	hazelnut	14%	Cladosporium	63%	
	wheat	29%	cat	81%	
	soybean	36%	dog	71%	
	crab	27%	house duste mite	73%	
Italy, Rome 26 children with CMA (DBPCFC)	goat's milk 92% (DBPCFC)				Bellioni-Businco et al. 1999
Italy, Rome 25 children with CMA (DBPCFC)	mare's milk 8% (SPT) mare's milk 4% (DBPCFC)				Businco et al. 2000
Sweden, Malmö 20 infants with CMA (age of <12 months)	soybean in 35%				Jakobsson & Lindberg 1979
Thailand, Bangkok cow's milk-sensitive children	soybean 17%				Harikul et al. 1995
USA, New Haven, CT 98 infants and children with multiple gastrointestinal allergies	soy and milk 62% milk and gluten 3%				Gryboski & Kocoshis 1980
USA, San Diego, CA cow's milk-sensitive infants	soybean 25%				Wilson & Hamburger 1988
USA, San Diego, CA 93 children with CMA (<3.5 years)	soybean 14 % (DBPCFC, open challenge, or convincing history of an anaphylactic reaction)				Zeiger et al. 1999

2 Outgrowing of Cow's Milk Allergy

Country / Subjects	Sensitivity	References
Australia, Victoria 47 with CMA (age of 3-66 months) with onset of symptoms a) <1 hour (n=15), b) 1 to 20 hours (n=24) or, c) >20 hours (n=8)	Oral tolerance acquired at follow-up of 16 months in: a) 40%, b) 42%, c) 25% of patients	Hill et al. 1989
Australia, Victoria 97 children with CMA	Tolerance in 28% by 2 years, in 56% by 4 years, and 78% by 6 years of age (DBPCFC)	Bishop et al. 1990
Canada 150 children with CMA	Tolerance in 6% by 1 year, 20% by 2 years, in 30% by 3 years, and 53% by 12 years of age	Gerrard et al. 1967
Denmark, Odense 39 children with CMA	Total recovery in 56% by 1 year, 77% by 2 years, and 87% by 3 years of age; cow's milk allergy persisted in 24% of patients with early IgE sensitization to cow's milk	Host & Halken 1990
Finland, Oulu 56 children with CMA in infancy (re-examinations at the age of 10 years)	Positivity to cow's milk proteins: 66% by SPT 13% by RAST 7.1% by clinical reactivity	Tikkanen et al. 2000

Finland, Tampere 37 patients with a history of CMA (mean age of 28 months)	Oral tolerance acquired at follow-up of 13 months in 65% of patients	Isolauri et al. 1992
France, Nancy and Toulouse 68 children with CMA	Sensitivity to cow's milk according to age groups: 0-1 year in 22% 1-3 years in 56% 3-6 years in 19% 6-15 years in 2.9% (SPT and/or RAST, food challenge)	Rance et al. 1999b
Germany, Berlin and Freiburg 216 children of a prospective birth cohort (sensitization rates were estimated for the reference population of 4082 children by weighted analysis)	Point prevalence of sensitization: 1-3 years in appr. 5-6% 5 years in appr. 6-7% 6 years in appr. 5-6% Annual incidence of sensitization: 1 years in appr. 5-6% 2 years in appr. 4% 3 years in appr. 3-4% 5 years in appr. 1-2% 6 years in appr. 1-2% (Sensitivity to cow's milk during follow-up by RAST)	Kulig et al. 1999
Italy, Palermo 86 consecutive children with IgE-mediated or non-IgE-mediated CMA (median age at diagnosis 4 months)	Oral tolerance acquired in 30%, 55%, and 70% of children after 1, 2, and 3 years of cow's milk free diet, respectively (DBPCFC)	Carroccio et al. 2000b
Italy, Rome 37 children with CMA	Tolerance acquired in 68% at age of 2 years; 33% did not tolerate cow's milk at age of 6 years	Businco et al. 1985
Israel, Tel-Aviv 347 subjects sensitized to food (n=347)	**Sensitivity to cow's milk** / **RAST** 0-2 years 5.5% 3-5 years 4.3% 6-10 years 4.9% 21-30 years 2.3% >30 years 5.2% total 16.4%	Kornizky et al. 1999
Japan, Gifu 22 children with CMA and atopic dermatitis	41% Improvement rate in children aged from <1 year to >6 years	Iida et al. 1995
Netherlands, Groningen 23 children with CMA	Oral tolerance acquired in 13%, 48%, 74% and 78% of children at the age of 1, 2, 3 and 4 years, respectively	Olsder et al. 1995
Netherlands, Maastricht 37 children with CMA	Oral tolerance acquired in 15%, 22%, 51% and 67% of the children at the age of 1, 2, 3 and 4 years, respectively; 90% with initial IgE levels <10 kU/L and 47% with initial IgE >/= 10 kU/L became tolerant	Schrander et al. 1992
Switzerland, Zurich 34 adults with CMA	Oral tolerance acquired in 28% after 4 years of disease	Stoger & Wüthrich 1993
Turkey, Adana 21 children with CMA (age 15 weeks)	29% recovered within 2 years	Altintas et al. 1995
USA Food allergic patients	soy, egg, milk, wheat, and peanut: 26% loss (after 1 year of onset, DBPCFC)	Sampson & Scanlon 1989
USA, Baltimore, MD 29 children with CMA	Tolerance acquired in 38% at median age of 3 years (DBPCFC)	James & Sampson 199

3 Symptoms of Cow's Milk Allergy

Symptoms & Case Reports

systemic reactions
anaphylaxis (20, 21, 24, 36, 40, 46, 44, 54, 55, 56, 64, 70, 71, 76, 78, 82, 92, 93***, 96, 100), excercise induced anaphylaxis (55, 59, 62, 75), fatal reactions (47, 49**, 89)

cutaneous symptoms
angioedema (8, 18, 17, 44, 55, 78, 81, 100), angioneurotic edema (91), atopic dermatitis (22, 23, 24, 27, 35, 78, 87, 88, 92), contact urticaria (19), dermatitis (68), eczema (3, 6, 8, 9, 17, 25, 29, 30, 51, 69), eczematous lesions (91), erythema (29, 55, 88, 96), exanthema (6), red itchy eyes (100), hives (100), lips edema (10, 100), pruritus (2), redness (55), swelling of eyelids (55), urticaria (2, 6, 8, 10, 17, 18, 22, 23, 26, 30, 39, 44, 51, 55, 69, 78, 81, 87, 88, 91, 92), generalized urticaria (100), localized urticaria (100***), acute-onset urticaria (86, 100***), chronic urticaria (63)

gastrointestinal symptoms
abdominal cramps (2), abdominal distention (42), abdominal pain (44, 91, 92, 96), colic (3, 51, 68, 91, 92), infantil colic syndrome (1, 5, 6), colitis (57, 65), constipation (3, 68), chronic constipation (49, 52, 90), diarrhea (2, 3, 6, 10, 11, 15, 17, 25, 29, 39, 42, 44, 51, 68, 69, 92), chronic diarrhea (12, 74), gastric dysrhythmia (98), delayed gastric emptying (98), food protein-induced enterocolitis syndrome (absence of specific IgE) (72, 95), protein-sensitive enteropathy (94), eosinophilic colitis (31, 85), eosinophilic gastroenteritis (28, 99), gastroenteritis (11), gastro- oesophageal reflux (13, 58, 60, 67), morphologic lesion (15), nausea (44), proctitis (32), allergic proctocolitis (84), eosinophilic proctocolitis (97), progressive small bowel mucosal damage (26), occult intestinal bleeding (4), oropharyngeal itching / swelling (39, 44), oropharyngeal pruritus (73), edema of tongue (10, 100), acute pancreatitis (33), loose stools (69, 91), vomiting (2, 3, 6, 11, 17, 22, 25, 68, 69, 81, 83, 91, 92), protracted vomiting (92), in general (30, 78, 87)

respiratory symptoms
allergic alveolitis (7, 16), asthma (3, 10, 11, 18, 22, 39, 44, 45, 48, 50, 55, 70, 76, 83), bronchospasm (29), bronchial obstruction (91), bronchitis (6, 17), choking (100), conjunctivitis (76), conjunctival injection (100), cough (25, 51, 96), dyspnea (51, 55, 73), nasal blockade (73), allergic rhinitis (22), rhinitis (29, 44, 55, 81, 91), rhinoconjunctivitis (44, 45, 55), rhinorrhea (100), serious rhinorrhea (73), sneezing (73, 100), upper respiratory symptoms (100***), wheeze (25, 51, 68, 80, 87, 81, 100)

other symptoms
association with cytomegalovirus colitis* (66), infantile autism* (53), aversion (91), anal fistula and fissures (49), growth retardation / failure to thrive (3, 6), insomnia (14), iron deficiency anemia in 20-70% (11), irritability (91), lactic acidosis (79), Melkersson-Rosenthal syndrome* (61), migraine* (38), necrotizing enterocolitis (43), steroid- resistant nephrotic syndrome (41), recurrent otitis media (77), pallor (17), psychological disturbance (3), pulmonary hemosiderosis (34), sleep disturbances (91), tension-fatigue syndrome (37), lethargy (71)

* controversial / hypothetical, ** possibly due to partially hydrolyzed whey formula, *** mediated by skin contact

(1) Harris et al. 1977
(2) Bonifazi et al. 1978
(3) Buisseret 1978
(4) Ivady et al. 1978
(5) Jakobsson & Lindberg 1978
(6) Jakobsson & Lindberg 1979
(7) Chetty 1982
(8) Firer et al. 1982
(9) Taylor et al. 1982
(10) Businco et al. 1983a
(11) Podleski et al. 1984
(12) Businco et al. 1985
(13) Forget & Arends 1985
(14) Kahn et al. 1985, 1987
(15) Kuitunen et al. 1985
(16) Vergesslich et al. 1985
(17) Hill et al. 1986
(18) Koers 1986
(19) Salo et al. 1986
(20) Wüthrich & Hofer 1986
(21) Jarmoc & Primack 1987
(22) Host & Samuelsson 1988
(23) Prahl et al. 1988
(24) Businco et al. 1989
(25) Hill et al. 1989
(26) Iyngkaran et al. 1989
(27) Cantani et al. 1990
(28) Hill & Milla 1990
(29) Husby et al. 1990
(30) Isolauri et al. 1990
(31) Wilson et al. 1990
(32) Lake 1991
(33) de Diego et al. 1992
(34) Fossati et al. 1992
(35) James & Sampson 1992
(36) Jones et al. 1992
(37) Kondo et al. 1992
(38) Mylek 1992
(39) Norgaard & Bindslev-Jensen 1992
(40) Sampson et al. 1992
(41) Sieniawska et al. 1992
(42) Hayashi et al. 1993
(43) Michaud et al. 1993
(44) Stoger & Wüthrich 1993
(45) Bernaola et al. 1994
(46) Businco et al. 1994
(47) Malmheden Yman et al. 1994
(48) Rossi et al. 1994
(49) Tarim et al. 1994
(50) Vargiu et al. 1994
(51) Altintas et al. 1995
(52) Iacono et al. 1995a
(53) Lucarelli et al. 1995
(54) Moneret-Vautrin & Kanny 1995
(55) Wüthrich & Johansson 1995
(56) Wüthrich et al. 1995
(57) Armisen Pedrejon et al. 1996
(58) Cavataio et al. 1996
(59) Guinnepain et al. 1996
(60) Iacono et al. 1996
(61) Levy et al. 1996a
(62) Levy et al. 1996b
(63) Paranos & Nikolic 1996
(64) Tabar et al. 1996
(65) Weisselberg et al. 1996
(66) Jonkhoff-Slok et al. 1997
(67) Iacono et al. 1998a, 1998b
(68) Iacono et al. 1998c
(69) Jarvinen et al. 1998
(70) Kanny et al. 1998
(71) Laoprasert et al. 1998
(72) Sicherer et al. 1998
(73) Vila Sexto et al. 1998
(74) Altuntas et al. 1999
(75) Fiocchi et al. 1999
(76) Goh et al. 1999
(77) Juntti et al. 1999
(78) Rance et al. 1999b
(79) Rizk et al. 1999
(80) Yazicioglu et al. 1999
(81) Businco et al. 2000
(82) Eigenmann & Calza 2000
(83) Nucera et al. 2000b
(84) Patenaude et al. 2000
(85) Rossel et al. 2000
(86) Saarinen & Savilahti 2000
(87) Szabó & Eigenmann 2000
(88) Schade et al. 2000
(89) Bock et al. 2001
(90) Daher et al. 2001
(91) Eggesbø et al. 2001
(92) Järvinen et al. 2001
(93) Kawano et al. 2001
(94) Kokkonen et al. 2001a
(95) Marr et al. 2001
(96) Moneret-Vautrin et al. 2001
(97) Pumberger et al. 2001
(98) Ravelli et al. 2001
(99) Sicherer et al. 2001
(100) Tan et al. 2001

Percentage of Reactions

Symptoms / Ref.	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**	**(8)**	**(9)**	**(10)**	**(11)**	**(12)**	**(13)**
Anaphylaxis [%]	5	100			5				2		7.8		1
Cutaneous [%]				64		31	79	93		58			
+ Gastrointestinal										19			
+ Respiratory										13			
All 3 organ systems										4			
Atopic dermatitis	41		21					100		100	50		44
Conjunctivitis											3.1		4
Urticaria / Exanthema													52
Urticaria / Angio-oedema											28		
Angio-oedema		66			65				13				
Urticaria	10				100							73	
Generalized urticaria		69			45				10				
Contact urticaria		59			80								
Eczema					33				13				
Flare eczema												7	
Circumoral lesions									26				
Gastrointestinal [%]				59		50	42	65		4	7.8		20
Vomiting	34				13				41			14	
Diarrhoea	47				3				48			*	
Colic									14			*	
Colitis									4				
Abdominal pain	41											*	
Respiratory [%]				33		19	91	48		2		14	15
Allergic rhinitis	43		43		28				21			15	
Asthma	37	55	40										
Cough / Wheeze		48			65				29				
Other [%]	6												
Failure to thrive									22				
Gastro-oesophageal reflux									6				
Convulsion					2				2				
No. of patients	45	29	97	39	75	26	34	54	100	47	68	143	118

References

(1) Goldman et al. 1963a
(2) Schwartz et al. 1987
(3) Bishop et al. 1990
(4) Host & Halken 1990
(5) Schwartz 1991
(6) Schrander et al. 1993b
(7) Stoger & Wüthrich 1993
(8) Sampson & Ho 1997
(9) Hill et al. 1999
(10) Niggemann et al. 1999b
(11) Rance et al. 1999b
(12) Sporik et al. 2000
(13) Saarinen et al. 2001

Children with CMA
diagnosed by
(1) clinical history, oral challenge
(2) clinical history of anaphylactic reactions, RAST
(3) parents reported
(4, 6) elimination/challenge
(5) clinical history, SPT
(8, 10) DBPCFC
(11) labial food challenge
(12) DBPCFC; * together 21%
(13) open challenge

Adults with CMA
diagnosed by
(7) clinical history, RAST

Symptoms, Onset and Doses for Elicitation of Symptoms in IgE-mediated and non-IgE-mediated CMA

75 IgE-positive and 43 IgE-negative infants with CMA at open challenge (mean age of 6.7 months):

Symptoms	**IgE-positive**	**IgE-negative**
Anaphylactic reaction	1%	0%
Atopic dermatitis	28%	72%
Urticaria / Exanthema	76%	9%
Vomiting	9%	30%
Immediate vomiting (<2 h)	9%	9%
Continuous regurgitation	0%	21%
Diarrhoea	0%	23%
Rhinorrhoea	12%	16%
Cough / Wheeze	1%	14%
Allergic conjunctivitis	5%	2%
Multiple organ symptoms	19%	30%
Onset of Symptoms	**IgE-positive**	**IgE-negative**
< 2 hours	68%	16%
2-24 hours	25%	33%
> 24 hours	7%	51%
Cumulative Dose of Cow's Milk	**IgE-positive**	**IgE-negative**
< 20 mL (appr. 750 mg protein)	59%	14%
20-200 mL (appr. 0.75-7.5 g protein)	32%	37%
> 200 mL (appr. 7.5 g protein)	9%	49%

Saarinen & Savilahti 2000

Onset of Symptoms

Type of Reactions	**(1)**	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**
immediate	53%		46%	64%		
delayed reactions	47%		54%	28%		
both				8%		
< 30 min					77%	
< 2 hours					23%	49%
< 6 hours		51%				
within 2-24 hours						28%
within 6-12 hours		13%				
within 12-24 hours		10%				
> 24 hours		26%				23%
No. of patients	47	125	50	47	67*	118

* patients selected because of symptoms suggesting immediate-type CMA

(1) Björkstén et al. 1983
(2) Ventura & Greco 1988
(3) Sutas et al. 1997
(4) Niggemann et al. 1999b
(5) Garcia-Ara et al. 2001
(6) Saarinen et al. 2001

Children with CMA
diagnosed by
(1) clinical history
(2) elimination / challenge
(3, 4) DBPCFC
(5, 6) open challenge

Onset of Symptoms

Type of Reactions	At diagnosis	1 year	2 years	3 years of follow-up
immediate (<45 min)	8.1%	5.0%	7.8%	0%
intermediate (1-24 h)	77%	67%	51%	31%
delayed (24-72 h)	15%	23%	26%	38%
very delayed (>72 h)*	0%	5.0%	15%	31%
No. of symptomatic patients	86	60	39	26

86 consecutive children with IgE-mediated or non-IgE-mediated CMA (median age at diagnosis 4 months, DBPCFC)
* symptoms of constipation, dermatitis, and wheezing

Carroccio et al. 2000b

Onset of Symptoms

Immediate onset reactions occurred in 43% of positive challenges after a cumulative time of 36 min (3 min to 2.0 h) and late onset reactions in 57% of positive challenges after a cumulative time of 54 h (2 to 192 h) (DBPCFC, 59 children with CMA)

Sütas et al. 2000

Age at Onset of CMA

Onset in 30% of children with CMA in the first month of life (1) and in 96% at <1 year of age (2)

(1) Savilahti 1981
(2) Bock 1987

Cluster Groups

3 clusters of patients with CMA using a K-means algorithm (data of case history and effects of a standardized milk challenge):

Percentage of patients	Onset of Symptoms	Symptoms	Diagnostics
a) 27-32%	after <45 min	predominantly urticarial and angioedematous eruptions	positive skin tests, elevated total and milk specific serum IgE
b) 51-53%	45 min to 20 hours	pallor, vomiting, or diarrhea	relatively IgA deficient* (1)
c) 17-20%	after >20 hours	eczematous or bronchitic or diarrheal symptoms	positive skin tests and elevated specific IgE only in patients with eczema

*milk- specific IgA, IgG and IgM levels similar in all groups and controls (2)

- (1) 100 cow's milk allergic children (mean age of 6 month)
- (2, 3) 47 cow's milk allergic children (age 4-66 months)

(1) Hill et al. 1986
(2) Firer et al. 1987
(3) Hill et al. 1989

Threshold for Elicitation of Symptoms

Challenge Tests:

- Amounts of cow's milk inducing symptoms ranged from 5 g to 250 g (DBPCFC) (1)
- Amounts of milk (dry weight) inducing symptoms: </= 500 mg in 55% (including 26 and 3 positive challenges with 250 mg and 100 mg, respectively) (DBPCFC, 196 food allergic children with atopic dermatitis) (4)
- A cumulative dose of 0.78 mg cow's milk powder (0.01 to 6.1 mg) elicited immediate onset reactions in 43% of positive challenges and a cumulative dose of 31.2 mg cow's milk powder (4 to 100 mg) elicited late onset reactions in 57% of positive challenges (DBPCFC, 59 children with CMA) (5)
- A dose of 2 to 25 mL of cow's milk infant formula elicited symptoms in 58%, a dose of 50 mL in 13%, of 100 mL in 9.2%, and a dose of >100 mL in 7.9% of 76 infants with CMA (age <1 year, open challenge) (6)
- A threshold of </= 0.1 mL and 1 mL of cow's milk observed in 1.7% and 5% of patients, respectively (59 patients with CMA, placebo-controlled food challenges) (7)

Accidental Ingestion:

- Fatal anaphylaxis after ingestion of 100g of a sausage containing 60 mg CAS (2)
- The quantity of ingested whey proteins elicited anaphylactic reactions in a 3-year-old boy was estimated to be 120-180 µg (equivalent to 23 to 24 µL of milk) (3)

(1) Norgaard & Bindslev-Jensen 1992
(2) Malmheden Yman et al. 1994
(3) Laoprasert et al. 1998
(4) Sicherer et al. 2000
(5) Sütas et al. 2000
(6) Garcia-Ara et al. 2001
(7) Morisset & Moneret-Vautrin 2001

4 Diagnostic Features of Cow's Milk Allergy

Family History / Maternal Factors

Family History

Subjects / Follow-up	Manifestation of CMA	Family History of Atopic Disease	Ref.
children (siblings with CMA)	in 33%	positive	(1)
formula fed infants (5th day to 3 months)	in 40%*	positive	(2)
formula fed infants (5th day to 3 months)	in 13%*	negative	(2)
29 children with severe CMA (1 to 10 months)		in 89% (1 parent) in 50% (both parents)	(3)
91 children (8 months)	with gastrointestinal symptoms	in 34% (14%)	(4)
57 children (8 months)	with extraintestinal symptoms	in 53% (5%)	(4)
12 infants (birth to 5 years)	persistent** (a)	in 83%	(5)
26 infants (birth to 5 years)	resolved within 1-2 years (b)	in 38%	(5)
26 children (3 years)	persistent	in 80%	(6)
60 children (3 years)	tolerance acquired	in 20%	(6)

- (3) occurence of severe CMA in a pair of identical twins and HLA-identical siblings
- (4) family history of CMA in paranthesis
- (6) 86 consecutive children with IgE-mediated or non-IgE-mediated CMA (median age at diagnosis 4 months)

References

(1) Gerrard et al. 1973
(2) Vandenplas & Sacre 1986
(3) Schwartz et al. 1987
(4) Ventura & Greco 1988
(5) Iacono et al. 1998c
(6) Carroccio et al. 2000b

*significance P <0.001
**symptoms at onset predominantly gastrointestinal, at the end of the study increased frequency of wheezing, constipation, and delayed reactions
(a, b) multiple food intolerance in a) 92%, and b) 12%, respectively

Maternal Parameters in Breast Milk

Mothers from	IgG	IgA	TGF-beta-1	HLA-DR #	Total No. of Leukocytes	TNF-alpha	IFN-gamma	Ref.
6 infants with CMA		(-)*						(1)
65 infants with IgE-mediated CMA			(-)*					(3)
37 with non-IgE mediated CMA			(+)*					(3)
36 infants with CMA				(-)***	(+)			(2)
24 healthy infants				(+)***	(-)			(2)
48 infants with challenge-proven CMA		(-)**						(4)
27 infants with challenge-proven CMA (0.25-8.0 months)						(-)	(+/-)	(5)

*in colostrum, ** in colostrum and breast milk, ***significance p=0.012
(-) lower, (+) higher values, and (+/-) no difference as compared to controls
expression on breast milk macrophages

- (2) asymptomatic mothers
- (3) TGF-beta-1 positive correlation to beta-LG spec. IgA and CAS spec. IgG, negative correlation to SPT and lymphocyte stimulation with beta-LG or CAS
- (4) total and cow's milk specific IgA; levels of specific IgA positively correlated with levels of total IgA but not with the development of CMA in the infants
- (5) spontaneous and mitogen-induced TNF-alpha and IFN-gamma production of human milk leucocytes

(1) Savilahti et al. 1991
(2) Järvinen et al. 1999a
(3) Saarinen et al. 1999b
(4) Järvinen et al. 2000a
(5) Järvinen et al. 2000b

Maternal Serum IgG

(1) Mothers of infants who a) developed allergy or b) presented no symptoms: Statistically lower serum IgG anti- beta-LG levels in a) than in b) ($P < 0.001$)

(1) Casimir et al.1989

Humoral Parameters	References
Risk Factors for Specific Serum IgE Significant risk factors for the presence of cow's milk specific IgE in 75 infants with IgE-mediated reactions to cow's milk (mean age of 6.7 months)*: - long breast-feeding - exposure to cow's milk at the maternity hospital - breast-feeding during the first 2 months at home either exclusively or combined with infrequent exposure to small amounts of cow's milk	(1) Saarinen & Savilahti 2000 * see Footnote (1)

Footnote:
(1) All mothers should be encouraged to breastfeed their newborns in the first year of life. However, in the genetically predisposed newborn, who can not yet be accurately identified prior to or at birth, exposure to cow's milk allergens via breast milk, in the newborn nursery, and infrequent feeding of small amounts of cow's milk are significant risk factors for the development of cow's milk specific IgE (and eventually IgE-mediated CMA). Evidence-based strategies to prevent this from happening have not yet been developed.

