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

Authors in alphabetical order [contact information]

Matthias BESLER (Hamburg, Germany)
Philippe EIGENMANN (Genève, Switzerland)
Robert H. SCHWARTZ (Rochester, NY, USA)

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, or milk-induced enteropathy. 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 unselected 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 yoghurt, 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. Due to clinically important residual allergenicity in some hypoallergenic formulas controlled clinical testing is necessary in each cow's milk sensitive infant before use. Due to the high homology of protein composition sheep's and goat's milk are cross-reactive in approximately 80% of subjects with CMA.
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.

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.
(Internet Symposium on Food Allergens 2000, 2(1):9- 74)

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
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
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
Germany 1235 unselected preschool children (5-6 years)	cow's milk 3.9% (SPT)	Schäfer et al. 1999
Iceland, Reykjavik 502 unselected adults	cow's milk 1.2% (RAST)	Gislason 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
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, 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)	cow's milk in 4.1% (SPT)	Dean 1997

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, 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, 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 8.3%, goat's milk 0.3% (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, 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, Tokyo 39 children with positive food challenge	cow's milk 28% (food challenge)	Iwasaki et al. 1994
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
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, Zurich 402 food allergic adults	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
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, Denver, CO 180 food allergic children	cow's milk 23% (DBPCFC)	Bock & Atkins 1990
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
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, 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
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
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 1992

3 Symptoms of Cow's Milk Allergy

Symptoms & Case Reports

systemic reactions
anaphylaxis (20, 21, 24, 36, 40, 46, 44, 53, 54, 55, 62, 68, 69, 73, 74), excercise induced anaphylaxis (54, 60, 72), fatal reactions (47a, **48)

cutaneous symptoms
angioedema (8, 18, 17, 44, 54, 74), atopic dermatitis (22, 23, 24, 27, 35, 74), contact urticaria (19), dermatitis (66), eczema (3, 6, 8, 9, 17, 25, 29, 30, 50, 67), erythema (29, 54), exanthema (6), lips edema (10), pruritus (2), redness (54), swelling of eyelids (54), urticaria (2, 6, 8, 10, 17, 18, 22, 23, 26, 30, 39, 44, 50, 54, 67, 74), chronic urticaria (61)

gastrointestinal symptoms
abdominal cramps (2), abdominal distention (42), abdominal pain (44), colic (3, 50, 66), infantil colic syndrome (1, 5, 6), colitis (56, 63), constipation (3, 66), chronic constipation (48, 51), diarrhea (2, 3, 6, 10, 11, 15, 17, 25, 29, 39, 42, 44, 50, 66, 67), chronic diarrhea (12), food protein-induced enterocolitis syndrome (absence of specific IgE) (69), eosinophilic colitis (31), eosinophilic gastroenteritis (28), gastroenteritis (11), gastro- oesophageal reflux (13, 57, 58, 65), morphologic lesion (15), nausea (44), proctitis (32), progressive small bowel mucosal damage (26), occult intestinal bleeding (4), oropharyngeal itching / swelling (39, 44), oropharyngeal pruritus (71), edema of tongue (10), acute pancreatitis (33), loose stools (67), vomiting (2, 3, 6, 11, 17, 22, 25, 66, 67), in general (30, 74)

respiratory symptoms
allergic alveolitis (7, 16), asthma (3, 10, 11, 18, 22, 39, 44, 45, 47, 49, 54, 68, 73), bronchospasm (29), bronchitis (6, 17), conjunctivitis (73), coughing (25, 50), dyspnea (50, 54, 71), nasal blockade (71), allergic rhinitis (22), rhinitis (29, 44, 54), rhinoconjunctivitis (44, 45, 54), serous rhinorrea (71), sneezing (71), wheeze (25, 50, 66)

other symptoms
association with cytomegalovirus colitis* (64), infantile autism* (52), anal fistula and fissures (48), growth retardation / failure to thrive (3, 6), insomnia (14), iron deficiency anemia in 20-70% (11), lactic acidosis (75), Melkersson-Rosenthal syndrome* (59), migraine* (38), necrotizing enterocolitis (43), steroid- resistant nephrotic syndrome (41), pallor (17), psychological disturbance (3), pulmonary hemosiderosis (34), tension-fatigue syndrome (37), lethargy (69)

* controversial / hypothetical, ** possibly due to partially hydrolyzed whey formula