Specific Serum IgE

Positivity and mean values of cow's milk specific serum IgE:

Patients / Reference	(1)	(2)	(3)
with history of CMA	(+) in 71%		
cow's milk tolerant children	(+) in 27%		
cow's milk DBPCFC positive		34 kU/L*	3.9 kU/L**
cow's milk DBPCFC negative		1.7 kU/L*	0.6 kU/L**

(+) increased IgE levels, *significance P<0.0001, **significance P<0.001

- (1) 69 children with food intolerance, IgG levels seemed to parallel IgE levels, no differences in IgA levels in allergic and control subjects
- (2) 196 children and adolescents with atopic dermatitis (90% family history of atopic diseases)
- (3) 107 children with atopic dermatitis

(1) Dannaeus et al. 1977
(2) Sampson & Ho 1997
(3) Niggemann et al. 1999b

Specific IgE, Persistent Allergy

Significantly elevated levels of milk- and CAS- specific IgE in children with persitent CMA (age of >9 years) as compared to children with CMA at the age of <3 years (RAST) (1)

(1) Sicherer & Sampson 1999

Total / Specific IgE, SPT, and Persistent Allergy

26 children with persistent CMA had significantly elevated levels of total serum IgE, and cow's milk and cow's milk proteins specific IgE, and higher frequency of positive SPT to cow's milk and proteins (86 consecutive children with IgE-mediated or non-IgE-mediated CMA, median age at diagnosis 4 months)

Carroccio et al. 2000b

Native / Denatured CAS, Specific IgE, Persistent Allergy

36 children with CMA: a) 11 became clinically tolerant, and b) 25 had persistent CMA; (6 controls without CMA). Compared to group b) children of group a) had significantly higher ratios of specific IgE antibodies against linear (denatured by reducing agent) than against conformational (native) epitopes of alpha-S1 and beta-CAS; none of group a) children developing tolerance and 9 of group b) children with persistent CMA possessed IgE to linearized beta-LG (immunodot-blots)

Vila et al. 2001

CAS Specific B Cell Epitopes, Persistent Allergy

- 2 IgE-binding regions of alpha-S1-CAS (aa 69-78 and aa 173-194) detected by 67% and 100% of sera from patients with persistent CMA (>9 years of age) but by none of children less than 3 years of age who are likely to outgrow CMA. No differences in IgG binding observed (24 children with CMA) (1)
- 6/10 children with persistent CMA detected a peptide from alpha-S1-CAS (aa 69-78) while none of 10 children who outgrew CMA had IgE binding to this epitope (immunodot-blot) (3)
- 3 IgE binding regions on beta-CAS and 6 on kappa-casein detected by the majority of 15 children with CMA (age of 4-18 years) with high levels of cow's milk specific IgE, but not by sera from children with CMA (age of <3 years) with low levels of specific serum IgE, who are likely to outgrow CMA (2)

(1) Chatchatee et al. 2001a
(2) Chatchatee et al. 2001b
(3) Vila et al. 2001

alpha-LA Specific B Cell Epitopes, Persistent Allergy

4 IgE-binding regions of alpha-LA detected with sera from 11 patients with persistent CMA (4-18 years of age, IgE to cow's milk >100 $kU_{(A)}/L$) none of these detected by sera from 8 children <3 years of age (IgE to cow's milk <30 $kU_{(A)}/L$) who are likely to outgrow CMA (SPOTs membrane technique) (1)

(1) Järvinen et al. 2001

beta-LG Specific B Cell Epitopes, Persistent Allergy

7 IgE-binding regions of beta-LG detected with sera from 11 patients with persistent CMA (4-18 years of age, IgE to cow's milk >100 $kU_{(A)}/L$) only 3 of these regions detected by sera from 8 children <3 years of age (IgE to cow's milk <30 $kU_{(A)}/L$) who are likely to outgrow CMA (SPOTs membrane technique) (1)

(1) Järvinen et al. 2001

Specific IgE, Immediate Reactors, Tolerance

69 IgE- sensitized immediate reacting children with CMA (median age of 24 months) median study period of 2 years: 22% developed clinical tolerance, had lower specific IgE levels at the beginning and the end of study period, and significant fall in SPT reactivity (1)

(1) Hill et al. 1993b

beta-LG Specific B Cell Epitopes, Immediate and Delayed Type CMA

8 immediate type patients with CMA (systemic reactions) and 6 delayed type patients with CMA (skin reactions) recognized same B cell epitope (beta-LG aa 95-113), no difference in IgE- binding peptide pattern (RAST inhibition, Pin-ELISA) (1)

(1) Heinzmann et al. 1999

Specific Serum IgG and IgA

Percentage of positivity of specific serum IgA and IgG antibodies:

Specificity	IgA	IgG	Ref.
alpha-LA	a) 43% b) 44%	a) 57% b) 69%	(1)
beta-LG	a) 71% b) 50%	a) 43% b) 75%	(1)
beta-LG		a > b	(2)
beta-LG		a, c > b	(3)
BSA		a > b	(2)
BSA		a, c > b	(3)
CAS	a) 86% b) 44%	a) 86% b) 69%	(1)
CAS		a > b "	(3)
pooled alpha-LA, beta-LG, CAS	a) 71% b) 38%	a) 57% b) 63%	(1)

NS = no significant differences

- (1) children (age of 3 months to 6 years): a) 7 with CMA (cutaneous symptoms), b) 16 with CMA (gastrointestinal symptoms)
- (2) a) 10 infants fed cow's milk- based formula, b) 10 infants fed a CAS hydrolysate formula until the age of 9 months
- (3) 129 children a) cow's milk formula fed, b) CAS hydrolysate formula fed, c) breast fed during the first 3 days of life, otherwise exclusively breast fed, follow-up for 2 years (" at 8 and 12 months)

(1) Bottaro et al. 1992
(2) Vaarala et al. 1995
(3) Juvonen et al. 1999

Specific IgE and IgG Subclass, IgA, Ratios

spec. Ig	Cow's Milk	CAS	beta-LG	alpha-LA
IgE		a > b (4) + (8) a) 90%, b) 0% (9)	a > b (4) a) 50%, b) 0% (9)	 a) 20%, b) 0% (9)
IgE/IgG		a > b (4)	a > b (4)	
IgE + IgG		a) 80% (9)	a) 40% (9)	a) 20% (9)
IgG1		a > b (4); + (8)	c > d, e, f** (6); + (8)	
IgG4	NS (1) a > b > c (2)	a > b > c (2) a > b (4) a) 80%, b) 30% (9)	a > c; b > c (2) + (8) a) 80%, b) 20% (9)	a) 10%, b) 10% (9)
IgE/IgG1		a > b (4)	a > b (4)	
IgE/IgG4		a > b (4)	a > b (4)	
IgG	(+) (3) (-) NS (5)	NS (4) a) 90%, b) 50% (9)	NS (4) NS (7) a) 70%, b) 40% (9)	 a) 60%, b) 10% (9)
IgE + IgG + IgG4		70% (9)	40% (9)	0% (9)
IgA	(-) (3)			

(1) Björkstén et al. 1983
(2) Schwartz 1991
(3) Tainio & Savilahti 1990
(4) James & Sampson 1992
(5) Stoger & Wüthrich 1993
(6) Saalman et al. 1995
(7) Iacono et al. 1998c
(8) Little et al. 1998
(9) Szabó & Eigenmann 2000

(+) increase, (-) decrease, (NS) no significant differences
**ratios of IgG1/IgG, IgG1/IgG3 and IgG1/IgG4 same tendency

- (1) no relation to provocation test in 14 children with immediate reactions to cow's milk, 15 cow's milk tolerant children
- (2) children with immediate type CMA, SPT positive to a) cow's milk (n=20), b) cow's milk and whey hydrolyzed formula (n=17), c) cow's milk, whey and CAS hydrolyzed formulas (n=13)
- (3) 21children with challenge proven CMA
- (4) a) 18 children with CMA, b) 11 children acquired tolerance
- (5) 28 adults with CMA (aged from 16 to 58 years)
- (6) c) children with CMA predominantly gastrointestinal , or d) skin symptoms of immediate-onset, e) children with untreated coeliac disease and f) healthy children
- (7) a) 12 children with persistent CMA up to age of 5 years, b) 26 controls
- (8) 15 adults with CMA (average age of 39.5 years)
- (9) positivity in a) 10 children with CMA (age of 7 months to 68 months) and b) 10 age-matched non-allergics

Symptoms and Prevalence of Specific IgE

Positivity of cow's milk specific serum IgE in 148 children with CMA according to symptoms:

Symptoms	IgE	Symptoms	IgE
Respiratory	100%	Persisting diarrhea	33%
Eczema	71%	Severe colics	27%
Urticaria / Anaphylaxis	56%	Total	48%
Vomiting	47%	Gastrointestianl	33%
Failure to thrive	33%	Extraintestinal	72%

Ventura & Greco 1988

Serum Eosinophilic Cationic Protein (ECP)

After 4 weeks of elimination diet; measurement of ECP before oral cow's milk challenge, 27 hours and 1 week after in 28 cow's milk allergic children (age of 5.8 to 43 months): Increased, transient ECP serum levels during challenge in patients with skin manifestations but not in patients with gastrointestinal symptoms (1)
After elimination diet; determination of ECP before milk challenge test, as well as 2 and 24 hours after it in 35 cow's milk allergic children (average age of 16 months; 6-49 months): Basic ECP level significantly higher than in control group; ECP level significantly decreased 2 hours after milk challenge test, after 24 hours back to basic ECP level; no significant differences in ECP levels of children with (n=10) and without clinical reactions (n=25), either before or after challenge test (2)

(1) Suomalainen et al. 1994b

(2) Hidvegi et al. 2001

Soluble IL-2 Receptor

Elevated serum levels of soluble IL-2 receptor in 16 children with non- IgE mediated CMA and in 8 children with IgE mediated CMA as compared to 19 children with other IgE-mediated food intolerance (1)

(1) Blanco Quiros et al. 1993

IL-12 and sCD30

Increased serum IL-12 levels and normal sCD30 levels in children with CMA while pollen-sensitized children had normal IL-12 and higher sCD30 levels than controls; no differences in patients with asthma or allergic dermatitis (11 children with CMA, open elimination-challenge test, SPT, RAST)

(1) Blanco Quiros et al. 1999

Specific TABM

Elevated serum levels of T-cell derived antigen- binding molecules (TABM) specific for alpha-LA, beta-LG, and CAS in 6 to 7 of 15 adults with CMA (1)

(1) Little et al. 1998

Eosinophil-related Markers

In a girl (at age of 12 months to 3 years) with CMA and multiple food allergies: high total eosinophil count, increased eosinophil activity, low IFN-gamma : IL-5 ratio, poor wheight gain, increasing respiratory symptoms (1)

(1) Nilsson et al. 1999

Cellular Parameters

Lymphocyte Subclasses, Antigen Expression

Patients	T-Cells	B-Cells	PBMC	not specified	Ref.
29 children with severe CMA			(NS) HLA-A, -B, -DR		(1)
7 children with CMA and atopic dermatitis	(+)* CLA+				(2)
children with CMA	(+) CD8+				(3)
37 children with CMA	(+)* HLA-DQ7				(4)
24 children with CMA (0.4-10 months)	(-)* CD8+	(+)* total No. (+)* CD19+			(5)
9 children with IgE-CMA	(+)* alpha4beta7 integrin		(NS) CD3+CD4+ (-)* CD3+CD8+		(6)
15 fed with cow's milk formula			(+)* PCNA		(7)
7 breast fed children			(+)* CD23+		(7)
12 patients with and without CMA	CD4+				(8)
6 patients with CMA				(+) CD1d	(9)

(+) increase, (-) decrease, * significant, (NS) no significant difference

- (1) preparations from unstimulated PBMC
- (2) in vitro stimulation with CAS
- (3) stimulation with alpha s1-CAS
- (4) majority of HLA-DQ7 positive patients presented a high humoral response rather than cellular response (stimulation with beta-LG)
- (5) challenge proven patients, compared to healthy controls (no stimulation)
- (6) mean age of 28 months (7 months to 9.3 years), beta-LG stimulated PBMC
- (7) children with IgE- mediated CMA (3-11 months of age), PCNA expression >/=10% as specific and sensitive marker of CMA in cow's milk fed infants, low cow's milk antigen diets are related with reduced lymphocyte reactivity in whey hydrolyzed fed and breast fed infants (stimulation with beta-LG)
- (8) patients with atopic dermatitis; stimulation with CAS, alpha-LA, and beta-LG
- (9) expression of CD1 in duodenal biopsy: CD1d positive cells found in lamina propria during symptomatic and asymptomatic periods, 6 healthy controls virtually devoid of CD1d expression; localization of CD1d positive cells in areas where B cells, plasma cells and dendritic cells were present; positive correlation between the numbers of CD1d(+) and CD19(+) cells in the lamina propria

CLA - cutaneous lymphocyte antigen (responsible for skin homing)
PCNA - proliferating cell nuclear antigen

T-Cells, Cell Surface Markers

Cow's milk protein specific T-cell clones (TCCs) were established from blood of infants with a) CMA and atopic dermatitis, from b) atopic controls (atopic dermatitis, without CMA), from c) nonatopic controls, and d) from infants with CMA after spontaneously developed tolerance:

Cell-Surface Marker	CD25	CD30	CD26
Expression Levels	a > b, c, d	a > b, c, d	a < c, d

References

(1) Schwartz et al. 1987
(2) Abernathy-Carver et al. 1995
(3) Nakajima et al. 1996
(4) Camponeschi et al. 1997
(5) Jarvinen et al. 1998
(6) Eigenmann et al. 1999
(7) Papadopoulos et al. 1999
(8) Schade et al. 2000
(9) Ulanova et al. 2000

(1) Schade et al. 2002

Lymphocyte / PBMC** Proliferation*

Patients / Stimulation with	Cow's Milk Proteins	beta-LG	BSA	CAS	Ref.
17 children with CMA		(+)	(+)		(1)*
children with CMA (challenge proven)		(+)			(2)*
a) children with CMA b) children with CMA (immediate type, RAST positive)		a) (+) b) (-)	a) (+) b) (-)		(3)**
children with CMA and atopic dermatitis			(+)		(4)**
a) children with CMA (gastrointestinal symptoms) b) children with CMA (skin or no symptoms)	a > b				(5)*
10 children with CMA	NS"			NS	(6)**
a) <5 years, b) >6 years of age			a > b		(7)**
a) 10 infants fed cow's milk- based formula b) 10 infants fed a CAS hydrolysate formula		a > b	a > b	a > b"	(8)**
a) 27 children with IgE mediated CMA b) 9 children with milk induced enterocolitis syndrome	a) (+) a vs b: NS				(9)*
a) 22 patients with cow's milk responsive atopic eczema b) 66 patients with atopic eczema (non-responsive)				a > b	(10)**

(+) higher stimulation index or proliferation, (NS) no significant differences

- (1) significant proliferation with at least one milk antigen in 15 patients
- (2) in children without specific IgE
- (3) 3 children with CMA and tension- fatigue sydrome (cow's milk RAST scores in a) negative or slightly positive)
- (4) as compared to children with immediate allergic symptoms and controls
- (5) 44 children with CMA (mean age of 16 months) after 2-4 weeks of elimination diet, proliferation response abrogated after clinical challenge
- (6) as compared to control group (" stimulation with whey hydrolyzed formula and proteins), lower stimulation with hydrolyzed formula
- (7) 22 children with CMA and atopic dermatitis, proliferative response decreased rapidly after elimination diet
- (8) fed until the age of 9 months (" stimulation with alpha-CAS)
- (9) a) as compared to control group (significant, but extensive overlapp), group a) also responded to soybean antigen
- (10) age of 16-67 years (median 28 years)

(1) Endre & Osvath 1975
(2) Tainio & Savilahti 1990
(3) Kondo et al. 1992
(4) Kondo et al. 1993
(5) Suomalainen et al. 1994a
(6) Eigenmann et al. 1995
(7) Iida et al. 1995
(8) Vaarala et al. 1995
(9) Hoffman et al. 1997
(10) Werfel et al. 1997b

Lymphocyte Transformation

Lymphocyte transformation test a) before and b) 30 days after elimination of cow's milk from the diet: a) significantly increased lymphoblastogenesis (P <0.01), b) no differences in 19 children with CMA (1)

(1) Brarda et al. 1989

CBMC Proliferation, IFN-gamma

Stimulation of cord blood mononuclear cells (CBMC) with cow's milk proteins: pronounced proliferation of cells stimulated with alpha-LA, beta-LG, and alpha-CAS; preferentially reduced IFN-gamma levels in individuals with positive parental allergic history (39 randomly selected newborns) (1)

(1) Szepfalusi et al. 1997

Cytokine Production by Lymphocytes

Patients / Cytokines	IFN-gamma	TNF-alpha	IL-4	IL-5	IL-10	IL-13	Ref.
a) immediate- reacting b) late- reacting c) milk tolerant	a < c, b*						(1)
a) children with CMA b) children who acquiered tolerance	a < b < c						(2)
children with CMA		(+)					(3, 4)
a) children with CMA b) children who acquiered tolerance		a > b					(4)
a) immediate- reacting b) late- reacting	a) (+) b) (-)						(5)
children with atopic dermatitis (milk responsive)			(-)				(6)
a) children with CMA (cutaneous symptoms) b) children with CMA (predominantly digestive symptoms) d) children who acquiered tolerance		a > b > c, d (")					(7)
31 children with CMA	(-)*	(-)*					(8)
a) 6 infants with CMA b) 6 infants without CMA	a < b		a > b	a > b		a > b	(9)
a) 22 immediate-reacting children b) 29 late-reacting children d) cow's milk tolerant children		a, b > d			a > b		(10)

* significant, c) healthy control group, (+) positive response

- (1) 75 (a) and 17 (b) children with CMA and 59 (c) tolerant children (age of 1-9 years) (stimulation with beta-LG)
- (2) 22 children
- (3, 4) stimulation of PBMC with cow's milk proteins
- (5) lower thresholds of stimulation in a) as compared to b)
- (5) 50 cow's milk allergic children (age of 2-60 months) (DBPCFC positive) with atopic dermatitis, after DBPCFC difference in IFN-gamma generation abolished
- (6) IL-4 production of CD4+ CAS specific T-cell clones (compared to house dust mite sensitive patients)
- (7) 83 children, measured in whole blood cultured with cow's milk proteins, day 1 (") followed by TNF-alpha degradation, day 5: secretion peak in group b)
- (8) challenge proven children with either skin or gastrointestinal symptoms or both compared to healthy controls (age of 0.12-11.2 months), unstimulated PBMC and mitogen-induced production
- (9) infants with atopic dermatitis (age of 3.8-12.3 months); cow's milk protein-specific TCC derived from PBMCs stimulated with CAS, alpha-LA, and beta-LG; 2 patients with TCC reactivity to CAS and whey proteins and 2 patients with exclusive reactivity to CAS in both groups; CMA in infants with atopic dermatitis associated with production of TH-2 cytokines by circulating antigen-specific CD4+ T cells; significant correlation with IL-4 of both IL-5 and IL-13 production
- (10) stimulation of PBMC with cow's milk; IL-10 concentrations increased in response to DBPCFC in challenge-positive children

(1) Hill et al. 1993a
(2) Suomalainen et al. 1993a
(3) Heyman et al. 1994
(4) Benlounes et al. 1996
(5) Sutas et al. 1997
(6) Werfel et al. 1997b
(7) Benlounes et al. 1999
(8) Österlund et al. 1999
(9) Schade et al. 2000
(10) Sütas et al. 2000

Cytokine Secreting Cells in Blood and Duodenal Mucosa Frequency of spontaneously cytokine secreting mononuclear cells in the **blood** / **duodenal mucosa** INF-gamma: a, b > c / a > c IL-4: b > a > c / a > c IL-5: a, b > c / a = c IL-10: a, b > c / a < c Children with a) CMSE, b) CMA, and c) age matched controls Cytokine secreting cells more frequently in duodenal mucosa than in the blood	(1) Hauer et al. 1997
PBMC, Migration Inhibition Factor In vitro assay of lymphocyte migration inhibition factor (MIF), stimulation of peripheral blood lymphocytes with beta-LG: significant higher MIF production in 24 children with CMA than in control subjects; most of 18 children recovered from CMA had negativ assay (1)	(1) Ashkenazi et al. 1980
Lymphocytes, Suppressor Activity Decreased suppressor activity of isolated lymphocytes induced by either Concanavalin A or cow's milk in 10 children with CMA as compared to controls and patients who acquired cow's milk tolerance (1)	(1) Suomalainen et al. 1993b
Cell Mediated Cytotoxicity Antibody- dependent cell- mediated cytotoxicity (ADCC) to beta-LG- coated cells rather induced in most sera of children with CMA and predominantly gastrointestinal symptoms than in sera of children with skin reactions (immediate- type), children with untreated coeliac disease, or healthy children; ADCC reactivity of individual sera correlated with their IgG1 antibody levels (1)	(1) Saalman et al. 1995
Homing Receptor Expression Stimulation of a) cord blood mononuclear cells and b) peripheral blood mononuclear cells (at age of >3 months) with alpha-S1 CAS: a) higher percentage of alpha-E-beta-7-positive T cells than in healthy controls; no difference in cord blood T-cell proliferation; CLA was not induced on T cells b) no induction of alpha-E-beta-7-positive T cells; CLA was expressed on T cells (4 infants with atopic dermatitis and CMA)	(1) Kohno et a. 2001

Gastrointestinal Parameters	**References**
Salivary IgA 158 healthy mature infants at birth: Salviary anti-CAS IgA was significantly higher (P <0.05) in high risk infants than in no risk or low risk infants; salviary anti-CAS IgA values correlated with maternal allergy, but not with paternal allergy (1)	(1) Renz et al. 1990
Pancreatic Enzymes children with CMA (median age 3 months) fed with a) a hydrolyzed CAS- based formula or b) a soy- protein based formula: No significant difference in pancreatic secretion between both groups for any of the enzymes studied (trypsin, chymotrypsin, lipase, and phospholipase) during diet of 6 weeks (1)	(1) Carroccio et al. 1997
Duodenal Fluid, Specific IgE and IgD increased levels of cow's milk protein (and soybean agglutinin) specific IgE and IgD in basal and pancreozymin- stimulated duodenal fluid in 13 children with various intestinal diseases (1)	(1) Freier et al. 1983
Jejunal Fluid, Hyaluronic acid, Albumin Jejunal fluid levels of hyaluronan (hyaluronic acid) and albumin increased after milk perfusion challenges in 5 adults with CMA (DBPCFC positive, SPT and RAST negative, lactose tolerant) as compared with control group (1)	(1) Bengtsson et al. 1996
Small Intestine Mucosa, IgE and IgM Plasma Cells local reaginic reaction after ingesting cow's milk: increased mucosal IgE and IgM plasma- cells, increased degranulation of mast cells, staining of connective tissue and basement membranes with antisera to IgG and C3 complement in 2 cow's milk sensitive infants (1)	(1) Shiner et al. 1975

Small Intestine Mucosa and Serum, Alkaline Phosphatase

Levels of alkaline phosphatase (ALP) after cow's milk protein challenge: Significant depletion in upper jejunal mucosa tissue and serum in infants with clinical and histological reactions (n=10); tissue ALP depressed in 3/5 patients with histological but no clinical reactions to cow's milk (1)

(1) Iyngkaran et al. 1995

Small Intestinal IgE Plasma Cells, Specific Serum IgE

Patients / Cow's Milk Specific	IgE Plasma Cells	Serum IgE	Ref.
16 children with CMA	(+) in 56%	(+) in 38%	(1)
15 without CMA	(+) in 6.7%	(+) in 13%	(1)

- (1) elimination / challenge proven CMA

(1) Schrander et al. 1993a

Intestinal Total Immunoglobuline Secreting Cells

Intestinal immune responses after diagnostic milk provocation:

Patients / No. of Secreting Cells	IgM	IgA	IgG	Ref.
a) with CMA (acute urticaria)	(+)	(-)	(-)	(1)
b) with CMA (gastrointestinal symptoms)	(+)	(+)	(-)	(1)
c) with CMA (skin and gastrointestinal symptoms)	(+)	(+)	(+)	(1)
d) 13 with persistent CMA	(+)	(+)	(+)	(2)
e) 24 acquired tolerance	(-)	(-)	(-)	(2)
d) 27 with CMA (age of 9-69 months)	(+)	(+)	(+)	(3)

(+) significant increase during challenge, (-) no increase

- (1) IgM and IgA responses: in group b) > a)
- (3) increase in all isotypes associated with clinically positive cow's milk challenge; specific antibody secreting cells against beta-LG and CAS (and gliadin) increased in IgM class only

(1) Isolauri et al. 1990
(2) Isolauri et al. 1992
(3) Suomalainen et al. 1992

Intestinal Eosinophils, Lymphocytes, Mast Cells

Patients	Eosinophils	Lymphocytes	TIA-1**	Mast Cells	Ref.
12 children with CMA	(+) in 58%			(-)	(1)
47 children with coeliac disease	(+) in 60%			(-)	(1)
children with CMA and chronic diarrhea	(+)*				(2)
21 children with CMA/CMI	(+) in 38%	(+)*			(3)
35 children with gluten intolerance	(+) in 27%	(+)*			(3)
10 children with CMA/CMI		(+)*	(+)*		(4)

* significant, (+) increase, (-) decrease
**TIA-1 (= cytotoxic granule-associated protein) expressing lymphocytes

- (1) in lamina propria of jejunum
- (2) in lamina propria of duodenal mucosa
- (3) cellular infiltration of small intestinal mucosa
- (4) number of TIA1- expressing intraepithelial lymphocytes (IEL) and the TIA1/IEL ratio in patients on cow's milk-free diet of various duration, negative correlation between the TIA1/IEL ratio and the duration of the diet (duodenal biopsies)

(1) Kosnai et al. 1984
(2) Challacombe et al. 1986
(3) Kaczmarski et al. 1989
(4) Hankard et al. 1997

Intestinal ECP, MBP, Histamine, VCAM-1

Patients	ECP *	MBP *	Histamine*	VCAM-1**	Ref.
5 adults with CMA	(+)		(+)		(1)
14 patients with cow's milk-sensitive enteropathy		(+)		(+)	(2)

(+) increased, (-) decreased, *intestinal secretion, **expression on mononuclear cells

- (1) DBPCFC positive, SPT and RAST negative, lactose tolerant patients (perfusion challenges with milk, CAS, and whey)
- (2) Challenge positive, SPT and RAST negative patients, endoscopic duodenal biopsy
- ECP = eosinophil cationic protein
- MBP = eosinophil major basic protein
- VCAM-1 = vascular cell adhesion molecule-1

(1) Bengtsson et al. 1997
(2) Chung et al. 1999

Intestinal Epithelial Cells, CD23 Expression

CD23 expression on intestinal epithelial cells increased in 3 children with CMPI (age < 1 year) associated by high levels of specific IgE

Kaiserlian et al. 1995

Fecal alpha-1 Antitrypsin, TNF-alpha, ECP, IgE

Indicators of intestinal inflammation in jejunal fluid after cow's milk challenge:

Patients	alpha-1 Antitrypsin	TNF-alpha	ECP	IgE	Ref.
13 children with CMA (gastrointestinal symptoms)		(+)*	(-)	(-)	(1)
a) positive DBPCFC with cow's milk b) negative DBPCFC with cow's milk	(+) in 43% (+) in 11%	(+)** (-)	(+)*** (-)		(2)
15 children with CMA	(+) in 58%				(3)

(+) significant increase after challenge, (-) no increase
*in challenge positive children
**particularly in delayed type patients, ***particularly in immediate reactors

- (2) children with atopic eczema
- (3) out of 26 atopic infants with confirmed food allergy; all 9 patients with increased fecal concentration of alpha-1-antitrypsin had positive challenge with cow's milk while only 6 in those with normal alpha-1-antitrypsin concentration (fecal samples collected before elimination diet and 3 months later)

(1) Kapel et al. 1999
(2) Majamaa et al. 1996
(3) Majamaa et al. 2001

Gastrointestinal Permeability

Urinay Recovery / Test Substances	Permeability	Alteration after cow's milk challenge	Ref.
polyethylenglycol (PEG)		*	(1)
lactulose/mannitol excretion ratios		(+)	(3)
cellobiose/mannitol excretion ratios		(+)	(4)
lactitol/mannitol excretion ratios	a > b		(5)
Jejunal Biopsy / Test Substances			
horseradish peroxidase (HRP)		(+)*	(2)

*significantly changed, (+) increased, (-) decreased

- (1) 16 children with CMA (immediate- type), greatest alteration in children with most severe symptoms
- (2) 15 children with CMA (age of 1-24 months), jejunal transepithelial fluxes
- (3) 51 children with CMA (skin symptoms and patients with gastrointestinal symptoms), 3 days after challenge
- (4) 32 children with CMA (age of 3-84 months), 24 hours after challenge
- (5) children with symptoms suggestive of CMA (age of 0.5-168 months): a) 95 children with proven CMA and b) 105 controls (challenge negative); defining a cut-off value intestinal permeability exhibited a 68% sensitivity and a 77% NPV for CMA;. highest sensitivity (70%) at ages 6-12 months; abnormal intestinal permeability in 80% of CMA children with digestive manifestations, in 43% with extra-digestive, 68% with mixed and 40% with anaphylactic manifestations; lactitol/mannitol ratio correlated negatively with age in control group, no correlation in CMA group

(1) Falth-Magnusson et al. 1986
(2) Heyman et al. 1988
(3) Jalonen 1991
(4) Troncone et al. 1994
(5) Kalach et al. 2001

Protein / Allergen Absorption

Concentrations in blood serum samples

Patients	human alpha-LA	bovine beta-LG	Ref.
17 children with CMA (age of 3-78 months)		0.3 to 2 µg/L (in 29%)	(1)
20 infants (followed up to 8 months)	3-4 days after birth 31 µg/L at 1 month 6 µg/L at 2 months 2 µg/L at >3 months trace amounts	after weaning 1 week 7 µg/L (in 38%) 2 weeks 4 µg/L (in 21%)	(2)

- (1) 24 h after cow's milk challenge
- (2) median serum levels (per g alpha-LA or beta-LG given per kg body weight)

(1) Husby et al. 1990
(2) Kuitunen et al. 1994

Diagnostic Significance of Tests

SPT, Atopy Patch Test (APT), RAST

Patients / Reference	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Age (months)		adults	2-36	2-24	50*	62*	<24	21*
a) acute onset	14			36			22	
b) delayed onset				18			50	
SPT - positive (cutoff point, 3 mm)			a) 67% b) (-)	a) (+)	55%		14%	
sensitivity specificity PPV NPV					66% 100% 100% 28%	96% 51% 66% 93%		
APT - positive			a) (-) b) 89%	b) (+)			44%	
sensitivity specificity PPV NPV								
RAST - positive (cutoff point, >0.35 kU/L)							26%	
sensitivity specificity PPV NPV	79 % 80 %	75-100% 71% 60-67% 83-100%				100% 30% 57% 100%		85% 38% 61% 71%

* mean age, (-) tendency of negative results, (+) association to positive results

- (1) 14 children with immediate reactions to cow's milk, 15 cow's milk tolerant children
- (2) 21 adults with cow's milk / egg allergy (DBPCFC, 5 different RAST systems)
- (3) 183 children with CMA and atopic dermatitis (DBPCFC or open challenge, 54% challenge positive)
- (4) 54 children with CMA and atopic dermatitis
- (5) 430 food allergic children and adolescents (labial food challenge positive) age from 0.2 to 20 years
- (6) 54 of 109 DBPCFC positive to cow's milk (study population: 196 food allergic children and adolescents with atopic dermatitis, age from 0.6 to 17.9 years)
- (7) 72 children with CMA (challenge proven)
- (8) 107 children with atopic dermatitis (47 DBPCFC positive) age from 5 months to 12 years

References

(1) Björkstén et al. 1983
(2) Norgaard et al. 1995
(3) Isolauri & Turjanmaa 1996
(4) Kekki et al. 1997
(5) Rance et al. 1997
(6) Sampson & Ho 1997
(7) Majamaa et al. 1999
(8) Niggemann et al. 1999b

SPT, Atopy Patch Test (APT), RAST (continued)

Patients / Reference	**(9)**	**(10)**	**(11)**	**(12)**	**(13)**
Age (months)	2-11	1-192	<12	13*	6.3-7.5
a) acute onset	100	125	75		58
b) delayed onset	76	17			60
SPT - positive (cutoff point, 3 mm)					a) (+)
sensitivity	69%	79%	99%	78%	61%
specificity	91%		38%	69%	76%
PPV	79%		56%	81%	71%
NPV	85%		97%	64%	67%
APT - positive					a) (+)
sensitivity	18%			47%	37%
specificity	87%			96%	77%
PPV	40%			95%	61%
NPV	69%			51%	56%
RAST - positive (cutoff point, >0.35 kU/L)					a) (+)
sensitivity	58%		85%	84%	72%
specificity	88%		56%	38%	49%
PPV	70%		61%	70%	58%
NPV	81%		83%	59%	64%
Serum ECP - positive (cutoff point, >15 µg/L)					
sensitivity					27%
specificity					74%
PPV					67%
NPV					34%

* mean age, (-) tendency of negative results, (+) association to positive results

- (9) 301 children with suspected CMA (176 DBPCFC positive)
- (10) 310 children with suspectd CMA (43% challenge positive), specifity of SPT in children less than 2 years of age was 91%
- (11) 170 children with suspected CMA age <1 year (mean 4.8 months); 4-year follow-up; SPT and RAST: at least one positive result for whole milk and/or major milk proteins (alpha-LA, beta-LG, or CAS)
- (12) 45 of 71 DBPCFC positive to cow's milk (study population: 98 children with atopic dermatitis and suspected food allergy, age from 2 months to 11.2 years); combination of positive APT with evidence of specific IgE or with a positive SPT resulted in a PPV of 100%
- (13) 239 children with suspected CMA (mean age of 6.9 months); 49% challenge positive; with a cut-off level in SPT of 8 mm sensitivity and NPV decreased (to 19% and 55%, respectively) while specificity and PPV increased (to 98% and 92%, respectively); using protein fractions (beta-LG, bovine serum albumin, CAS) in APT sensitivity and NPV were 26% and 57%, respectively, while specificity and PPV increased (to 92% and 77%, respectively); with a cut-off level in RAST of >3.5 kU/L sensitivity and NPV decreased (to 25% and 57%, respectively) while specificity and PPV increased (to 98% and 94%, respectively); serum ECP measured after challenge (day 4); with a cut-off level of 24.7 µg/L serum ECP sensitivity decreased to 13% while specificity, PPV, and NPV increased (to 98%, 93%, and 37%, respectively)

(9) Vanto et al. 1999
(10) Sporik et al. 2000
(11) Garcia-Ara et al. 2001
(12) Roehr et al. 2001
(13) Saarinen et al. 2001

Predictive Decision Points of Specific IgE

It should be noted that pedictive decision points are significantly affected by specific conditions within each study population (e.g. atopic dermatitis or selection criteria)

Patients / Reference	**(1)**	**(1)**	**(1)**	**(1)**	**(2)**	**(2)**	**(3)**	**(3)**
Age (months)	62*	62*	62*	62*	<12	<12	13*	13*
a) acute onset					75	75	100%	-
b) delayed onset							-	100%
Predictive Decision Point ($kU_{(A)}/L$)**	<0.8	<1.0	>23	>32	>2.5	>5	>17.5	>17.5
sensitivity	98%	95%	58%	51%	48%	30%	22%	17%
specificity	41%	48%	94%	98%	95%	99%	96%	96%
PPV			90%	95%	90%	95%	86%	75%
NPV	95%	90%			69%	64%	54	63%

Patients / Reference	**(4)**	**(4)**	**(5)**	**(5)**
Age (months)	6.9*	6.9*	45.6*	45.6*
a) acute onset	58	58		
b) delayed onset	60	60		
Predictive Decision Point ($kU_{(A)}/L$)**	>0.7	>3.5	>15	>32
sensitivity	45%	25%	57%	34%
specificity	87%	98%	94%	100%
PPV	78%	94%	95%	100%
NPV	61%	57%	53%	44%

* mean age, ** CAP system FEIA

- (1) 54 of 109 DBPCFC positive to cow's milk (study population: 196 food allergic children and adolescents with atopic dermatitis, age from 0.6 to 17.9 years)
- (2) 170 children with symptoms suggesting immediate-type CMA (age <1 year, mean 4.8 months); 4-year follow-up
- (3) 45 of 71 DBPCFC positive to cow's milk (study population: 98 children with atopic dermatitis and suspected food allergy, age from 2 months to 11.2 years); combination of positive APT with evidence of specific IgE in a PPV of 100%
- (4) 239 children with suspected CMA (age of 6.3-7.5 months); 49% challenge positive
- (5) 100 children and adolescents with suspected IgE-mediated food allergy (age of 3 months to 14 years); 61% with atopic dermatitis, appr. 50% with asthma, and 90% with atopic family history, 21/62 DBPCFC positive to cow's milk

(1) Sampson & Ho 1997
(2) Garcia-Ara et al. 2001
(3) Roehr et al. 2001
(4) Saarinen et al. 2001
(5) Sampson 2001

Diagnostic Significance of Tests (continued)

References

Predictive Decision Points of SPT

It should be noted that pedictive decision points are significantly affected by specific conditions within each study population (e.g. atopic dermatitis or selection criteria)

Patients / Reference	**(1)**	**(1)**	**(2)**	**(2)**
Age (months)	<24	31*	6.9*	6.9*
a) acute onset		37%	58	58
b) delayed onset		5%	60	60
Predictive Decision Point (wheal diameter in mm)	>6	>8	>6	>8
sensitivity	100%	100%	37%	19%
specificity			93%	98%
PPV			83%	92%
NPV			60%	55%

* mean age

- (1) 310 children with suspected CMA (age of 1-192 months; 120 children < 24 months); 55% of challenges were positive, 37% negative, and 8% inconclusive (open oral food challenges)
- (2) 239 children with suspected CMA (age of 6.3-7.5 months); 49% challenge positive; SPT with cow's milk formula

(1) Sporik et al. 2000
(2) Saarinen et al. 2001

Cut-Off Levels: Specific IgE vs. SPT

In EAST 62 children from 640 children with suspected food allergy (<2 years of age) were CMA positive according to specific IgE levels grade 3+ and 4+ (>3.5 AEU/mL) while 63 children had IgE-mediated CMA by SPT (100% diagnostic SPT level: >6 mm) but not by EAST;
in CAP RAST 4 children from 127 children with suspected food allergy (<2 years of age) were CMA positive according to specific IgE levels grade 4, 5, and 6 (>17.5 $kU_{(A)}/L$) while 11 children had IgE-mediated CMA by SPT (100% diagnostic SPT level: >6 mm) but not by CAP RAST

Hill et al. 2001

SPT, IgE and Oral Challenge

Diagnostic tests in comparison with oral challenge test in 11 children with CMA (1-15 years of age):

	SPT	**RAST**	**MAST**	**Case History**
Sensitivity	85%	71%	71%	
Specificity		100%	100%	
Match	60%	81%	81%	63%

Roger et al. 1994

SPT, IgE, APT, ECP and Oral Challenge

Positivity of tests in 239 children challenged with cow's milk at a mean age of 6.9 months:

Oral Challenge	**SPT**	**RAST**	**APT**	**ECP**
118 positive	61%	45%	26%	21%
121 negative	24%	13%	8%	13%

Combination of the 4 tests correctly classified 73% of the infants with a sensitivity of 76% and a specificity of 67% (cut-off levels: SPT >/ = 3 mm; RAST cow's milk-specific IgE >/ = 0.7 kU/L; ECP >/ = 20 µg/L)

Saarinen et al. 2001

Clinical History, IgE, Oral Challenge

Children with atopic dermatitis:

Diagnosis of CMA by	(1)	(2)
History only	-	18%
RAST only	0%	0%
History and RAST	57%	27%
Oral challenge	43%	73%
No. of patients	7	11

(1) Eigenmann et al. 1998

(2) Eigenmann & Calza 2000

SPT and DBPCFC

Significant differences in SPT (wheal sizes) between cow's milk allergic or tolerant individuals (DBPCFC) ($P < 0.001$); SPT cut-off values mean diameter 5 mm / surface area of wheal 29 mm^2

Eigenmann & Sampson 1998

Skin Tests, RAST, Histamine Release and Lymphocyte Stimulation

Positive results with cow's milk (and alpha-CAS*)

Test	a)	b)
SPT	57%	0%
Patch Test*	33%	0%
RAST	59%	33%
Histamine Release	55%	17%
Lymphocyte Proliferation	77%	17%

a) 22 children with CMA (positive challenge test)
b) 12 non- milk- allergic controls with atopic dermatitis
Panel of tests detected 21/22 children positive and 5/12 false- positive

(1) Rasanen et al. 1992

Specific Serum IgG

Patients / Reference	(1)	(2)	(3)
Age	16-58, median 26 years	1-48 (1-72) months	
cow's milk specific IgG			
	NS		NS
beta-LG specific IgG			
sensitivity specificity		89% 85%	

NS no diagnostic significance

- (1) 28 adults with CMA
- (2) 218 healthy children, 205 with CMA, 96 with other (atopic) diseases (commercial betalactotest)
- (3) 702 infants divided into six groups of different feeding (breast fed, infant formula fed); the shorter the breast feeding period and the earlier cow's milk formula is introduced, the higher the IgG levels

(1) Stoger & Wüthrich 1993
(2) Iacono et al. 1995b
(3) Keller et al. 1996

SPT and RAST

41 children with suspected CMA (age of 3 months to 13 years; mean 2.6 years): 32% SPT positiv, 61% IgE positiv; concordance of SPT and IgE results in 51% (1)

(1) Campbell et al. 1987

Histamine Release, SPT and RAST

26 children with suspected CMA: 77% positive in oral challenge test; patients with urticaria: high degree of correlation between histamine test, RAST and skin test; patients with gastrointestinal symptoms only a few positive results in histamine test, RAST and skin test (1)

(1) Prahl et al. 1988

Positivity of Open Challenge and DBPCFC in children with history of CMA **Patients** / **Open Challenge** / **DBPCFC** / **Ref.** 265 children suspected for CMA (mean age 3 months) / 56% (n=155) / 44% (n=110) / (2) a) 16 probable immediate reactors (mean age 37 months) / / a) 62.5% with adverse reactions (up to 2 h after milk exposure) / (1) b) 53 probable delayed reactors (mean age 17 months) / / b) 28.8% with predominantly gastrointestinal symptoms (2h to 6 days after milk exposure) / (1)	(1) Baehler et al. 1996 (2) Kaila & Isolauri 1997

Other Features

Parameters / Subjects	Outcome	References
Gender of Adults with CMA 34 patients with CMA (aged from 16 to 58 years)	Gender: 91% females, 39% of them experienced first symptoms during or soon after a pregnancy; 47% of patients were nonatopic and showed a monovalent sensitization to cow milk proteins	Stoger & Wüthrich 1993
Intrauterine Sensitization A newborn presenting symptoms suggestive of CMA	First hour of life: hemorrhagic meconium Next few days: bloody diarrhea Day 14: elevated total IgE, specific IgE to cow's milk and an eosinophilia in peripheral blood; symptoms disappeared when milk feed was changed to extensively hydrolyzed casein-formula. Day 30 and at 7 months of age: 2 challenges with cow's milk formula followed by recurrence of vomiting, watery diarrhea and failure to thrive. Age of 17 months: cow's milk well tolerated well	Feiterna-Sperling et al. 1997
Intrauterine Sensitization An infant with non-IgE mediated CMA	Symptoms of food-induced enterocolitis occurred before any oral intake of antigen	Kalayci et al. 2000
Sensitization / First Symptoms 118 infants with challenge proven adverse reactions to cow's milk (mean age of 6.7 months)	50 infants showed first adverse symptoms during exclusive breast-feeding (37 had cow's milk specific IgE), and 32 infants were sensitized during exclusive breast-feeding (23 had cow's milk specific IgE)	Saarinen & Savilahti 2000
Cow's Milk Exposure 25 children with CMA (age <1 year)	Exposure to cow's milk formulas (significantly more often than in control group, $p < 0.01$): 16 during their first week of life 6 before fifth week of life 3 infants not exposed	Stintzing & Zetterstrom 1979
SPT, IgE in Immediate Type CMA 26 (1), 50 (2, 3), and 21 (4) children with IgE mediated acute reactions of CMA	Differentiation of 3 groups by positive SPT to: A) cow's milk only B) cow's milk and whey hydrolysate formula C) cow's milk, whey and CAS hydrolysate formula (1, 2, 3) Significant differences in cow's milk specific serum IgE: A < B < C (1, 2) Significant differences in beta-LG and CAS specific serum IgE: A < C and B < C (1, 2, 3) Most significant difference in intensity scores of IgE-binding to CAS and beta-LG in SDS-PAGE immunoblot: A < C (4)	(1) Schwartz et al. 1989 (2) Schwartz 1991 (3) Schwartz et al. 1991 (4) Amonette et al. 1993

SPT, IgE and Delayed Reactions 49 infants with clinical history suggestive of CMA, positive SPT and RAST (alpha-LA, beta-LG, and CAS) (age of <6 months): 94% had immediate reactions 6% had delayed type reactions (>2 h after challenge)	Reexamination of 24 children with negative SPT and RAST at 1 year of age after exclusion diet: 79% challenge negative 21% challenge positve (all presenting late reactions at mean of 7 days after milk ingestion)	Plaza Martin et al. 2001
Frequencies of IgE- and non-IgE CMA 52 of 101 DBPCFC positive to cow's milk (study population of 139 children with atopic dermatitis suspected for food allergy)	IgE-mediated CMA (SPT and/or RAST positive) in 88% non-IgE-mediated CMA (SPT and RAST negative) in 12%	Niggemann et al. 2001b
Adverse vs Allergic Reactions 9 children with "unequivocal symptoms attributable to cow's milk"	CMA in 1 patient, abnormal disaccharide absorption in 3 patients (gastrointestinal and immunoallergic investigations)	Davidson et al. 1976
"Residual" Allergic Disease Reexamination of a) 53 10-year-old children who manifested CMA before 1 year of age and achieved small-dose tolerance b) age-matched control group of 90 school children	**a)** / **b)** reported milk-related gastro-intestinal symptoms: 45% / 10% response of intestinal symptoms*: 3/6 / 7/10 growth: retarded / "normal" specific IgA and IgG: lower / higher lactose malabsorption: 14% / 3% * 4-week blind elimination-challenge test with 1 week of low-lactose milk flour	Kokkonen et al. 2001b
SPT: Commercial Extract vs. Fresh Food 4-month-old infant with severe atopic dermatitis and positive skin reaction upon contact with cow's milk	Reexamination 1 year later: SPT with commercial CAS, alpha-LA, and beta-LG solutions all negative; in drop test with pasteurized cow's milk a severe generalized urticaria resulted within a few minutes	Di Berardino et al. 2001

5 Therapy of Cow's Milk Allergy

Elimination Diets	Outcome	References
Elimination Diet 173 mainly adults with food allergy	Strict elimination diet: some 2/3 reported after 3-5 years that a strict elimination diet had to be followed, otherwise prompt relapse of allergic symptoms was noted. About 1/3 of patients, mainly with milk, cheese or egg allergy, show spontaneous desensitization by appropriate diet (case history, RAST)	Wüthrich & Hofer 1986
Elimination Diet 148 children with CMA (age of <1 year)	All cases improved on a milk free diet, in 18% a further modification of the diet was required after the first prescription	Ventura & Greco 1988

Elimination Diet 70 children with cow's milk protein intolerance (mean age 30 days)	Remission of symptoms (severe colic) in 71% after elimination of cow's milk protein from the diet; successive challenges caused the return of symptoms in all infants	Iacono et al. 1991
Elimination Diet, Nutritional Status 19 children with CMA (age of 0.6 to 4.1 years)	Nutritional status of children was followed during an elimination diet (2 children soy- based formula, other children other foodstuffs and supplementary calcium): significant reduction in serum prealbumin values; low serum zinc values in 12 children; low serum iron in 2 children; 2 had high serum alkaline phosphatase values; dietary intake of energy below recommendation in some children; protein intake high; low intakes of riboflavin in some children	Paganus et al. 1992
Elimination Diet, Calcium a 4 year old boy with CMA	Calcium deficiency rickets caused by prolonged elimination diet of cow's milk; adequate intake of calcium resulted in rapid improvement	Davidovits et al. 1993
Elimination Diet infants with CMA	Clinical disappearance of symptoms after removal of milk from the mother's diet and/or elimination from the child's diet, significant correlation between alterations of intestinal permeability and ingestion of reputedly hypoallergenic foods, breast milk, and hydrolyzed protein formulas	Barau & Dupont 1994
Elimination Diet, Growth 100 children (mean age 7 months) with atopic dermatitis and challenge-proven CMA	Mean length SD score and weight-for-length index of patients decreased compared with healthy controls; low serum albumin in 6% of patients, 24% had an abnormal urea concentration, and low serum phospholipid docosahexaenoic acid in 8%; delay in growth more pronounced in subgroup of patients with early onset of symptoms	Isolauri et al. 1998
Proposed Diet in case of CMA	Avoidance of all products containing milk, milk protein, lactoprotein, lactoserum protein, CAS, caseinate, lactalbumin, lactose, margarine, cream (contains a list of "allowed" and "prohibited" foods)	Moneret-Vautrin 1999

Medication*	**Outcome**	**References**
Terfenadine / TNF-alpha children with CMA	In vitro stimulation of PBMC with milk proteins (beta-LG, alpha-LA and CAS) with or without terfenadine: dose-dependent decrease in TNF-alpha secretion in the presence of terfenadine	Benlounes et al. 1997
Treatment with DSCG 8 children with CMA	Food challenge before and after a seven- day pre- treatment period with oral sodium chromoglycate: Full protection in 6 children (asthmatic symptoms persisted in 2 patients)	Businco et al. 1983a
Treatment with DSCG 7-year-old child experienced acute, severe anaphylaxis after ingestion of cow's milk	After 3 months of oral cromolyn therapy, the patient was able to tolerate small amounts of milk and moderate amounts of foods containing milk	Jones 1985
Treatment with DSCG 16 children with CMA	Pretreatment with sodium cromoglycate diminished the effect of milk challenge on gastrointestinal permeability, and usually decreased the severity of elicited symptoms	Falth-Magnusson et al. 1986
Treatment with DSCG 30 children with suspected CMA, a) with clinically positive challenge, b) with negative challenge	Oral disodiumcromoglycate (DSCG) pretreatment did not alter the number of clinically positive challenges; significant increase in urinary lactose/mannitol ratio (intestinal permeability test) with placebo pretreatment as compared b); no significant differences after DSCG pretreatment	Van Elburg et al. 1993
Treatment with Ketotifen 1 patient with CMA	White blood cells were pretreated with Ketotifen: inhibition of eosinophils degranulation	Podleski et al. 1984

Anti-Idiotypic Antibodies *(In Vitro Study)* 2 sera from patients with CMA	Concept of specific immune treatment by antibodies capable of specifically neutralizing anti-allergen antibodies; polyclonal antibodies against a peptide that is complementary to a major epitope of beta-LG were produced; these antibodies neutralized in vitro both well-characterized anti-beta-LG monoclonal antibodies from mice sensitized to beta-LG and anti-beta-LG IgE from 2 patients with CMA	Sélo et al. 2002

* Studies may be experimental, unproved, or controversial. Please notice the disclaimer !

Oral Desensitization*	Outcome	References
Oral Desensitization 2 cow's milk and cheese allergic adults	Effective oral desensitization with milk or CAS extracts (desensitization protocol)	Wüthrich & Hofer 1986
Oral Desensitization 16 female patients with IgE-mediated CMA (study period 1980-95)	Complete milk tolerance was achieved after a treatment period of 3-5 years in 50% of patients (partial tolerance in 25%), in the other 25% desensitization was interrupted due to repeated allergic reactions during treatment. Desensitization protocol: starting dose established by SPT end point titration with milk diluted in water; oral desensitization starts with one drop given sublingually; dose increased daily up to 10 mL within 24 days; then the next dilution was given and so on until 250 mL undiluted milk were reached; maintenance dose of at least 1 dL of milk per day	Wüthrich 1996
Oral Desensitization 6 children with CMA (age 4-11 years)	Diluted milk followed by increased pure milk was administered following a standardized protocol, at the beginning pretreatment with oral sodium cromoglycate, length of therapy 5 months, after therapy milk was tolerated (maintenance dose: 100 mL 2-3 times / week); 4 patients finished oral desentization successfully, 2 dropped	Patriarca et al. 1998
Oral Desensitization 24 patients with CMA (age 3-43 years)	Treatment was sucessfully completed in 3-8 months in 16 cases; in 5 cases it was abandoned by the patients while in 3 cases the physicians decided to stop (same desensitization protocol as Patriarca et al. 1998)	Nucera et al. 2000a
Oral Desensitization 1 patient with CMA (age 6 years)	Desensitization accomplished in 4 month (same protocol as Patriarca et al. 1998); SPT at the beginning positive for milk, CAS, alpha-LA and beta-LG turned negative after 7 months; specific IgE against milk proteins decreased, while specific IgG4 and IgA increased; reduced production of IL-4 both in vitro (stimulated mononuclear blood cells) and in serum; increased production of IFN-gamma by T-lymphocytes (both spontaneously and after stimulation with beta-LG); results indicating a switch from a Th2 response (production of IL-4) to a Th1 response (with production of IFN-gamma) during oral desensitization	Nucera et al. 2000b
Oral Desensitization 12-year-old girl with persistent IgE-CMA	Effective oral desensitization starting with diluted milk (under clinical conditions, 4-6 doses per day) for 5 days, maintenance with daily intake of fresh milk	Bauer et al. 1999
Oral Tolerization a) 10 infants fed cow's milk- based formula b) 10 infants fed a CAS hydrolysate formula until the age of 9 months	Exposure to cow's milk proteins after the age of 9 months resulted in depressed cellular and humoral responsiveness (beta-LG, BSA, CAS specific IgG and PBMC proliferation)	Vaarala et al. 1995

* Studies may be experimental, unproved, or controversial. Please notice the disclaimer !

6 Composition of Cow's Milk

6.1 Distribution of Nutrients (Whole Milk)

For other milk products see: USDA Nutrient Database

Nutrients: Content per 100 g		
Energy 274 kJ (65 kcal) Water 87.7 g Protein 3.3 g Lipid 3.6 g Carbohydrate 4.6 g Organic Acids 0.2 g Minerals 0.7 g **Minerals** Sodium 50 mg Potassium 155 mg Magnesium 12 mg Calcium 120 mg Manganese 3 µg Iron 45 µg Copper 17 µg Zinc 380 µg Phosphorus 90 mg Chloride 100 µg Fluoride 17 µg Iodine 3 µg	**Vitamins** Vitamin A 30 µg Carotin 17µg Vitamin D 60 ng Vitamin E 85 µg Vitamin K 4 µg Vitamin B1 35 µg Vitamin B2 180 µg Nicotinamide 90 µg Pantothenic acid 350 µg Vitamin B6 45 µg Biotin 4 µg Folic acid 6 µg Vitamin B12 420 µg Vitamin C 2 mg **Amino Acids** Arg 120 mg His 90 mg Ile 210 mg Leu 350 mg	Lys 260 mg Met 85 mg Phe 170 mg Thr 150 mg Trp 45 mg Tyr 170 mg Val 230 mg **Carbohydrates** Lactose 4550 mg **Lipids** Palmitic acid 930 mg Stearic acid 400 mg Oleic acid 890 mg Linolic acid 90 mg Linoleic acid 25 mg Cholesterol 12 mg **Others** Citric acid 210 mg

Reference: Deutsche Forschungsanstalt für Lebensmittelchemie, Garching bei München (ed), **Der kleine "Souci-Fachmann-Kraut" Lebensmitteltabelle für die Praxis**, WVG, Stuttgart 1991

6.2 Proteinfraction

Proteins / Glycoproteins	**Amount** of total protein	**Concentration in Milk**
Caseins	80%	29.5 g/L
alpha S1	36%	12-15 g/L
alpha S2	10%	3-4 g/L
beta	34%	9-11 g/L
kappa	13%	3.5 g/L
gamma	7%	1.2 g/L
Whey Proteins	20%	6.3 g/L
beta-LG	50%	3-4 g/L
alpha-LA	22%	1-1.5 g/L
Immunoglobulines	15%	0.6-1.0 g/L
BSA	5%	0.1-0.4 g/L
Lactoferrin	2%	0.09 g/L

References: Jensen 1995, Wal et al. 1995, Wal 1998

7 Allergens of Cow's Milk

Proteins / Glycoproteins	Allergen Nomenclature	References
alpha-Lactalbumin [14.2 kDa]	Bos d 4	Goldman et al. 1963a, Gjesing et al. 1986
beta-Lactoglobulin [18.3 kDa]	Bos d 5	Goldman et al. 1963a, Gjesing et al. 1986
Serum Albumin [67 kDa]	Bos d 6	Goldman et al. 1963a, Gjesing et al. 1986
Immunoglobulin [160 kDa]	Bos d 7	Gjesing & Lowenstein 1984, Gjesing et al. 1986, Bernhisel-Broadbent et al. 1991
Caseins [20-30 kDa]	Bos d 8	Goldman et al. 1963a, Gjesing et al. 1986, Docena et al. 1996
Lactoferrin [80 kDa]		Wal et al. 1995a

7.1 Sensitization to Cow's Milk Allergens

<table>
<tr><th>Country / Subjects</th><th>Sensitivity to</th><th>References</th></tr>
<tr><td>Argentina, La Plata
80 patients with CMA (3 months to 25 years, mean 6 years)</td><td>CAS in 100%
beta-LG in 13%
alpha-LA in 6.3%
(SDS-PAGE immunoblot, RAST)</td><td>Docena et al. 1996</td></tr>
<tr><td>Australia, North Ryde, NSW
children with immediate-type CMA</td><td>beta-LG in 63%
alpha-LA in 75%
(RAST)</td><td>Adams et al. 1991</td></tr>
<tr><td>Denmark, Odense
a) 21 infants with IgE-CMA
b) 18 infants with non-IgE-CMA</td><td><table><tr><th></th><th>(a)</th><th></th><th>(b)</th><th></th></tr><tr><td>beta-LG</td><td>50%</td><td>(45%)</td><td>20%</td><td>(76%)</td></tr><tr><td>alpha-LA</td><td>6%</td><td>(25%)</td><td>7%</td><td>(6%)</td></tr><tr><td>BSA</td><td>63%</td><td>(75%)</td><td>27%</td><td>(88%)</td></tr><tr><td>bovine IgG</td><td>19%</td><td>(40%)</td><td>0%</td><td>(59%)</td></tr><tr><td>Lactoferrin</td><td>0%</td><td>(25%)</td><td>7%</td><td>(0%)</td></tr></table>at 6 months (12 months)
(specific serum IgE in CRIE after milk challenge)</td><td>Host et al. 1992</td></tr>
<tr><td>Finland, Turku
challenge proven patients with CMA (age of <17 years) (n=11 in SPT, n=12 in RAST)</td><td><table><tr><th></th><th>SPT</th><th>RAST (>/= 2)</th></tr><tr><td>alpha-CAS</td><td>91%</td><td>25%</td></tr><tr><td>alpha-LA</td><td>82%</td><td>67%</td></tr><tr><td>beta-LG</td><td>64%</td><td>50%</td></tr><tr><td>BSA</td><td>73%</td><td>25%</td></tr></table></td><td>Vanto et al. 1987</td></tr>
</table>

France, Lille, Gif sur Yvette 92 patients with CMA	<table><tr><th></th><th>(1)</th><th>(3)</th></tr><tr><td>beta-LG</td><td>in 61%</td><td>68%</td></tr><tr><td>CAS</td><td>in 65%</td><td>66%</td></tr><tr><td>alpha-LA</td><td>in 51%</td><td>58%</td></tr><tr><td>BSA</td><td>in 43%</td><td>50%</td></tr><tr><td>colostral IgG</td><td></td><td>36% (2)</td></tr><tr><td>Lactoferrin</td><td>in 35%</td><td>45%</td></tr></table>(RAST) Association of sensitivities (1): CAS in 87% of alpha-LA sensitive patients beta-LG in 78% of alpha-LA sensitive patients BSA sensitivity seemed independent Lactoferrin negative correlation to CAS	(1) Wal et al. 1995a (2) Lefranc-Millot et al. 1996 (3) Bernard et al. 1998
Germany, Kiel 13 children with strongly suspected CMA (age of 8 months to 8 years)	alpha-LA in 85% beta-LG B in 77% beta-LG A in 69% CAS in 69% alpha-S CAS in 46% beta-CAS in 62% kappa-CAS in 54% (SPT)	Kaiser et al. 1990
Italy, Milan 6 children with CMA	alpha-CAS 100% beta + gamma-CAS 50% kappa-CAS 33% alpha-LA 17% beta-LG 50% BSA 0% (according to graded staining in SDS-PAGE immunoblot)	Restani et al. 1999
Italy, Rome 25 children with CMA (DBPCFC)	CAS (23-36 kDa) 72% alpha-LA (14.2 kDa) 72% beta-LG (18.3 kDa) 72% BSA (66 kDa) 72% Lactoferrin (80 kDa) 28% (SDS-PAGE immunoblot)	Businco et al. 2000
Japan, Tokyo 8 children with CMA	CAS 75% (RAST)	Hasegawa et al. 2000
Switzerland, Geneva 10 children with CMA	CAS 90% alpha-LA 20% beta-LG 50% (SDS-PAGE immunoblot)	Szabó & Eigenmann 2000
Switzerland, Zurich (1) 34 adults with CMA (2) 8 adults with CMA	<table><tr><th></th><th>(1)</th><th>(2)</th></tr><tr><td>CAS</td><td>in 71%</td><td>in 100%</td></tr><tr><td>beta-LG</td><td>in 3%</td><td>in 13%</td></tr><tr><td>alpha-LA</td><td>in 15%</td><td>in 0%</td></tr></table>(RAST)	(1) Stoger & Wüthrich 1993 (2) Wüthrich & Johansson 1995