(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
(47a) Malmheden Yman et al. 1994
(47) Rossi et al. 1994
(48) Tarim et al. 1994
(49) Vargiu et al. 1994
(50) Altintas et al. 1995
(51) Iacono et al. 1995a
(52) Lucarelli et al. 1995
(53) Moneret-Vautrin & Kanny 1995
(54) Wüthrich & Johansson 1995
(55) Wüthrich et al. 1995
(56) Armisen Pedrejon et al. 1996
(57) Cavataio et al. 1996
(58) Iacono et al. 1996
(59) Levy et al. 1996a
(60) Levy et al. 1996b
(61) Paranos & Nikolic 1996
(62) Tabar et al. 1996
(63) Weisselberg et al. 1996
(64) Jonkhoff-Slok et al. 1997
(65) Iacono et al. 1998a, 1998b
(66) Iacono et al. 1998c
(67) Jarvinen et al. 1998
(68) Kanny et al. 1998
(69) Laoprasert et al. 1998
(70) Sicherer et al. 1998
(71) Vila Sexto et al. 1998
(72) Fiocchi et al. 1999
(73) Goh et al. 1999
(74) Rance et al. 1999b
(75) Rizk et al. 1999

Percentage of Reactions

Symptoms / Ref.	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Anaphylaxis	5%	100%			5%				2%		7.8%
Cutaneous				64%		31%	79%	93%		58%	
+ Gastrointestinal										19%	
+ Respiratory										13%	
All 3 organ systems										4%	
Atopic dermatitis	41%		21%					100%		100%	50%
Conjunctivitis											3.1%
Urticaria / Angio-oedema											28%
Angio-oedema		66%			65%				13%		
Urticaria	10%				100%						
Generalized urticaria		69%			45%				10%		
Contact urticaria		59%			80%						
Eczema					33%				13%		
Circumoral lesions									26%		
Gastrointestinal				59%		50%	42%	65%		4%	7.8%
Vomiting	34%				13%				41%		
Diarrhoea	47%				3%				48%		
Colic									14%		
Colitis									4%		
Abdominal pain	41%										
Respiratory				33%		19%	91%	48%		2%	
Allergic rhinitis	43%		43%		28%				21%		
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

Onset of Symptoms

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

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

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

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

(1) Björkstén et al. 1983
(2) Ventura & Greco 1988
(3) Sutas et al. 1997
(4) Niggemann et al. 1999b

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

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 of Ingestion

Amounts of cow's milk inducing symptoms ranged from 5 g to 250 g (DBPCFC) (1)
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 Diagnostic Features of Cow's Milk Allergy

[Family History / Maternal Factors] [Humoral Parameters] [Cellular Parameters]
[Gastrointestinal Parameters] [Test Significance] [Other Features]

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)

*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
(3) occurence of severe CMA in a pair of identical twins and HLA-identical siblings
(4) family history of CMA in paranthesis

References

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

Maternal Parameters in Breast Milk

Mothers from	IgG	IgA	TGF-beta-1	HLA-DR #	Total No. of Leukocytes	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)

*in colostral breast milk samples, **significance p=0.012
(-) lower, (+) higher values
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

(1) Savilahti et al. 1991
(2) Jarvinen et al. 1999a
(3) Saarinen et al. 1999b

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

Specifc 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 cow's milk allergy (age of >9 years) as compared to children with CMA at the age of <3 years (RAST) (1)

(1) Sicherer & Sampson 1999

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
IgE		a > b (4); + (8)	a > b (4)
IgE/IgG		a > b (4)	a > b (4)
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 > c; b > c (2) + (8)
IgE/IgG1		a > b (4)	a > b (4)
IgE/IgG4		a > b (4)	a > b (4)
IgG	(+) (3) (-) NS (5)	NS (4)	NS (4), NS (7)
IgA	(-) (3)		

(+) 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)

(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

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)

(1) Suomalainen et al. 1994b

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

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

Cellular Parameters

Lymphocyte Subclasses, Antigen Expression

Patients	T-Cells	B-Cells	PBMC	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)

(+) 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)

CLA - cutaneous lymphocyte antigen (responsible for skin homing)

PCNA - proliferating cell nuclear antigen

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

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

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(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	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)

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

(1) 75 (a) and 17 (b) children with CMA and 59 (c) tolerant children (age of 1 to 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 to 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

(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

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

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.
a) 13 children with CMA (gastrointestinal symptoms)		(+)*	(-)	(-)	(1)
b) positive DBPCFC with cow's milk	(+) in 43%	(+)**	(+)***		(2)
c) negative DBPCFC with cow's milk	(+) in 11%	(-)	(-)		(2)

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

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

Gastrointestinal Permeability

Alteration after cow's milk challenge

Urinay Recovery / Test Substances	Alteration	Ref.
polyethylenglycol (PEG)	*	(1)
lactulose/mannitol excretion ratios	(+)	(3)
cellobiose/mannitol excretion ratios	(+)	(4)
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