<table>
<tr>
<td>Taiwan, Taipei
30 children with suspected CMA (1 to 9 years of age)</td>
<td>CAS in 80%
beta-LG in 53%
alpha-LA in 80%
(RAST)
multiple sensitization to
alpha-LA and beta-LG in 13%
CAS and alpha-LA in 27%
CAS, alpha-LA and beta-LG in 37%</td>
<td>Lin et al 1998</td>
</tr>
<tr>
<td>USA, Baltimore, MD
22 cow's milk- sensitive patients</td>
<td>bovine Immunoglobulins in 73% (RAST)</td>
<td>Bernhisel-Broadbent et al. 1991</td>
</tr>
<tr>
<td>USA, Galveston, TX
45 children with CMA (96% < 6 months of age)</td>
<td>
<table>
<tr><th></th><th>Skin Test</th><th>n=</th><th>OCT*</th><th>n=</th></tr>
<tr><td>alpha-LA</td><td>in 53%</td><td>34</td><td>in 50%</td><td>20</td></tr>
<tr><td>beta-LG</td><td>in 62%</td><td>37</td><td>in 52%</td><td>23</td></tr>
<tr><td>BSA</td><td>in 52%</td><td>44</td><td>in 42%</td><td>26</td></tr>
<tr><td>CAS</td><td>in 60%</td><td>45</td><td>in 63%</td><td>27</td></tr>
</table>
*frequencies in 27 oral challenge test (OCT) positive children
</td>
<td>(1) Goldman et al. 1963a
(2) Goldman et al. 1963b</td>
</tr>
<tr>
<td>USA, Rochester, NY
(1) 29 children with CMA (age of onset 1 day to 10 months)
(2) 21 children with CMA</td>
<td>
<table>
<tr><th></th><th>RAST (>/= 3)</th><th>n=</th><th>IB*</th></tr>
<tr><td>alpha-LA</td><td>in 71%</td><td>24</td><td>in 4.8%</td></tr>
<tr><td>beta-LG</td><td>in 54%</td><td>24</td><td>in 14%</td></tr>
<tr><td>BSA</td><td></td><td></td><td>in 14%</td></tr>
<tr><td>CAS</td><td>in 46%</td><td>26</td><td>in 57%</td></tr>
<tr><td>Reference</td><td>(1)</td><td></td><td>(2)</td></tr>
</table>
*SDS-PAGE immunoblot (graded scale >/= 2+)
</td>
<td>(1) Schwartz et al. 1987
(2) Amonette et al. 1993</td>
</tr>
</table>

7.2 Properties of alpha-Lactalbumin

7.2.1 Molecular Biological Properties

alpha-Lactalbumin (alpha-LA)		References
Allergen Nomenclature Bos d 4		(1) Allergen Nomenclature Sub-Committee 2001
Isoallergens and Variants Genetic variants A and B (1)		(1) Bell et al. 1970
Molecular Mass SDS-PAGE: 14.2 kDa (1), 13 kDa (2) ESI-MS: 14178 Da (3)		(1) Docena et al. 1996 (2) del Val et al. 1999 (3) Slangen & Visser 1999
Isoelectric Point pI 4.8		(1) Wal 1998
Amino Acid Sequence, mRNA, and cDNA		(1) Brew et al. 1970 (2) Hurley & Schuler 1987 (3) Vilotte et al. 1987 (4) Wang et al. 1989 (5) Bleck & Bremel 1993
alpha-LA		
SWISS-PROT:	P00711	
GenBank:	X06366, M18780, J05147, M90645	
PIR:	LABO	
Amino acids	123 residues (1)	
mRNA	703 bp (2), 724 bp (4)	
cDNA		
Gene	3090 bp (3), 2044 bp (5)	
recombinant Protein expression in *Escherichia coli*: expression of recombinant alpha-LA (1) expression in yeasts: expression of recombinant alpha-LA in Saccharomyces cerevisiae (2) expression in transgenic mice: expression of recombinant alpha-LA (3)		(1) Wang et al. 1989 (2) Viaene et al. 1991 (3) Soulier et al. 1994
3D-Structure X-ray studies of alpha-LA: significance of conformation for action in lactose synthase (1) 3D-structures of alpha-LA compared with beta-LG and lactoferrin (2)		(1) Pike et al. 1996 (2) Sharma et al. 2001
Posttranslational Modifications Disulfide Bridges: 4 disulfide bonds: 6-120, 28-111, 61-77, 73-91 (2) Glycosylation: Carbohydrate composition: GlcNAc, GalNAc, Man, Gal, Fuc, NeuAc (1) Single glycosylation site: Asn-45 (3) Detection of a glycosylated isoform (16-kDa in SDS-PAGE) with carbohydrate detection kit (4) Mixture of 14 different glycosylated isoforms and proposed composition of monosaccharides (15.8 to 16.7 kDa by ESI-MS) (5) Analysis of carbohydrates released from alpha-LA by mass spectrometry (5)		(1) Barman 1970 (2) Vanaman et al. 1970 (3) Hopper & McKenzie 1973 (4) Kim & Jiminzez-Flores 1994 (5) Slangen & Visser 1999
Biological Function alpha-LA belongs to the family 22 of glycosyl hydrolases (lysozyme c superfamily), regulatory subunit of lactose synthase (1) Calcium binding properties (2), 2 Ca2+ binding sites one of which with high affinity (3)		(1) SWISS-PROT (2) Hiraoka et al. 1980 (3) Kronman et al. 1981
Location production in mammary gland (1)		(1) SWISS-PROT

Sequence Homology alpha-LA from water buffalo: aa sequence identity 99% (1) alpha-LA from goat and sheep: aa sequence identities 95% and 94% (1) human alpha-LA: aa sequence identity 78% (3) lysozyme from hen's egg white: alpha-LA evolved from the calcium- binding lysozyme along the mammalian lineage after the divergence of birds and mammals (2) lysozyme from various species: aa sequence identity up to 46% (1)	(1) BLAST at PIR (2) Nitta & Sugai 1989 (3) Wal 1998

7.2.2 Allergenic Properties

alpha-Lactalbumin (alpha-LA) — **References**

Frequency of Sensitization
IgE-binding to alpha-LA in 0-80% of patients (1)

(1) see 7.1 Sensitization to Cow's Milk Allergens

B-Cell Epitopes
IgE binding sites located on alpha-LA:

Peptides	Positivity in Patients	Ref.
1-16 (synthetic peptide)	64% (c)	(3)
5-18 (synthetic peptide)	+ (a)	(1)
6-10 :S-S: 115-123 (tryptic peptide)	11% (a)	(2)
13-26 (synthetic peptide)	45% (c)	(3)
17-58 (tryptic peptide)	26% (a)	(2)
47-58 (synthetic peptide)	27% (c)	(3)
59-94 (reduced tryptic peptide)	16% (a)	(2)
59-93 (native tryptic peptide)	26% (a)	(2)
93-102 (synthetic peptide)	27% (c)	(3)
109-123 (tryptic peptide)	11% (b)	(2)

(a) direct ELISA, EAST / RAST
(b) EAST / RAST-inhibition
(c) dot / immunoblot (SPOTs membrane technique)

(1) 2 patients with CMA
(2) 19 patients with CMA
(3) 11 patients with persistent CMA (4-18 years of age, IgE to cow's milk >100 $kU_{(A)}/L$), positivity of 73% to at least 1 of the 4 IgE-binding epitopes; none of these epitopes detected by sera from 8 children <3 years of age (IgE to cow's milk <30 $kU_{(A)}/L$) who are likely to outgrow CMA; 3 IgG binding regions identified using 7 sera from patients with persistent CMA (1)

(1) Adams et al. 1991
(2) Maynard et al. 1997
(3) Järvinen et al. 2001

Cross-Reactivity
sequence homology of beta-LG peptide 124-134 and alpha-LA 5-18, both IgE-binding (1)

(1) Adams et al. 1991

PBMC Proliferation
stimulation with alpha-LA (1)

(1) see Diagnostic Features of CMA: CBMC Proliferation

T-Cell Clone (TCC) Reactivity CMA in infants with atopic dermatitis associated with production of TH-2 cytokines; number of reactive TCC to alpha-LA (all TCC CD4+ and expressed alpha/beta T-cell receptor): **TCC reactivity** / **No. of TCC** / **alpha-LA** 2 patients with CMA / 40 / 8 2 patients without CMA / 36 / 0	(1) Schade et al. 2000
Alteration of Allergenicity trypsin hydrolysis: IgE binding to different tryptic peptides of alpha-LA in 8/19 sera from cow's milk allergic patients (ELISA) (1)	(1) Maynard et al. 1997 see also 10 Stability of Cow's Milk Allergens

7.3 Properties of beta-Lactoglobulin

7.3.1 Molecular Biological Properties

beta-Lactoglobulin (beta-LG)	**References**
Allergen Nomenclature Bos d 5	(1) Allergen Nomenclature Sub-Committee 2001
Isoallergens and Variants Main genetic variants A (Asp-64, Val-118) and B (Gly-64 and Ala-118) (1, 3) Minor genetic variants of subtype B with single substitution: variant C (Gln-59 > His-59) (SWISS-PROT), variant D (Glu-45 > Gln-45) (2), variant W (Ile-56 > Leu-56) (4), variants I (Glu-108 > Gly-108) and J (Pro-126 > Leu-126) (5)	(1) Braunitzer et al. 1973 (2) Brignon & Ribadeau-Dumas 1973 (3) Ebeler et al. 1990 (4) Godovac-Zimmermann et al. 1990 (5) Godovac-Zimmermann et al. 1996
Molecular Mass Mr in SDS-PAGE: 18 kDa (1, 2)	(1) Docena et al. 1996 (2) del Val et al. 1999
Isoelectric Point pI 5.3 (2) variant A: 5.13 (1), variant B: 5.23 (1)	(1) Fredriksson 1972 (2) Wal 1998
Amino Acid Sequence, mRNA, and cDNA **Bos d 5** / **beta-LG** / **Variant B** **SWISS-PROT:** P02754 **GenBank:** M19088, X14712, M27732, K01086, X52581 / Z48305 **PIR:** LGBO **Amino acids** 162 residues (1) **mRNA** 790 bp (3) **cDNA** 601 bp (2) / 9432 bp (4)	(1) Braunitzer et al. 1973 (2) Jamieson et al. 1987 (3) Alexander et al. 1989 (4) Hyttinen et al. 1998

recombinant Protein expression in *Escherichia coli:* expression using a tac promoter vector, pTTQ18 (1) expression of 2 site-directed mutants with an additional disulfide bond, increased thermostability (3) expression in strain DH5alpha, positive IgE binding from 5 patients with CMA (4) expression in a denatured form in periplasm using the pET26 vector (8) expression in yeasts: expression of recombinant beta-LG (2) and a site directed mutant (6) in Saccharomyces cerevisiae, mutant inhibited the proliferation of CD4+ TCC from mice (6) expression in native conformation in Pichia pastoris (5) epression in mouse cells: expression in native conformation in COS-7 cells and in vivo in mouse tibialis muscle (8) expression in transgenic mice: Bovine beta-LG gene was expressed mammary gland- specifically in transgenic mice, expression levels of beta-LG in milk > 1 mg/mL (7)	(1) Batt et al. 1990 (2) Totsuka et al. 1990 (3) Cho et al. 1994 (4) Chatel et al. 1996 (5) Kim et al. 1997 (6) Totsuka et al. 1997 (7) Hyttinen et al. 1998 (8) Chatel et al. 1999
3D-Structure X-ray studies of beta-LG (1) NMR studies of recombinant beta-LG (2) 3D-models of native and oxidized beta-LG, and partly and fully reduced beta-LG mutants (3) 3D-structures of beta-LG compared with alpha-LA and lactoferrin (4)	(1) Brownlow et al. 1997 (2) Kuwata et al. 1998 (3) del Val et al. 1999 (4) Sharma et al. 2001
Posttranslational Modifications Disulfide Bridges: beta-LG occurs naturally as a mixture of monomers and 36-kDa dimers (2) 2 disulfide bonds: 66-160, 106-(119 or 121) (1)	(1) Brownlow et al. 1997 (2) Wal 1998
Biological Function belongs to lipocalin family (2), binds retinol (1)	(1) SWISS-PROT (2) Virtanen et al. 1999
Sequence Homology beta-LG from water buffalo and mouflon: aa sequence identies 98% and 95% (1) beta-LG from goat and sheep: aa sequence identies 94% and 93% (1) cockroach allergen Bla g 4: aa sequence homology about 20% (2)	(1) BLAST at PIR (2) Arruda et al. 1995

7.3.2 Allergenic Properties

beta-Lactoglobulin (beta-LG)

Frequency of Sensitization
IgE-binding to in 13-76% of patients (1)

Allergenicity of Variants A and B
No difference in IgE titers specific for genetic variants A and B of beta-LG (1)

B-Cell Epitopes
IgE binding sites located on beta-LG:

Peptides	Positivity in Patients	inhibition of IgE binding to beta-LG [%]	3D-Location on beta-LG	Ref.
1-16 (synthetic peptide)	36% (e)*			(7)
1-8 (tryptic peptide)	58% (b)			(6)
8-24 (CNBr peptide)	53% (b)	max. 34%		(4)
9-14 (tryptic peptide)	40% (b)			(6)
15-26 (synthetic peptide)	44% (c)	max. 20%		(3)
25-107 (CNBr peptide)	79% (4), + (1) (b)	max. 38% (4)		(1, 4)
25-61 (fragment)	+ (b)			(1)
25-40 (tryptic peptide)	72% (b)			(6)
31-48 (synthetic peptide)	45% (e)*			(7)
35-46 (synthetic peptide)	25% (c)	max. 40%		(3)
41-107 (fragment)	+ (b)			(1)
41-60 (tryptic peptide)	92% (b)		surface	(6)
47-60 (synthetic peptide)	73% (e)*			(7)
49-60 (synthetic peptide)	+ (e) **			(7)
62-107 (fragment)	+ (b)			(1)
67-78 (synthetic peptide)	55% (e)*			(7)
75-86 (synthetic peptide)	91% (e)*			(7)
78-83 (tryptic peptide)	28% (b)			(6)
84-91 (tryptic peptide)	40% (b)		cryptic	(6)

References

(1) see 7.1 Sensitization to Cow's Milk Allergens

(1) van Beresteijn et al. 1995

(1) Otani et al. 1989
(2) Adams et al. 1991
(3) Ball et al. 1994
(4) Selo et al. 1998
(5) Heinzmann et al. 1999
(6) Selo et al. 1999
(7) Järvinen et al. 2001

B-Cell Epitopes (continued)
IgE binding sites located on beta-LG:

Peptides	Positivity in Patients	inhibition of IgE binding to beta-LG [%]	3D-Location on beta-LG	Ref.
85-96 (synthetic peptide)	44% (c)	max. 10%		(3)
92-100 (tryptic peptide)	52% (b)			(6)
95-113 (synthetic peptide)	100% (d)	14 - 38% (c, d)		(5)
97-108 (synthetic peptide)	100% (c)	max. 70% (20%*)		(3)
102-124 (tryptic peptide)	97% (b)		surface	(6)
108-145 (CNBr peptide)	68% (4), + (1) (b)	max. 57% (4)		(1, 4)
117-128 (synthetic peptide)	13% (c)	max. 30%		(3)
119-128 (synthetic peptide)	+ (e) **			(7)
124-134 (synthetic peptide)	+ (b)	60%		(2)
125-145 (fragment)	+ (b)			(1)
125-135 (tryptic peptide)	28% (b)		surface	(6)
127-144 (synthetic peptide)	82% (e)*			(7)
129-138 (synthetic peptide)	+ (e) **			(7)
141-152 (synthetic peptide)	55% (e)*			(7)
143-152 (synthetic peptide)	+ (e) **			(7)
146-162 (CNBr peptide)	42% (4), + (1) (b)	max. 28% (4)		(1, 4)
149-162 (tryptic peptide)	89% (b)			(6)
151-162 (synthetic peptide)	31% (c)	max. 20%		(3)

(a) SDS-PAGE / immunoblot
(b) direct ELISA, EAST / RAST
(c) EAST / RAST-inhibition
(d) Pin-ELISA
(e) dot / immunoblot (SPOTs membrane technique)

(1) 2 patients with CMA
(2) 2 patients with CMA
(3) 16 patients with CMA, * pooled serum
(4) 19 patients with CMA
(5) 14 children with CMA (age 6 months to 9 years)
(6) 46 patients with CMA (location of epitopes in 3D-model of beta-LG)
(7) * 11 patients with persistent CMA (4-18 years of age, IgE to cow's milk >100 $kU_{(A)}/L$); ** 8 children <3 years of age (IgE to cow's milk <30 $kU_{(A)}/L$) who are likely to outgrow CMA (pooled serum); positivity of 100% to at least 1of the 7 IgE-binding epitopes in patients with persistent CMA; 6 IgG binding regions identified using 7 sera from patients with persistent CMA

(1) Otani et al. 1989
(2) Adams et al. 1991
(3) Ball et al. 1994
(4) Selo et al. 1998
(5) Heinzmann et al. 1999
(6) Selo et al. 1999
(7) Järvinen et al. 2001

Cross-Reactivity
beta-LG peptide 124-134 and alpha-LA 5-18 (1)

(1) Adams et al. 1991

T-Cell Epitopes
Specific T-Cell Proliferation with:
beta-LG 145-161 (peptide) (1)

(1) Piastra et al. 1994

PBMC Proliferation
stimulation with beta-LG (1)

(1) see Diagnostic Features of CMA

PBMC Stimulation / Cytokines PBMC stimulation with beta-LG: decrease in IFN-gamma production in cow's milk allergic children with atopic dermatitis as compared to immediate- type allergic or tolerant children (1)	(1) Hill et al. 1993
T-Cell Clone (TCC) Reactivity CMA in infants with atopic dermatitis associated with production of TH-2 cytokines; number of reactive TCC to beta-LG (all TCC CD4+ and expressed alpha/beta T-cell receptor): **TCC reactivity** / **No. of TCC** / **beta-LG** 2 patients with CMA / 40 / 11 2 patients without CMA / 36 / 33	(1) Schade et al. 2000
Alteration of Allergenicity cyanogen bromide cleavage: no alteration of IgE-binding in 50% of patients with CMA, in 10% increased IgE- binding to CNBr- cleaved beta-LG (EAST inhibition) (2) pepsin hydrolysis: IgE-binding in 40% of 10 patients with CMA to native beta-LG and in 100% to peptic and peptic- tryptic digested beta-LG (RAST) (1) trypsin hydrolysis: reduced IgE binding (about <50%) in 75% and increased IgE binding in 9% of sera from 46 patients with CMA (3) reduction of disulfide bonds: no alteration of IgE-binding (1) increased pepsin digestibility and IgE- binding capacity (in animal model) of b-LG after reduction of disulfide bonds with thioredoxin (4)	(1) Haddad et al. 1979 (2) Selo et al. 1998 (3) Selo et al. 1999 (4) del Val et al. 1999 see also 10 Stability of Cow's Milk Allergens

7.4 Properties of Bovine Serum Albumin

7.4.1 Molecular Biological Properties

Bovine Serum Albumin (BSA)	**References**
Allergen Nomenclature Bos d 6	(1) Allergen Nomenclature Sub-Committee 2001
Molecular Mass Mr in SDS-PAGE: 67.0 kDa (1), 66.3 kDa (2)	(1) Miller & Gemeiner 1993 (2) Wal 1998
Isoelectric Point pI 4.7-4.95 (1), 4.9-5.1 (2)	(1) Miller & Gemeiner 1993 (2) Wal 1998
Amino Acid Sequence, mRNA, and cDNA **BSA** **SWISS-PROT:** P02769 **GenBank:** M73993, X58989, Y17769 **PIR:** ABBOS **Amino acids** 583 residues (1), 607 (precursor) **mRNA** 2035 bp, 2061 bp, 1883 bp **cDNA**	(1) Brown 1975

Posttranslational Modifications Disulfide Bridges: 9 disulfide bonds (1)	(1) Brown 1974
Biological Function BSA belongs to the ALB/AFP/VDB family, main plasma protein (1) 3 homologous domains: I aa 4-177, II aa 196-369, III aa 388-567 (on precursor: I aa 28-201, II aa 220-393, III aa 412-591 (1) good binding capacity for water, Ca2+, Na+, K+, fatty acids, hormones, bilirubin and drugs, main function regulation of colloidal osmotic blood pressure (1)	(1) SWISS-PROT
Location production in plasma, extracellular secretion (1)	(1) SWISS-PROT
Sequence Homology serum albumin from sheep: aa sequence identity 92% (1) serum albumins from pig, cat, human, rhesus macaque, horse: aa sequence identities 74-79% (1)	(1) BLAST at PIR
Other Properties possible trigger of insulin-dependent diabetes mellitus: BSA peptide aa 126-144 (ABBOS) may be the reactive epitope (1)	(1) Karjalainen et al. 1992

7.4.2 Allergenic Properties

Bovine Serum Albumin (BSA)	**References**
Frequency of Sensitization IgE-binding to BSA in 0-88% of patients (1)	(1) see 7.1 Sensitization to Cow's Milk Allergens
B-Cell Epitopes IgE binding sites located on aa sequence of BSA: aa 500-574 (of BSA) / aa 524-598 (of precursor) (1) (1) tryptic peptides, SDS-PAGE immunoblotting, 5 beef allergic children	(1) Beretta et al. 2001
Alteration of Allergenicity heat treatment: Negative reaction to cooked BSA (1.8 g) and positive reaction to uncooked BSA (55 mg) in DBPCFC in a 19-year old woman (2) pepsin hydrolysis: ABBOS epitope (aa 126-144) not completely eliminated during digestion at pH 3-4 (mAb ELISA inhibition)* (1) * no IgE-binding studies	(1) Alting et al. 1997 (2) Kanny et al. 1998

7.5 Properties of Caseins

7.5.1 Molecular Biological Properties

Caseins (CAS)

References

Allergen Nomenclature Bos d 8

(1) Allergen Nomenclature Sub-Committee 2001

Isoallergens and Variants

CAS	alpha-S1	alpha-S2	beta	kappa
Genetic variants	A, B, C, D (1), F (5)	A, D (3)	A1, A2, A3, B, C, E F-5P (4)	A, B, B2 (2)

(1) Mercier et a. 1971, 1973
(2) Grosclaude et al. 1972
(3) Grosclaude et al. 1979
(4) Visser et al. 1995
(5) Prinzenberg et al. 1998

Molecular Mass

	CAS	alpha	beta	gamma	kappa
SDS-PAGE	24 kDa (2)	32.4 kDa (1)	26.6 kDa (1)		19 kDa (1)

(1) Docena et al. 1996
(2) del Val et al. 1999

Isoelectric Point

alpha-S1	alpha-S2	beta-CAS	gamma-CAS	kappa-CAS
pI 4.9-5	pI 5.2-5.4	pI 5.1-5.4		pI 5.4-5.6

(1) Wal 1998

Amino Acid Sequence, mRNA, and cDNA

Bos d 8	alpha-S1	alpha-S2	beta	kappa
SWISS-PROT:	P02662	P02663	P02666	P02668
GenBank:	S72388, M33123, X59856, M38641, X00564	M16644	S67277 (A3), M55158, X06359, M15132, M16645	X00565 (A), M36641 (B2), X14908
PIR:	KABOSB	KABOS2	KBBOA2	KKBOB
Amino acids	199 (1)	207 (4)	209 (3)	169 (2)
mRNA	1123 bp (5) 1172 bp (6) 1134 bp (7)	1024 bp (11)	1094 bp (8) 755 bp (9) 1126 bp (A3, 17)	850 bp (6) 838 bp (10)
cDNA	1862 bp (15)	2510 bp (16)		
Gene	17508 bp (14)	18483 bp (16)	10338 bp (13)	7595 bp (12)

(1) Mercier et al. 1971, 1973
(2) Grosclaude et al. 1972
(3) Ribadeau-Dumas et al. 1972
(4) Brignon et al. 1977
(5) Nagao et al. 1984
(6) Stewart et al. 1984
(7) Gorodetskii et al. 1986
(8) Baev et al. 1987
(9) Jimenez-Flores et al. 1987
(10) Gorodetskii & Kaledin 1987
(11) Stewart et al. 1987
(12) Alexander et al. 1988
(13) Bonsing et al. 1988
(14) Koczan et al. 1991
(15) Chen et al. 1992
(16) Groenen et al. 1993
(17) Simons et al. 1993

recombinant Protein

expression in	alpha-S1	alpha-S2	beta	gamma	kappa
Escherichia coli			(2)		(1)
Transgenic mice	(5)		(3), (4)		

(1) Kang & Richardson 1988
(2) Simons et al. 1993
(3) Hitchin et al. 1996
(4) Jeng et al. 1997
(5) Rijnkels et al. 1998

3D-Structure

Micelle aggregation:
CAS subunits associate in solution forming complexes and ordered aggregates of micelles in lactoserum by colloidal calcium phosphate and phosphoserine interactions: ratio alpha-S1 / beta / alpha-S2 / kappa-CAS is 37% / 37% / 13% / 13% (2)
Polymerisation
kappa-CAS: monomer or multimer linked by disulfide bonds (1)

(1) SWISS-PROT
(2) Wal 1998

Posttranslational Modifications **Numbers of** / **alpha-S1** / **alpha-S2** / **beta** / **kappa** Disulfide bonds / - / 1 / - / 1 Glycosylation sites / - / - / 7-8 / - Phosphorylation / 8-9 / 10 / 4-5 / 2 Glycosylation of kappa-CAS: O-glycosation sites: distribution of monosaccharide, disaccharide, trisaccharide (straight), trisaccharide (branched), and tetrasaccharide chains were 0.8, 6.3, 18.4, 18.5, and 56.0%, respectively (means of five kappa-CAS) (2)	(1) SWISS-PROT (2) Saito & Itoh 1992
Biological Function alpha-CAS: Calcium phosphate transport capacity of milk (1) kappa: Micelle formation stabilizing, preventing CAS precipitation in milk (1)	(1) SWISS-PROT
Location alpha-CAS, kappa-CAS: production in mammary gland, extracellular secretion (1)	(1) SWISS-PROT
Sequence Homology alpha-S1 and S2 CAS from cow's milk: aa identity 22.5% (2) alpha-S1 CAS from sheep's and goat's milk: aa identity 87-89% (2) alpha-S2 CAS from sheep's and goat's milk: aa identity 87-89% (2) alpha-S1 and S2 CAS from sheep's and goat's milk: aa identity 97-98% (2) beta-CAS from sheep's and goat's milk: aa identity 91% (1) beta-CAS from cow's milk and human milk: aa identity 50% (3) kappa-CAS from sheep's and goat's milk: aa identity 84% (1)	(1) BLAST at PIR (2) Spuergin et al. 1997 (3) Bernard et al. 2000b
Stability **alpha-CAS** / **beta-CAS** / **kappa-CAS** Ca2+ sensitivity / + / + / -	(1) Wal 1998

7.5.2 Allergenic Properties

Caseins (CAS)	**References**
Frequency of Sensitization IgE-binding to CAS in 65-100% of patients (1)	(1) see 7.1 Sensitization to Cow's Milk Allergens
Allergenicity of Subunits Major IgE- binding CAS subunits in 4 patients with CMA and atopic dermatitis: in 1 patient alpha- and kappa-CAS, in 2 patients alpha-CAS, and in 1 patient kappa-CAS (tested: alpha-, beta-, and kappa-CAS) (1) 85% of 58 children presented IgE against each CAS, only 1 child was monosensitized (to kappa-CAS), allergenic potencies according to statistical distribution of specific serum IgE levels: alpha S1-CAS > beta-CAS >> alpha S2-CAS = kappa-CAS (RAST) (2) IgE-binding to alpha-CAS in 100%, beta + gamma-CAS in 50%, and kappa-CAS in 33% of 6 children with CMA (3)	(1) Shimojo et al. 1997 (2) Bernard et al. 1998 (3) Restani et al. 1999

B-Cell Epitopes: alpha S1 CAS

IgE binding sites located on alpha S1 CAS:

Peptides	Positivity in Patients	inhibition of IgE binding to alpha S1 CAS [%]	Ref.
1-54 (fragment)	+ (a)		(1)
1-10 (synthetic peptide)	67% (b)	5% (max. 14%)	(2)
17-36 (synthetic peptide)	89% (d) * 50% (d) **		(4)
19-30 (synthetic peptide)	100% (c)		(2)*
20-31 (synthetic peptide)	58% (b)	7% (max. 40%)	(2)
34-45 (synthetic peptide)	50% (b)	5% (max. 18%)	(2)
39-48 (synthetic peptide)	44% (d) * 13% (d) **		(4)
58-73 (synthetic peptide)	42% (b)	3% (max. 15%)	(2)
61-123 (fragment)	+ (a)		(1)
69-78 (synthetic peptide)	67% (d) * 0% (d) **		(4)
69-78 (synthetic peptide)	60% (d) * 0% (d) **		(5)
86-103 (synthetic peptide)	100% (b)	19% (max. 42%)	(2)
93-98 (synthetic peptide)	100% (c)		(2)*
93-102 (synthetic peptide)	67% (d) * 13% (d) **		(4)
109-120 (synthetic peptide)	89% (d) * 13% (d) **		(4)
123-132 (synthetic peptide)	56% (d) * 13% (d) **		(4)
124-135 (fragment)	+ (a)		(1)
136-196 (CNBr fragment)	+ (a)		(1, 3)
139-154 (synthetic peptide)	56% (d) * 25% (d) **		(4)
141-150 (synthetic peptide)	92% (b)	8% (max. 20%)	(2)*
159-174 (synthetic peptide)	56% (d) * 18% (d) **		(4)
165-199 (fragment)	+ (a)		(1)
173-194 (synthetic peptide)	100% (d) * 0% (d) **		(4)
177-186 (synthetic peptide)	80% (d) * 20% (+50% weak) (d) **		(5)
181-199 (synthetic peptide)	100% (a)	92% and 30% (n=2) (b)	(3)
188-199 (synthetic peptide)	42% (b)	7% (max. 28%)	(2)

(1) 2 patients with CMA
(2) 12 patients with CMA, *similar IgG binding
(3) 9 patients with CMA
(4) * 9 patients with persistent CMA (4-18 years of age, IgE to cow's milk >60 $kU_{(A)}/L$); ** 8 children <3 years of age (IgE to cow's milk <30 $kU_{(A)}/L$) who are likely to outgrow CMA
(5) 36 children with CMA: * 25 with persistent CMA, and ** 11 became clinically tolerant

(1) Otani et al. 1989
(2) Spuergin et al. 1996
(3) Nakajima-Adachi et al. 1998
(4) Chatchatee et al. 2001a
(5) Vila et al. 2001

(a) EAST / RAST
(b) EAST / RAST-inhibition
(c) Pin-ELISA
(d) dot / immunoblot (SPOTs membrane technique)

B-Cell Epitopes: beta-CAS

IgE binding sites located on beta-CAS:

Peptides	Positivity in Patients	Ref.
1-139 (fragment)	+ (a)	(1)
1-93 (fragment)	+ (a)	(1)
1-16 (synthetic peptide)	+ (b) * + (b) **	(2)
1-60 (fragment)	+ (a)	(1)
26-93 (fragment)	+ (a)	(1)
45-54 (synthetic peptide)	+ (b) * + (b) **	(2)
55-70 (synthetic peptide)	+ (b) *	(2)
57-66 (synthetic peptide)	+ (b) **	
83-92 (synthetic peptide)	87% (b) * + (b) **	(2)
106-209 (fragment)	+ (a)	(1)
107-120 (synthetic peptide)	+ (b) * + (b) **	(2)
110-144 (fragment)	+ (a)	(1)
132-144 (fragment)	+ (a)	(1)
135-144 (synthetic peptide)	80% (b) * + (b) **	(2)
149-164 (synthetic peptide)	+ (b) *	(2)
151-160 (synthetic peptide)	40% (+10% weak) (b) * 50% (+50% weak) (b) **	(3)
157-185 (fragment)	+ (a)	(1)
167-184 (synthetic peptide)	+ (b) *	(2)
167-176 (synthetic peptide)	40% (+40% weak) (b) * 80% (+20% weak) (b) **	(3)
175-184 (synthetic peptide)	50% (+10% weak) (b) * 60% (+40% weak) (b) **	(3)
185-208 (synthetic peptide)	+ (b) * + (b) ** (weak)	(2)
186-209 (fragment)	+ (a)	(1)
193-202 (synthetic peptide)	50% (+20% weak) (b) * 100% (b) **	(3)

(a) EAST / RAST
(b) dot / immunoblot (SPOTs membrane technique)

(1) 2 patients with CMA
(2) * 15 patients with persistent CMA (4-18 years of age, IgE to cow's milk >60 $kU_{(A)}/L$);

** 8 children <3 years of age (IgE to cow's milk <30 $kU_{(A)}/L$) who are likely to outgrow CMA (pooled serum)
(3) 36 children with CMA: * 25 with persistent CMA, and ** 11 became clinically tolerant

(1) Otani et al. 1989
(2) Chatchatee et al. 2001b
(3) Vila et al. 2001

B-Cell Epitopes: kappa-CAS

IgE binding sites located on kappa-CAS:

Peptide	Positivity in patients	Ref.
9-26 (synthetic peptide)	93% (b) *	(1)
21-44 (synthetic peptide)	93% (b) * + (b) **	(1)
47-68 (synthetic peptide)	93% (b) *	(1)
53-64 (synthetic peptide)	+ (b) **	(1)
67-78 (synthetic peptide)	+ (b) *	(1)
95-116 (synthetic peptide)	+ (b) *	(1)
111-126 (synthetic peptide)	+ (b) *	(1)
137-148 (synthetic peptide)	+ (b) *	(1)
149-166 (synthetic peptide)	+ (b) *	(1)

(a) dot / immunoblot (SPOTs membrane technique)

(1) * 15 patients with persistent CMA (4-18 years of age, IgE to cow's milk >60 $kU_{(A)}/L$);

** 8 children <3 years of age (IgE to cow's milk <30 $kU_{(A)}/L$) who are likely to outgrow CMA

(1) Chatchatee et al. 2001b

Post-translational Phosphorylation

IgE-binding	response	inhibition
alpha S2 CAS (variant A) a) native and b) dephosphorylated form and c) alpha S2 CAS (variant D) lacking one major phosphorylation site	a = c (on averarge)	binding to a: a > c > b
beta CAS (variant A1) a) native and b) dephosphorylated form	a > b	binding to a: a > b (n=6)
tryptic fragment (aa 1-25) from beta CAS a) native and b) dephosphorylated form		binding to a: a > b (n=4)

53 sera positive to native beta-CAS, 29 sera positive to alpha S2 CAS (variant A), and 28 sera positive to variant D from 53 patients with symptoms of CMA and specific IgE (direct ELISA, and ELISA inhibition) (1)

(1) Bernard et al. 2000a

T-Cell Epitopes: alpha S1 CAS

alpha S1 CAS specific T-Cell Lines responsive to:

1-54 (CNBr fragment) (1)
31-50 (synthetic peptide) (1)
76-95 (synthetic peptide) (1)
91-110 (synthetic peptide) (1)
124-135 (CNBr fragment) (1)
136-155 (synthetic peptide) (1)

(1) 7 TCL from 2 patients with CMA

(1) Nakajima-Adachi et al. 1998

PBMC Proliferation

stimulation with CAS (1)

(1) see Diagnostic Features of CMA

PBMC Stimulation / Cytokines

PBMC stimulation with CAS:
Tendency of (4) and significantly higher (1) PBMC proliferation in cow's milk allergic children with atopic dermatitis as compared to children with atopic dermatitis without cow's milk allergy

16 of 28 CAS- or ovalbumin-specific TCC from cow's milk and egg allergic children were CD8+; 75% of CD4+ TCC and 44% of CD8+ TCC secreted IL-4; all TCC secreted INF-gamma (1)

27% of CD4+ CAS- specific TCCs from adolescent or adult patients with cow's milk-responsive atopic dermatitis, and the majority of house dust mite- specific TCCs, produced IL-4 on mitogen stimulation; INF-gamma was produced by the majority of TCCs with both specificities (3)

PBMC stimulation with kappa- CAS:
25 of 31 TCC from patients with milk- responsive atopic dermatits responded to mixed CAS (alpha-, beta-, kappa-) and kappa- CAS (2)

(1) Reekers et al. 1996
(2) Werfel et al. 1996
(3) Werfel et al. 1997b
(4) Schade et al. 2000

T-Cell Lines (TCL) / Cytokines

PBMC responsiveness to alpha s1- CAS activation was rather weak in cow's milk allergic patients; 26 alpha s1- CAS- specific T-cell lines were established; higher frequency of CD8+ T cells which produced INF-gamma and IL-4 (1)

(1) Nakajima al. 1996

T-Cell Clone (TCC) Reactivity

CMA in infants with atopic dermatitis associated with production of TH-2 cytokines; number of reactive TCC to CAS fractions (all TCC CD4+ and expressed alpha/beta T-cell receptor):

TCC reactivity	No. of TCC	alpha s1-	alpha s2-	beta -	kappa -	whole CAS
4 patients with CMA	50	4	15	1	6	5
4 patients without CMA	43	1	1	0	3	5

(1) Schade et al. 2000

Alteration of Allergenicity

Treatment	alpha-CAS	beta-CAS	kappa-CAS
heat denaturation	NS (1)		
acidic treatment (HCl)	NS (1)		
alkaline treatment (NaOH)	NS (1)		
sodium dodecyl sulfate	NS (1)		
urea denaturation	NS (1)		

NS no significant difference in IgE-binding
(1) patients with CMA

(1) Kohno et al. 1994

see also 10 Stability of Cow's Milk Allergens

8 Isolation & Preparation

Extract / Purified Allergens	Methods	References
CAS and whey proteins	Review of purification and analytical methods by chromatography and electrophoresis methods	Strange et al. 1993
alpha CAS	Purification of commercial CAS by IEC (DEAE Sepharose)	Spuergin et al. 1996 Spuergin et al. 1997

alpha S1-, alpha S2-, beta-, and kappa- CAS	Isoelectric precipitation of whole CAS from skimmed raw milk at pH 4.6; isolation of CAS fractions by successive, selective precipitations, followed by dissolving, dialysis and freeze drying steps; further purification by IEC (purity assessed by RP-HPLC)	Bernard et al. 1998
glycosylated and non-glycosylated alpha-LA fractions	Isolation from whey protein fraction by IEC (DEAE Sepharose) followed by SEC (Sephadex G-75)	Slangen & Visser 1999
beta-LG	Preparation from milk (1); purification by affinity chromatography (antibovine IgG column) followed by IEC (Q Sepharose), purity assessed by RP-HPLC and SDS-PAGE (2)	(1) Wal et al. 1995b (2) Selo et al. 1999
bovine IgG	Acid precipitation of colostral whey and concentration of supernatant, isolation of IgG by affinity chromatography (Avid Gel AL) and further purification by IEC, dialysis, lyophylization	Lefranc-Millot et al. 1996

9 Cross-Reactivities

Cross-Reacting Allergens	Subjects / Methods	References
Cow's Milk Allergens cow's dander allergens	6 patients with cow's milk and 5 with cow's dander allergy: 4/6 patients with CMA showed serum IgE binding to dander allergens of 20, 22, 36, 50 and >200 kDa, dander cross- reactive cow's milk allergens were CAS (2 cases) and beta-LG (1 case); 1/5 cow's dander allergic patients showed serum IgE binding to milk allergens of 69, 92 and >200 kDa (immunoblot inhibition)	Szepfalusi et al. 1993
Cow's Milk goat's, sheep, and modified cow's milk formulas	16 children with CMA: high inhibition of IgE- binding to cow's milk by goats', sheep, modified cows' milk formula and CAS formula (RAST inhibition)	Dean et al. 1993
Cow's Milk goat's milk	9 milk allergic patients: IgE- binding to cow's and goat's milk proteins corresponding in Mr to beta-LG and CAS (immunoblot)	Sabbah et al. 1996
Cow's Milk beef*	8/11 beef allergic children presented concomitant reactivity to cow's milk (DBPCFC)*	Werfel et al. 1997a
Cow's Milk bovine IgG (160 kDa) from beef	Complete inhibition of IgE-binding to bovine IgG from beef by cow's milk (immunoblot inhibition, pooled serum from 5 beef allergic patients)	Ayuso et al. 2000
Cow's Milk goat's milk	26 children with CMA (DBPCFC positive); Sensitivity to goat's milk in 92% (DBPCFC); cow's milk completely extinguished IgE- binding to goat's milk allergens, goat's milk partially inhibited IgE- binding to cow's milk allergens (SDS-PAGE inhibition)	Bellioni-Businco et al. 1999
Cow's Milk ewe, goat, buffalo milk	6 children with CMA: IgE- binding to milk allergens from cow, ewe, goat, and buffalo, but not from camel (SDS-PAGE immunoblot, inhibition)	Restani et al. 1999
Cow's Milk mare's milk	3 children with CMA: Up to 28% inhibition of IgE- binding to cow's milk allergens (CAS, alpha-LA, beta-LG, BSA, and lactoferrin) by mare's milk extract (SDS-PAGE immunoblot inhibition, densitometry)	Businco et al. 2000
alpha-LA lysozyme (hen's egg white)	6/9 egg allergic patients: 12-49% Inhibition of IgE- binding to lysozyme by alpha-LA (RAST inhibition)	Walsh et al. 1987

Caseins goat's, sheep's, and cow's milk	Inhibition of IgE- binding to goat's and sheep's CAS by cow's milk CAS in 1 adult (RAST inhibition)	Wüthrich & Johansson 1995
Caseins whole casein fractions from cow, goat, ewe, rabbit and rat milk *	Sera from 58 patients with CMA and specific IgE to bovine CAS: specific IgE titers: bovine > ovine > caprine CAS; 79% and 66% of sera showed IgE-binding to rabbit-CAS and rat-CAS of <10% intensity as compared to bovine CAS (ELISA)	Bernard et al. 1999
alpha Caseins goat's, sheep's, and cow's milk	17 children with CMA (immediate type): Inhibition of IgE binding to bovine alpha-CAS by alpha-CAS from cow, goat, and sheep (RAST inhibition), lower specific IgE levels to goat- and sheep alpha-CAS (RAST)	Spuergin et al. 1997
Cow's Milk human milk	Exclusively breast-fed children with atopic dermatitis: cross-reactivity between lactoferrin, serum albumin, beta-CAS, and alpha-LA from human and cow's milk, no specific IgE against bovine beta-LG; no clinical relevance of human milk proteins	Cantisani et al. 1997 Bertino et al. 2000
Cow's Milk beta-CAS from cow's milk and human milk	20 patients with CMA and specific IgE against bovine whole CAS: 7 sera contained IgE specific for human beta-CAS; inhibition studies using native human and bovine beta-CAS as well as bovine beta-CAS-derived peptides (aa 53-139, aa 106-209, and aa 1-52) demonstrated several common epitopes (ELISA)	Bernard et al. 2000b