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

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 ALA or BLG given per kg body weight)

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

Diagnostic Significance of Tests

SPT, Patch Test, RAST

Patients / Reference	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Age (months)		adults	2-36	2-24	50*	62*	<24	21*	2-11
a) acute onset	14			36			22		100
b) delayed onset				18			50		76
SPT - positive			a) 67% b) (-)	a) (+)	55%		14%		
sensitivity specificity PPV NPV					66% 100% 100% 28%	96% 51% 66% 93%			69% 91% 79% 85%
Patch Test - positive			a) (-) b) 89%	b) (+)			44%		
sensitivity specificity PPV NPV									18% 87% 40% 69%
RAST - positive							26%		
sensitivity specificity PPV NPV	79% 80%	60-67% 83-100%				100% 30% 57% 100%		85% 38% 61% 71%	58% 88% 70% 81%

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

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(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
(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
(5) 196 food allergic children and adolescents (54/109 DBPCFC positive) age from 0.6 to 17.9 years, PPV >95% for cow's milk specific IgE >32 kU/L
(6) 72 children with CMA (challenge proven)
(7) 107 children with atopic dermatitis (47 DBPCFC positive) age from 5 months to 12 years
(8) 301 children with suspected CMA (176 DBPCFC positive)

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
(9) Vanto et al. 1999

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 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

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(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
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
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

5 Therapy of Cow's Milk Allergy

[Elimination Diets] [Medication] [Oral Desensitization]

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

* 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 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 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)

Nutrients: Content per 100 g		
Energy 274 kJ (65 kcal)	**Vitamins**	Lys 260 mg
Water 87.7 g	Vitamin A 30 µg	Met 85 mg
Protein 3.3 g	Carotin 17µg	Phe 170 mg
Lipid 3.6 g	Vitamin D 60 ng	Thr 150 mg
Carbohydrate 4.6 g	Vitamin E 85 µg	Trp 45 mg
Organic Acids 0.2 g	Vitamin K 4 µg	Tyr 170 mg
Minerals 0.7 g	Vitamin B1 35 µg	Val 230 mg
	Vitamin B2 180 µg	
Minerals	Nicotinamide 90 µg	**Carbohydrates**
Sodium 50 mg	Pantothenic acid 350 µg	Lactose 4550 mg
Potassium 155 mg	Vitamin B6 45 µg	
Magnesium 12 mg	Biotin 4 µg	**Lipids**
Calcium 120 mg	Folic acid 6 µg	Palmitic acid 930 mg
Manganese 3 µg	Vitamin B12 420 µg	Stearic acid 400 mg
Iron 45 µg	Vitamin C 2 mg	Oleic acid 890 mg
Copper 17 µg		Linolic acid 90 mg
Zinc 380 µg	**Amino Acids**	Linoleic acid 25 mg
Phosphorus 90 mg	Arg 120 mg	Cholesterol 12 mg
Chloride 100 µg	His 90 mg	
Fluoride 17 µg	Ile 210 mg	**Others**
Iodine 3 µg	Leu 350 mg	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%	
alpha S1	36%	12-15 g/L
alpha S2	10%	3-4 g/L
beta	34%	9-11 g/L
kappa	13%	--
gamma	7%	3-4 g/L
Whey Proteins	20%	
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: 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 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 63%
(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
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
Taiwan, Taipei 30 children with suspected CMA (1 to 9 years of age)	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%	Lin et al 1998
USA, Baltimore, MD 22 cow's milk- sensitive patients	bovine Immunoglobulins in 73% (RAST)	Bernhisel-Broadbent et al. 1991

<table>
<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>
<tr><td colspan="5">*frequencies in 27 oral challenge test (OCT) positive children</td></tr>
</table>
</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>
<tr><td colspan="4">*SDS-PAGE immunoblot (graded scale >/= 2+)</td></tr>
</table>
</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 5		(1) Larsen & Lowenstein 1999
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)	(1) Pike et al. 1996
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:	(1) Adams et al. 1991 (2) Maynard et al. 1997 (a) direct ELISA, EAST / RAST (b) EAST / RAST-inhibition

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

(1) 2 patients with CMA
(2) 19 patients with CMA

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
Alteration of Allergenicity trypsin hydrolysis: IgE binding to different tryptic peptides of a-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) Larsen & Lowenstein 1999
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)

(1) Brownlow et al. 1997
(2) Kuwata et al. 1998
(3) del Val et al. 1999

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, binds retinol (1)