* multiple sensitization (not proved by inhibition-tests)

Unique Allergens	Subjects / Methods	References
Caseins goat's and sheep's vs cow's milk CAS	No inhibition of IgE- binding to goat's and sheep's CAS by cow's milk CAS in 1 adult (RAST inhibition)	Wüthrich & Johansson 1995
Caseins goat's and sheep's vs cow's milk CAS	1 cow's milk tolerant child with goat's and sheep's milk allergy: Decreased inhibition of IgE- binding to goat's milk and CAS by cow's milk and CAS, but not by goat's and sheep's milk and CAS (RAST inhibition); IgE binding to allergens in goat's milk at 22, 27, and 31 kDa, in sheep's milk at 31 kDa and cow's milk at 34 kDa (SDS-PAGE immunoblot)	Umpierrez et al. 1999
Cow's and Mare's Milk 16 and 18 kDa allergens (most likely representing alpha-LA and beta-LG) from mare's milk did not cross-react with corresponding cow's milk allergens	1 mare's milk allergic adult (cow's milk tolerant) (SPT, intracutaneous test, RAST, SDS-PAGE immunoblot)	Gall et al. 1996

10 Stability of Cow's Milk Allergens

<table>
<tr><th>Treatment</th><th>Effects</th><th>References</th></tr>
<tr><td>Heat
boiling of skimmed milk, 10 min</td><td>Reduction of IgE binding to alpha-LA about 50%, to CAS fractions >66% and to beta-LG, BSA and bovine Ig binding abolished (CRIE score)</td><td>Gjesing et al. 1986</td></tr>
<tr><td>Pasteurization, Homogenization, Hydrolysis
1) raw untreated, 2) pasteurized or, 3) homogenized and pasteurized cow's milk, and 4) a commercial hypoallergenic hydrolysed CAS infant formula</td><td>Similar positive reactions in SPT and DBPCFC to 1), 2) and 3), no reactions to 4) in 5 cow's milk allergic children (immediate- type); tendency of lower thresholds of processed milk</td><td>Host & Samuelsson 1988</td></tr>
<tr><td>Heat
boiling of milk, 2 and 10 min</td><td>Boiling of milk for 10 but not for 2 min eliminated SPT reactivity to BSA and beta-LG, whereas CAS was heat stabile (8 DBPCFC positive adults with CMA)</td><td>Norgaard et al. 1996</td></tr>
<tr><td>Heat
boiling of milk, 5 min</td><td>No difference in IgE- binding to raw and cooked milk from sera of 2 patients with CMA (immuno-dot-blotting)</td><td>Werfel et al. 1997a</td></tr>
<tr><td>Heat
boiling of extensively hydrolyzed CAS formula (Nutramigen)</td><td>Positive SPT to boiled and unboiled formula in a girl with CMA</td><td>Nilsson et al. 1999</td></tr>
<tr><td>Heat, Reduction, Hydrolysis
a) heat 96°C, pH 8.0
b) carboxymethylation
c) limited proteolysis</td><td>Thermoaggregated (a) and reduced forms (b) exhibited similar
anaphylactic effect on sensitized guinea pigs; allergenic properties of beta-LG appeared unaltered in food hydrolyzates after thermal treatment and limited proteolysis</td><td>Gmoshinskii et al. 1990</td></tr>
<tr><td>gamma Irradition
alpha-CAS, beta-LG</td><td>ELISA inhibition using patients' IgE and rabbit IgGs specific for alpha-CAS and beta-LG, respectively: reduced IgE-binding to irradiated proteins with different slopes of inhibition curves; rabbit IgG-binding increased up to a certain dose of irradiation and then decreased; main bands disappeared in SDS-PAGE with increasing doses while turbidity increased indicating a decrease of solubility (20 patients with CMA)</td><td>Lee et al. 2001</td></tr>
<tr><td>Pepsin Hydrolysis, Pancreatic Enzymes, Whey Proteins
hydrolysis with pepsin (pH 2, 3, and 4, for 90 min) followed by hydrolysis with a mixture of pancreatic enzymes (pH 7.5 for 150 min) of beta-LG, alpha-LA, BSA, and bovine IgG</td><td>Percent inhibition of IgE-binding from sera of patients with IgE- mediated CMA to native proteins by respective hydrolysates of homologue protein:
<table>
<tr><th>pepsin hydrolysis at</th><th>pH 2</th><th>pH 3</th><th>pH 4</th></tr>
<tr><td>beta-LG*</td><td>8%</td><td>0%</td><td>0%</td></tr>
<tr><td>alpha-LA</td><td>5%</td><td>14%</td><td>48%</td></tr>
<tr><td>BSA</td><td>0%</td><td>0%</td><td>58%</td></tr>
<tr><td>bovine IgG</td><td>2.5%</td><td>54%</td><td>91%</td></tr>
</table>
(RAST inhibition)
* beta-LG is barely hydrolysed by pepsin, but susceptible to pancreatic enzymes</td><td>Schmidt et al. 1995</td></tr>
</table>

Duodenal Digestion in vitro digestion of cow's milk proteins by duodenal fluid (1) and human trypsins and elastases (2)	Rate of hydrolysis: purified proteins > crude cow's milk or formula; rates of alpha-LA, beta-LG, and CAS digestion were 0.03, 0.12, and 16.1 mg/mL duodenal juice/min (same capacity to hydrolyze the milk proteins in infants with CMPI, celiac disease, or unclassified gastrointestinal disorder)	(1) Jakobsson et al. 1982 (2) Jakobsson et al. 1983
Intestinal Digestion intestinal digestion of beta-LG, alpha-LA and CAS (intestinal cells, 48h)	Lower TNF-alpha production by stimulation of PBMC from cow's milk allergic patients with intestinal digested cow's milk proteins as compared to intact proteins	Benlounes et al. 1996
Cell-Envelop Proteinase specific hydrolysis of CAS and ultrafiltration	Elimination of IgE-binding epitopes by degradation of CAS and removal of whey proteins by ultrafiltration	Alting et al. 1998
Pepsin Hydrolysis, beta-LG pepsin hydrolysis of beta-LG	222 cow's milk intolerant / allergic patients: Higher degree of IgG binding to native beta-LG than to pepsin digested LG as compared to controls; almost complete discrimination between patient groups by cross-reactive experiments (ELISA)	Duchateau et al. 1998
Lactic Acid Fermentation lactic acid fermentation of sterilized cow's milk with a mixed culture of meso- and thermophilic bacteria strains	About 99% reduced antigenicity of whey proteins as compared to raw milk (rabbit pAb, ELISA); allergenicity of alpha-LA and beta-LG only slightly attenuated (Skin Tests)	Jedrychowski & Wroblewska 1999

11 Allergen Sources

Reported Adverse Reactions	References
Human Milk Cow's milk taken by the mother precipitated allergic symptoms in 61 breast fed infants (elimination/challenge in mother's diet) (1) Proctocolitis triggered by cows' milk protein transferred to 11 infants via the breast milk; resolution of visible rectal bleeding within 72 to 96 hours after elimination of cow's milk from mother's diet (colonoscopy performed in 5 infants revealed benign eosinophilic proctocolitis) (2)	(1) Gerrard & Shenassa 1983a, 1983b (2) Pumberger et al. 2001
"Non-dairy" Foods Allergic reactions in 6 patients with CMA after ingestion of "non-dairy" products: tofu frozen dessert (2 cases), beef hot dog (2 cases), bologna (2 cases), rice frozen dessert, tuna packed in aqueous solution; contents of milk proteins due to contamination by manufacturing facilities (37-2202 µg/mL) or to unlabeled adding of caseinate (136 µg/mL) (1)	(1) Gern et al. 1991
Cake, Cookie, Pastry Near-fatal anaphylactic reactions in 2 children with CMA (age of 9 and 12 years) after ingestion of a cookie, a cake or pastry containing the allergen (1)	(1) Sampson et al. 1992
Chocolate, Candy Occupational asthma and rhinoconjunctivitis in a chocolate candy worker (positive conjunctival and bronchial challenge tests with lactalbumin) (1)	(1) Bernaola et al. 1994

Several Food Products 9 Adverse reactions to unexpected cow's milk allergens in a) Meatballs containing 1.1% CAS (undeclared) b) Hot dog containing 0.04% CAS (contaminated) c) Recombined ham containing 2.6% (undeclared) d) Sausage containing 1.0% CAS (undeclared) e) Sausage containing 0.06% CAS (contaminated) f) Dark chocolate containing 0.8% CAS (contaminated) g) Ice cream (soy based) containing 0.2% CAS (contaminated) h) Lollipop, strawberry / cream containing 0.2% CAS (undeclared) i) Meringue containing 1.1% CAS (undeclared)	Malmheden Yman et al. 1994
Sorbets Frozen desserts manufactured using the same equipment used for producing ice cream may contain milk allergens: Anaphylaxis in a 2-year-old boy after ingestion of a "pareve"- labeled raspberry sorbet (kosher labeling to select dairy-free foods) (1) Anaphylaxis in a 3-year-old boy within 20 min after ingestion of a lemon sorbet (ca. 113 to 170 g) containing trace amounts of milk allergens (whey proteins: 9 µg/mL) (2)	(1) Jones et al. 1992 (2) Laoprasert et al. 1998
Sausage Severe reactions after ingestion of sausage containing CAS (texturing agent) (1)	(1) Foucard et al. 1997
Cheese Anaphylaxis after ingestion of cheese in a 23-year old woman (1)	(1) Wüthrich & Hofer 1986
Goat's and Sheep's Cheese Several allergic reactions after ingestion of feta (cheese made from sheep's milk) in a 15-year-old boy, after ingestion of sheep's or goat's cheese in a 25-year old patient, both tolerated ingestion of diary procucts from cow's milk (1) Allergic reactions after eating goat's cheese and after touching of goat's and sheep's cheese in a 2-year-old girl with tolerance to dairy products from cow's milk (2)	(1) Wüthrich & Johansson 1995 (2) Umpierrez et al. 1999
Sheep's Cheese Several anaphylactic reactions after ingestion of food containing "pecorino" cheese made from sheep's milk in a 5-year-old atopic boy unaffected by cow's milk protein allergy (1)	(1) Calvani & Alessandri 1998
Mozarella / Ricotta / Parmesan Cheese Asthma, urticaria and rhinitis in a boy with atopic dermatitis after ingestion of mozarella cheese made from ewe's and cow's milk; several allergic reactions after ingestion of ricotta cheese containing ewe's milk and parmesan cheese made from cow's milk, respectively (1)	(1) Fiocchi et al. 1999
Baby Food A baby food, cereal flour P, containing alpha- lactalbumin (although labeled guaranteed free of cow's milk), caused failure to thrive and diarrhea, vomiting, and coughing fits in a 22- month-old child with cow's milk allergy (1)	(1) Fremont et al. 1996
Casein in Salmon A 30 year-old woman with CMA (without fish sensitivity) experienced anaphylaxis within 1 hour after ingestion of a slice of bread with salmon, prepacked from a supermarket, the salmon meat was restructured by microbial enzyme (transglutaminase) which crosslinks added CAS and meat proteins, assuming a consumption of 10 to 50 g salmon, about 10 to 50 mg CAS were ingested (1)	(1) Koppelman et al. 1999
Casein-containing Product A 25-year-old with asthmatic symptoms which were work-related to the production process of candy making due to inhalation of Hyfoama DS (bronchial challenge, SPT, RAST); Hyfoama DS is a colorless, water-soluble powder produced from CAS treated with calcium hydroxide solution and then dried. It is used as a substitute for egg white in a variety of baked goods. The manufacturer recommends labeling of the final product as containing “hydrolyzed milk protein.”	(1) Bader et al. 2001
Casein in Tryptone Powder Adult-onset sensitization to CAS in a 44-year-old male scientist after occupational exposure to aerosolized tryptone powder (CAS product used in preparation of culture media); subsequent systemic allergic reaction after ingestion of milk containing candy (SPT)	(1) Vaswani et al. 1999

Human Milk 16/17 of cow's milk allergic children showed allergic symptoms during cow's milk challenge through human milk from asymptomatic mothers (age of children 1.8 to 9.4 months)	(1) Jarvinen et al. 1999b
Infant Formulas	see 12.2 Allergenicity / Safety of Infant Formulas
Pharmaceuticals Anaphylaxis in a 12 months-old boy after cutaneous application of a CAS containing ointment to an inflamed diaper area (1) Severe anaphylactic reaction in a 33-year-old woman during artificial insemination due to sperm- processing medium containing BSA (SPT, RAST) (2) Generalized anaphylactic reaction a few hours after tooth extraction in a 54-year-old woman, hemofibrine (a hemostatic sponge made of bovine fibrin) elicited symptoms (Scratch test, RAST) (3) 3 out of 6 patients with positive RAST against CAS experienced allergic symptoms after taking antibiotics containing CAS (4)	(1) Jarmoc & Primack 1987 (2) Wüthrich et al. 1995 (3) Wüthrich et al. 1996 (4) Hasegawa et al. 2000
"Neutralizing" of Food Allergies 68-year-old woman with systemic mastocytosis was given "neutralizing" injections of milk and wheat and experienced flushing, palpitations, and lightheadedness with syncope (unproven technique of provocation/neutralization) (1)	(1) Teuber & Vogt 1999

Allergens in Products	Content / Products	References
Human Milk 38 mothers	Detectable amounts of immunoactive beta-LG (5-33 ng/mL) in 18/38 human milk samples	Jakobsson et al. 1985
Human Milk 25 mothers	Detectable amounts of beta-LG (5-800 ng/mL) in 40% of human milk samples, presence of symptoms in the infant such as diarrhoea, vomiting, colic, exanthema significantly correlated to high levels of beta-LG in the milk	Axelsson et al. 1986
Human Milk 57 breastfeeding mothers	Detectable amounts of bovine beta-LG (up to 6.4 ng/mL) in 45% of samples; persisted up to 3 days after maternal dietary elimination of cow's milk	Machtinger & Moss 1986
Human Milk 9 breastfeeding mothers	Detectable amounts of bovine beta-LG (0.5-45 ng/mL) in 30% of samples	Host et al.1988
Human Milk 36 samples of human breast milk	Detectable amounts of bovine IgG (mean 3.4 ng/ml)	Maeda et al. 1993
Human Milk 55 breastfeeding mothers (cow's milk allergy in 46 infants, oral challenge)	beta-LG in human milk before and after oral cow's milk load (given after 24 hour milk free diet): beta-LG levels >2 ng/mL in 75% of samples, increased levels in 50% after load	Sorva et al. 1994
Fat Substitutes 13 (16) egg and/or cow's milk allergic patients	Allergenicity of microparticulated egg and cow's milk proteins in fat substitues (Simplesse, Beta IL): No alteration of allergenic potencies in SDS-PAGE immunoblot	(1) Sampson & Cooke 1990 (2) Sampson & Cooke 1992
Flavourings / Seasonings dill-pickle seasoning (containing lactose)	Positive skin test reaction to lactose containing seasoning (1 patient with CMA); CAS and whey proteins identified in this seasoning, and whey proteins in pharmaceutical grade lactose	Watson et al. 1995
Lactose "food-quality" lactose	alpha-LA content in "food quality" lactose 1-5 µg/g (RAST inhibition)	Fremont et al. 1996
Natural Rubber Latex Gloves cow's milk CAS	15/30 commonly marketed natural rubber latex glove brands contained cow's milk CAS (rocket immunoelectrophoresis, ELISA inhibition)	Ylitalo et al. 1999

Allergen Depleted Products	Method	References
Cow's Milk depletion of beta-LG	Specific affinity matrix: beta-LG coupled to Sepharose 4B used to remove beta-LG from milk, significant retardation in its elution because reversible polymerization with soluble beta-LG; beta-LG depleted milk proposed as hyposensitizing milk formula to be used by lactating mothers	Chiancone & Gattoni 1993

Allergen Free Products	Method	References
Human Milk lactating mothers	No detection of beta-LG and bovine CAS in human milk (SDS-PAGE immunoblotting using mAb)	Restani et al. 2000

12 Food Allergen Labeling

Food Allergen	Labeling / Regulation Status	References
International Regulations Milk and milk products	Mandatory labeling of prepackaged food / advisary status (1)	(1) Codex Alimentarius Commission 1999
European Regulations Milk and milk products	Labeling appropriate / recommendation (1) Mandatory labeling of prepackaged food / proposal for directive (2)	(1) Bousquet et al. 1998 (2) European Commission 2001

13 Infant Formulas

13.1 Application of Infant Formulas in CMA

Parameters / Subjects	Outcome	References
Nutritional Status 18 children with CMA (age of 1-3.5 years)	Diets based on soy or CAS hydrolysate formula (taken by 72%) supplemented with calcium and in 11 children with vitamins A and D resulted in adequate mean intakes of nutrients	Tiainen et al. 1995
Infant Formulas 60 children with infantile colic	Improvement in 18% of children after receiving a soy formula, while symptoms were unchanged or worse in 53% (cow's milk formula and soy formula fed children), improvement with extensively hydrolyzed CAS formula (Nutramigen)	Lothe et al. 1982
Infant Formulas 36 children with CMA (age of 1 month to 3 years)	Application of a) soybean and b) partially hydrolyzed milk formula: No improvement in a) 10% (Prosobee), b) 12% (Humana SL) Partial or total relief of symptoms in a) 69% (Prosobee), b) 76% (Humana SL)	Iwanczak et al. 1995
Infant Formulas 100 children with CMA (age of 5 months to 9 years)	Application of a) soybean and b) extensively hydrolyzed CAS formula: Partial or total relief of symptoms in a) 37% (Prosobee), b) 42% (Nutramigen)	Korol et al. 1995
Casein Hydrolyzed Formula a 4-day-old female with cow's milk induced eosinophilic colitis	Rectal bleeding resolved upon an extensively hydrolyzed CAS formula, and endoscopy one week later showed improvement, with only scattered areas of erythema, and no friability	Wilson et al. 1990
Whey Hydrolyzed Formulas 79 infants with CMA / CMI (age of <3 months)	Application of 2 extensively whey hydrolyzed formulas (1 lactose free): during application / follow-up of 10 weeks improvement of symptoms in about 80% of children and normal growth with both formulas	Verwimp et al. 1995

Whey Hydrolyzed / Amino Acid Formulas 22 infants with CMA (mean age of 6 months)	Atopic eczema improved significantly and progressively in extensively hydrolyzed whey and amino acid formula- fed groups; downward trend of serum total and milk- specific IgE levels proving the efficacy of both formulas (follow-up study of 9 months)	Isolauri et al. 1995
Probiotics / Whey Hydrolyzed Formula 31 infants with atopic eczema and CMA	1-month study period: infants fed with extensively hydrolyzed whey formula a) fortified with Lactobacillus GG or b) not fortified formula clinical score of atopic dermatitis improved significantly in a); decreased concentrations of alpha 1-antitrypsin and fecal TNF-alpha in a); concentration of fecal eosinophil cationic protein unaltered in a) and b)	Majamaa & Isolauri 1997
Amino Acid Formula 12 infants with adverse reactions to soy formula, whey hydrolysate, or CAS hydrolysate	Infant formula composed of individual amino acids: no symptoms	Hill et al. 1995
Amino Acid Formula 22 infants allergic to cow's milk proteins who did not tolerate extensively hydrolyzed protein formulas	Follow-up after successful use of an amino acid-based diet 11.8 +/- 8.7 months (3-30 months): Cow's milk protein tolerance occurred earlier in 9 patients whose allergy was limited to cow's milk proteins and to extensively hydrolyzed protein formulas (age of 11.8 +/- 3.9 months) as compared to 13 patients with associated allergies to other foods (age of 25.8 +/- 6.9 months)	de Boissieu & Dupont 2000
Amino Acid Formula 31 consecutive children with proven CMA (median age 23.3 months; 6 months to 17.5 years): 29 with multiple food allergies, 17 with acute reactions and cow's milk-specific IgE, and 14 with allergic eosinophilic gastroenteritis; 13 did not tolerate extensively hydrolyzed formulas	Amino Acid-based formula (EleCare) tested performing blinded oral food challenges in nonrandomized feeding study (each child serving as own control): 18 subjects with allergic eosinophilic gastroenteritis and/or multiple food allergies followed up while receiving formula for a median of 21 months (range, 7 to 40 months): formula was hypoallergenic and effective in maintaining normal growth	Sicherer et al. 2001
Amino Acid Formula / Extensively Hydrolyzed Formula 73 infants (median age 5.7 months) with CMA/CMI and atopic dermatitis (DBPCFC positive): a) Amino acid formula fed group b) Extensively hydrolyzed formula fed group	Prospective, controlled, multi-center trial: - SCORAD index significantly improved in both groups after 6 months - length standard deviation score significant increase in group a), no difference in group b) - weight-for-length values stable in both groups - energy intake similar in both groups - significant clinical improvement in infants with early onset of symptoms CMA/CMI in both groups - improved growth in group a) as compared to group b)	Niggemann et al. 2001a
Chestnut Formula >50 infants with CMA or lactose intolerance	Supplemented chestnut formula: normal infant's development, 2 cases of intolerance	Osvaath et al. 1976
Soy Protein Formula 20 children with CMA and atopic dermatitis	Cow's milk- free diet using as a soy protein formula improved the skin lesions, in addition to insuring a regular growth in all infants; possible secondary sensitization to soy 1 infant	Cantani et al. 1990
Soy Milk Formula 17 children with CMA / CMI (age of 6 months to 3 years)	Clinical tolerance to follow-up soybean formula in 16 children, one patient developed a severe diarrhoea within 72 hours after introduction of the soybean formula	Buts et al. 1993
Soy Milk 20 infants with CMA	Incidence of allergic symptoms in 17% of infants fed a 2S protein fraction depleted soy milk	Marano et al. 1989

Soy / Beef Hydrolyzed Formula (a) 12 infants with protracted enteritis (b) 10 infants with atopic eczema	Fed with lactose-free soy and beef hydrolysate based formula: improvement of symptoms in both groups, allergic symptoms in 1 (a) and 3 (b) infants who were previously fed with intact soy protein	Donzelli et al. 1990
Hypoallergenic Rice, Amino Acid Formula 1child with cow's milk and soybean allergy (age of 11 months)	Biotin deficiency in an Japanese infant fed with an amino acid formula and hypoallergenic rice processed by protease; symptoms disappeared after oral supplementation with biotin	Higuchi et al. 1996
Lamp-Meat Based Formula 10 infants with adverse reactions to CAS hydrolyzed formulas (age of 6 months to 3 years)	Application of a modular lamb- meat- based formula, prompt resolution of symptoms (follow-up for 3 months to 5 years)	Weisselberg et al. 1996
Ass' Milk 9 unweaned infants with multiple food hypersensitivity presenting severe symptoms of CMA	Ass' milk plus medium chain triglycerides well tolerated by all patients	Iacono et al. 1992
Ass' Milk / Casein Hydrolyzed Formula a) 21 infants (median age at diagnosis 2 months) intolerant to extensively hydrolysed proteins treated with an ass' milk-based diet b) 70 cow's milk intolerant infants (median age at diagnosis 3 months) treated with casein hydrolysate milk-based diet.	Follow-up for a median period of 4 years (DBPCFC): Multiple food intolerance in 21/21of group a) (ass' milk group): more frequently to soybean, oranges, tomatoes and fish; goat's milk intolerance in 5/6, and sheep's milk intolerance in 4/7 receiving the respective food; these patients tolerated ass' milk; 3/21 patients in group a) became ass' milk intolerant; Multiple food intolerance in 20/70 infants of group b) (casein hydrolysate group); 52% of group a) and 78% of group b) became cow's milk-tolerant; age of children at tolerance was higher in group a) than in b) Higher frequency of cases with elevated serum total IgE and cow's milk specific IgE in group a)	Carroccio et al. 2000a
Mare's Milk 25 children with IgE-mediated CMA (age of 19 to 72 months, median 34 months)	**Mare's Milk** / **Cow's Milk** SPT: 8% (all 2+) / 100% (all 4+) DBPCFC: 4% / 100% IgE-binding*: lower percentage / higher percentage * SDS-PAGE immunoblotting	Businco et al. 2000

13.2 Allergenicity / Safety of Infant Formulas

Reported Adverse Reactions	References
Human Milk	see 11 Allergen Sources Reported Adverse Reactions
Infant Formulas Acute allergic reactions in a 7-year old girl with CMA after challenge with 6 different partially and extensively hydrolyzed whey and CAS formulas (DBPCFC); anaphylactic reactions to a extensively hydrolysed CAS formula (Alimentum) (1, 2)	(1) Amonette et al. 1991 (2) Schwartz & Amonette 1991
Infant Formulas 20 children with CMA (age of 15 to 76 months) allergic reactions (challenge tests) to a) extensively hydrolyzed CAS formula in 10%, b) extensively hydrolyzed whey formula 13%, c) partially hydrolyzed whey formula in 45%	(1) Ragno et al. 1993

Infant Formulas 4 children developed immediate anaphylactic symptoms after ingesting extensively hydrolyzed whey and casein formulas, respectively, and 4 children demonstrated subacute or chronic gastrointestinal symptoms. All children with anaphylactic symptoms had positive SPT and RAST to cow's milk and/or hydrolyzed proteins, while SPT and RAST were negative in 3 of 4 children with chronic symptoms (1)	(1) Sotto et al. 1999
Casein Hydrolyzed Formula Anaphylaxis in a newborn infant after ingestion of extensively hydrolyzed CAS formula (Pregestimil) (1)	(1) Lifschitz et al. 1988
Casein Hydrolyzed Formula Systemic urticaria in 1 of 11 children with CMA after DBPCFC with extensively hydrolyzed CAS formula (Alimentum) (1)	(1) Oldaeus et al. 1991
Casein Hydrolyzed Formula Anaphylaxis in a newborn infant after ingestion of extensively hydrolyzed CAS formula (Nutramigen) (1)	(1) Saylor & Bahna 1991
Whey Hydrolyzed Formula Anaphylaxis after ingestion of extensively hydrolysed whey protein formula (Alfa-ré) in infants aged 3 to 8 months (1)	(1) Businco et al. 1989
Whey Hydrolyzed Formula Sytemic urticarial and respiratory reactions in 8 of 13 children with more severe sytemic IgE-mediated CMA (groups B and C: positive SPT to cow's milk, whey and CAS hydrolyzed formulas) when fed a partially hydrolysed whey formula (Good Start) (1)	(1) Schwartz et al. 1991
Whey Hydrolyzed Formula Anaphylaxis after ingestion of partially hydrolyzed whey formula (Good Start) (1) Anaphylaxis after ingestion of partially hydrolyzed whey formula in 2 infants (2)	(1) Ellis et al. 1991 (2) Businco et al. 1994
Extensively Hydrolyzed Formula 13 infants allergic to extensively hydrolyzed cow's milk protein formulas fed for treatment of chronic digestive symptoms (1)	(1) de Boissieu et al. 1997
Soy Hydrolyzed Formula 43 patients with possible milk- and/or soy-protein enterocolitis: 23% had positive challenge with cow's milk, and 33% and 30% had positive challenge to 2 hydrolyzed soy protein isolates	(1) Burks et al. 1994

Reportedly Safe Applications	**References**
Casein Hydrolyzed Formula 1 extensively hydrolyzed CAS infant formula tested by DBPCFC in 5 children with IgE- mediated CMA, no symptoms occured (1)	(1) Host & Samuelsson 1988
Casein Hydrolyzed Formula 1 extensivelyhydrolyzed CAS infant formula tested by SDS-PAGE immunoblot, ELISA and DBPCFC in 25 cow's milk allergic children, even in open challenge no reactions occured (1)	(1) Sampson et al. 1991
Whey Hydrolyzed Formula All of 13 children with mild topical IgE- mediated CMA (group A: positive SPT to cow's milk, negative to whey and CAS hydrolyzed formulas) tolerated a whey hydrolysate formula (Good Start) when fed for at least 2 weeks (1)	(1) Schwartz et al. 1991
Whey Hydrolyzed Formula 1 ultrafiltrated (<8 kDa) whey hydrolysate infant formula could be administered safely to 66 children with CMA (elimination/challenge procedure)	(1) Halken et al. 1993a
Casein / Whey Hydrolyzed Formula 1 CAS-whey hydrolyzed infant formula tested by PBMC proliferation in 10 children with CMA: no significant T-cell activation (1)	(1) Eigenmann et al. 1995
Casein / Whey Hydrolyzed Formula Hydrolysate well tolerated by 31/33 cow's milk allergic children (1)	(1) Martin-Esteban et al. 1998

Several Infant Formulas 32 children with proven CMA (two-center study): **Formula** | **SPT** positive | **oral challenge** tolerance extensive hydrolysate whey formula (Nutrilon Pepti) | 19% | 97% extensive hydrolysate whey formula (Profylac) | 15% | 94% partial hydrolysate whey formula (Nan HA) | 32% | 64%	(1) Giampietro et al. 2001

Skin Tests and in vitro Tests of Infant Formulas

Allergens in Infant Formulas	Content / Products	References
Hydrolyzed Formulas 26 children with CMA (age of 1.3 to 13.8 years)	Positivity in SPT with a) whey hydrolyed formula 69% b) extensively hydrolyzed CAS formula 38%	Schwartz et al. 1989
Hydrolyzed Formulas 45 children with CMA (age of 3 months to 16 years)	Positivity in SPT (n=34-41) with a) partially and extensively hydrolysed whey formulas: Beba 24% and Profylac 15% b) extensively hydrolysed CAS formulas: 2.5% each (Alimentum and Nutramigen) Positivity in RAST with Beba 24%, other hydrolyzed formulas 7-13% Relative IgE- binding potency <0.06% for all tested formulas (RAST inhibition) Detectable amounts of bovine beta-LG in Beba 200 µg/g dry weight, other hydrolysed formulas 0.006-0.066 µg/g (ELISA)	Oldaeus et al. 1991
Hydrolyzed Formulas 15 children with CMA (age of 3 to 13 years)	Positivity in SPT with a) partially and extensively hydrolyed whey formulas: Beba 47% and Alfare 6.7% (1/15) b) extensively hydrolyzed CAS formulas: Nutramigen 0% (regular cow's milk formula 87%)	Oldaeus et al. 1992
Hydrolyzed Formulas 7 different infant formulas	Detectable amounts of bovine beta-LG in hydrolyzed formulas from cows' milk whey or CAS, and from bovine collagen and soy in (range 0.0056 to 200 µg/g dry weight, 0.84 to 31200 ng/mL ready-to-use product)	Makinen-Kiljunen & Sorva 1993
Hydrolyzed Formulas 13 children with CMA	Serum IgE against protein hydrolysates in 6 children	Plebani et al. 1990
Hydrolyzed Formulas children with CMA	6 hydrolyzed formulas tested: certain hydrolysates induced positive skin reactions and allergic symptoms after oral challenge; CAS hydrolysates had the least residual allergenic activity	Rugo & Wahn 1992 Wahn et al. 1992
Hydrolyzed Formulas 16 children with CMA	1 and 2 positive results to 2 extensively hydrolysed CAS formulas; 7 positive results to a extensively hydrolysed whey formula (RAST)	Dean et al. 1993
Hydrolyzed Formulas 1 girl with CMA (at age of 12 months)	Positive SPT to a) extensively hydrolysed whey formula (Profylac) and b) extensively hydrolysed CAS formula (Nutramigen)	Nilsson et al. 1999
Whey Hydrolyzed Formula 1 ultrafiltrated (<8 kDa), extensively hydrolysed whey infant formula	35 patients with IgE- mediated reactions: 6% had positive SPT, 11% positive RAST against formula (no reactions in oral challenge test)	Halken et al. 1993a

<table>
<tr><td>Whey Hydrolyzed Formula
1 ultrafiltrated, extensively hydrolysed whey infant formula</td><td>5 children with CMA:
Hydrolysate positive in 4/5 patients in SPT, inhibition of IgE-binding to cow's milk proteins by the formula ranged from 51-96%;
Peptides of > 2600 Da positive in SPT and RAST inhibition; peptides of < 1400 Da negative in SPT
but still able to inhibit to a small extent IgE- binding to the hydrolysate (SEC, SPT, RAST)</td><td>Van Hoeyveld et al. 1998</td></tr>
<tr><td>Casein Hydrolyzed Formula
10 children with CMA</td><td>Proliferative responses of PBMCs to hydrolysate formula: higher in 3 patients whose symptoms were not reduced by CAS hydrolysate formula</td><td>Nishida et al. 1995</td></tr>
<tr><td>Hydrolyzed Infant Formulas
a) extensively hydrolyzed CAS formula
b) extensively hydrolyzed whey formula
c) partially hydrolyzed whey formula</td><td>20 children with CMA (age of 15 to 76 months); positive SPT and specific RASTto
a) in 15% and 15%,
b) in 15% and 20%
c) in 45% and 65%, respectively</td><td>Ragno et al. 1993</td></tr>
<tr><td>Hydrolyzed Infant Formulas
a) non hydrolysed formula
b) whey-based formula
c) whey-based and ultra-filtrated formula
d) CAS/whey-based formula</td><td>12 children with CMA:
All hydrolysed formulas showed reduced IgE- binding capacity; 25% of patients sera showed IgE- binding to b) and c), and 42% to d);
b) and d) contained bovine serum albumin, beta-LG, CAS and their fragments (3-67 kDa)
c) contained CAS fragments (3-6 kDa) and beta-LG and its fragments (6-18 kDa)
(RAST, immunoblot)</td><td>Gortler et al. 1995</td></tr>
<tr><td>Hydrolyzed Infant Formulas
11 whey and 1 CAS hydrolysed formulas</td><td>Inhibition of IgE binding to
<table><tr><th></th><th>positive samples</th><th>inhibition</th></tr><tr><td>alpha-LA</td><td>12</td><td>18-93%</td></tr><tr><td>beta-LG</td><td>12</td><td>2-84%</td></tr><tr><td>BSA</td><td>6</td><td>2-75%</td></tr><tr><td>bovine IgG</td><td>8</td><td>3-72%</td></tr><tr><td>CAS</td><td>11</td><td>3-89%</td></tr></table>(RAST inhibition)</td><td>(1) van Beresteijn et al. 1995</td></tr>
<tr><td>Hydrolyzed Infant Formulas
9 whey or CAS hydrolysed formulas</td><td>CAS- specific mAb: 0.05-0.67% CAS components in all partly and 2 extensively whey hydrolysate formulas, not detectable in 2 extensively CAS hydrolysate and the amino acid based formulas (SDS-PAGE immunoblot, ELISA inhibition)</td><td>(1) Restani et al. 1995, 1996
(2) Plebani et al. 1997</td></tr>
<tr><td>Extensively Hydrolyzed Formulas
children with CMA</td><td>IgE-binding to residual protein fractions
less than 20 kDa in several extensively hydrolyzed cow milk-based formulae (RAST inhibition)</td><td>Hoffman & Sampson 1997</td></tr>
<tr><td>Several Infant Formulas
a) partially hydrolysed whey formula
b) partially hydrolysed whey/CAS formula
c) soy/pork collagen hydrolysate
d) amino acid formula</td><td>20 cow's milk allergic children (mean age 1.6 years):
Inhibition of IgE- binding to cow's milk by cow's milk > a > b > c > d (RAST inhibition); SPT to d) all negative</td><td>Niggemann et al. 1999a</td></tr>
</table>

Several Infant Formulas 12 different partially and extensively hydrolyzed cow's milk formulas	Proteins with Mr of 7 to >30 kDa detected by gel filtration; proteins with Mr >20 kDa even detected in extensively hydrolyzed formulas by SDS-PAGE; residual beta-LG detected in all products by ELISA; by immunoblot and dot-immunoblot with antibodies against total whey, caseins, or Kunitz soybean trypsin inhibitor antigenic material mainly detected in partially hydrolyzed products	Rosendal & Barkholt 2000
Human Milk	Cow's milk proteins	see 11 Allergen Sources

13.3 Infant Formulas for Allergy Prophylaxis

It should be noticed that multiple parameters are involved in (food) allergy prevention. Nutritional intervention and environmental allergen avoidance are factors in allergy prevention. The role of infant formulas is controversial because the results of several studies have not been reproduced and the objective experimental conditions are difficult to achieve and maintain when studying human subjects. Please notice the disclaimer !

Prevention of	Feeding / Formula	References
Atopic Disease 328 children with a positive family history of allergy (15 years follow up)	Breast fed infants were found to have approximately one-half the incidence of atopy of cow's milk or soy based formula fed infants	Gruskay 1982
Atopic Disease 101 newborn infants of atopic parents (total serum IgE)	Development of atopic disease in Breast-fed group: 38% with IgE > 0.8 U/ml 12% with IgE < 0.8 U/ml Soy-fed group: 33% with IgE > 0.8 U/ml 16% with IgE < 0.8 U/ml Cow's milk-fed group: 90% with IgE > 0.8 U/ml 17% with IgE < 0.8 U/ml	Businco et al. 1983b
Atopic Eczema 97 brest fed and 124 non brest fed infants	Development of atopic eczema Breast-fed group: 22% (restricted maternal diet) 48% (no restricted maternal diet) Soy-fed group: in 63% Cow's milk-fed group: in 70% CAS hydrolysate-fed group: in 21%	Chandra et al. 1989a
Atopic Disease 72 infants with family history of atopy (each group)*	Incidence of atopic eczema, wheezing, rhinitis, gastrointestinal symptoms, or colic Breast-fed group: in 20% Soy-fed group: in 37% Cow's milk-fed group: in 36% Partially hydrolysed whey-fed group: in 7% Cumulative incidence of atopic disease: breast-fed and whey hydrolysate-fed group < cow's milk and soy-formula fed group	Chandra et al. 1989b Chandra & Hamed 1991 Chandra 1997
Atopic Disease 155 infants with family history of atopy	Incidence of atopic symptoms (at 18 months) Extensively CAS hydrolysate fed group: in 51% Partially hydrolysate fed group: in 64% Regular cow's milk formula fed group: in 84%	Oldaeus et al. 1997

Atopic Disease, Cow's Milk Allergy 91 high risk infants (follow-up to 18 months of age)	Development of atopic diseases similar in all groups; development of cow's milk allergy / intolerance: Exclusively breast fed group: none Regular cow's milk formula fed group: in 3 infants with skin symptoms Ultrafiltered, extensively hydrolysed whey-fed group: none	Odelram et al. 1996
Atopic Disease, Humoral Response high risk infants (formula fed >3 months) a) 31 fed with extensively CAS hydrolyzed formula b) 29 fed with partially hydrolyzed formula c) 34 fed with regular cow's milk formula	Development of any atopic disease: a) in 29%, b) in 38%, c) in 50% (at 9 months) a) in 35%, b) in 48%, c) in 62% (at 18 months) associated to detection of spec. IgE and high spec. IgG responses Cow's milk specific IgE: a) in 6.5%, b) in 10%, c) in 65% beta-LG specific IgG: a < b < c	Oldaeus et al. 1999
Atopic Dermatitis, Cellular and Humoral Response 72 infants from families with atopic symptoms a) fed with extensively hydrolyzed formula b) fed with partially hydrolyzed formula c) breast fed (not received any formula at 6 months of age)	Development of atopic dermatitis: no differences in numbers and severity among groups during first 12 months PBMC proliferation: significantly decreased proliferation to CAS in b) as compared to c) at 6 months of age Cow's milk specific IgE: a) in 9.5%, b) in 0%, c) in 13% at 6 months of age CAS specific IgG levels: b > a at 12 months of age	Nentwich et al. 2001
Cow's Milk Allergy 21 infants with gastrointestinal symptoms of cow's milk and/or soy protein intolerance	Fed with whey protein hydrolysate formula: improvement of symptoms	Merrit et al. 1990
Cow's Milk Allergy 158 high-risk infants (1 year of age, prospective study)	Development of cow's milk allergy / intolerance: Exclusively breast-fed group: in 1/20 Extensively hydrolysed CAS formula-fed group: in 1/59 Extensive whey hydrolysate-fed group: in 3/62 (no symptoms to formulas occurred)	Halken et al. 1993b
Cow's Milk Allergy 58 formula-fed "at risk" infants (all children not breast-fed, formulas fed for first 6 months of life)	Development of cow's milk allergy / intolerance at age of 6, 12, 36, and 60 months: Regular cow's milk formula fed group: in 43%, 53%, 57%, and 60% Partially whey hydrolysate-fed group: in 7%, 21%, 25%, and 29%	Vandenplas et al. 1995
Cow's Milk Allergy unselected healthy, full-term infants a) 1789 fed with cow's milk formula b) 1859 with pasteurized human milk c) 1737 with extensively hydrolysed whey formula d) 824 exclusively breast-fed	18 to 34 months follow-up Cumulative incidence of CMA: in a) 2.4%, b) 1.7%, c) 1.5%, d) 2.1% of infants	Saarinen et al. 1999a Saarinen et al. 2000

Cow's Milk Allergy 478 infants with high-risk of atopy fed during the first 4 months of life: a) 232 exclusively breast-fed b) 79 extensively hydrolyzed casein formula c) 82 extensively hydrolyzed whey formula d) 85 partially hydrolyzed whey formula (study period 1994-95) Group a) children were exposed less to tobacco smoke and pets at home and belonged to higher social classes, whereas groups b), c), and d) were identical concerning environmental factors	Followed-up at the age of 12 and 18 months: Cumulative incidence of confirmed CMA: a) 1.3%, b) and c) 0.6%, and d) 4.7% of infants Cumulative incidence of parental-reported CMA: b) 2.5, c) 0%, and d) 7.1% of infants No significant differences in b), c), and d) regarding the cumulative incidence of atopic dermatitis or respiratory symptoms	Halken et al. 2000
Humoral Response infants at risk of atopy (age of 6 months) a) breast fed group b) regular cow's milk formula fed group c) partially whey hydrolysate fed group	IgE, IgG, and IgG subclasses: lower total IgE, cow's milk specific IgG, and alpha-lactalbumin and beta- lactoglobulin specific IgG4 in a) and c) than in b) (no significant differences at 5 days of age)	Chirico et al. 1997
Humoral Response 129 unselected infants a) breast fed b) cow's milk formula fed c) CAS hydrolysate fed during the first 3 days of life, otherwise exclusively breast fed	Follow-up for 2 years: Exposure to cow's milk stimulated cow's milk proteins specific IgG production, while feeding with a CAS hydrolysate was associated with low specific IgG levels	Juvonen et al. 1999

* Studies may be experimental, unproved, or controversial. Please notice the disclaimer !

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