(1) SWISS-PROT

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.
1-8 (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)
35-46 (synthetic peptide)	25% (c)	max. 40%		(3)
41-107 (fragment)	+ (b)			(1)
41-60 (tryptic peptide)	92% (b)		surface	(6)
62-107 (fragment)	+ (b)			(1)
78-83 (tryptic peptide)	28% (b)			(6)
84-91 (tryptic peptide)	40% (b)		cryptic	(6)
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)
124-134 (synthetic peptide)	+ (b)	60%		(2)
125-145 (fragment)	+ (b)			(1)
125-135 (tryptic peptide)	28% (b)		surface	(6)
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)

(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)

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

(a) SDS-PAGE / immunoblot
(b) direct ELISA, EAST / RAST
(c) EAST / RAST-inhibition
(d) Pin-ELISA

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
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) Larsen & Lowenstein 1999
Molecular Mass Mr in SDS-PAGE: 67.0 kDa (1), 66.3 kDa (2)	(1) Miller et al. 1993 (2) Wal 1998
Isoelectric Point pI 4.7-4.95 (1), 4.9-5.1 (2)	(1) Miller et al. 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) **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 (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
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) Larsen & Lowenstein 1999

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) kappa-CAS from sheep's and goat's milk: aa identity 84% (1)	(1) BLAST at PIR (2) Spuergin et al. 1997
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)
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)
58-73 (synthetic peptide)	42% (b)	3% (max. 15%)	(2)
61-123 (fragment)	+ (a)		(1)
86-103 (synthetic peptide)	100% (b)	19% (max. 42%)	(2)
93-98 (synthetic peptide)	100% (c)		(2)*
124-135 (fragment)	+ (a)		(1)
136-196 (CNBr fragment)	+ (a)		(1, 3)
141-150 (synthetic peptide)	92% (b)	8% (max. 20%)	(2)*
165-199 (fragment)	+ (a)		(1)
181-199 (synthetic peptide)	100% (a)	92% and 30% (n=2) (b)	(3)
188-199 (synthetic peptide)	42% (b)	7% (max. 28%)	(2)

(1) Otani et al. 1989
(2) Spuergin et al. 1996
(3) Nakajima-Adachi et al. 1998

(a) EAST / RAST
(b) EAST / RAST-inhibition
(c) Pin-ELISA

(1) 2 patients with CMA
(2) 12 patients with CMA, *similar IgG binding
(3) 9 patients with CMA

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)
1-60 (fragment)	+ (a)	(1)
26-93 (fragment)	+ (a)	(1)
106-209 (fragment)	+ (a)	(1)
110-144 (fragment)	+ (a)	(1)
132-144 (fragment)	+ (a)	(1)
157-185 (fragment)	+ (a)	(1)
186-209 (fragment)	+ (a)	(1)

(1) Otani et al. 1989

(a) EAST / RAST
(1) 2 patients with CMA

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: Significantly higher PBMC proliferation in cow's milk allergic children with atopic dermatitis as compared to children with atopic dermatitis without cow's milk allergy (1) 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
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
Alteration of Allergenicity	(1) Kohno et al. 1994 see also 10 Stability of Cow's Milk Allergens

Treatment	alpha-	beta	kappa
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

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 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
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
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

* 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
Mare's Milk / Cow'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

Treatment	Effects	References
Heat boiling of skimmed milk, 10 min	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)	Gjesing et al. 1986
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	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	Host & Samuelsson 1988
Heat boiling of milk, 2 and 10 min	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)	Norgaard et al. 1996
Heat boiling of milk, 5 min	No difference in IgE- binding to raw and cooked milk from sera of 2 patients with CMA (immuno-dot-blotting)	Werfel et al. 1997a
Heat, Reduction, Hydrolysis a) heat 96°C, pH 8.0 b) carboxymethylation c) limited proteolysis	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	Gmoshinskii et al. 1990

<table>
<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>
<tr>
<td>Duodenal Digestion
in vitro digestion of cow's milk proteins by duodenal fluid (1) and human trypsins and elastases (2)</td>
<td>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)</td>
<td>(1) Jakobsson et al. 1982
(2) Jakobsson et al. 1983</td>
</tr>
<tr>
<td>Intestinal Digestion
intestinal digestion of beta-LG, alpha-LA and CAS (intestinal cells, 48h)</td>
<td>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</td>
<td>Benlounes et al. 1996</td>
</tr>
<tr>
<td>Cell-Envelop Proteinase
specific hydrolysis of CAS and ultrafiltration</td>
<td>Elimination of IgE-binding epitopes by degradation of CAS and removal of whey proteins by ultrafiltration</td>
<td>Alting et al. 1998</td>
</tr>
<tr>
<td>Pepsin Hydrolysis, beta-LG
pepsin hydrolysis of beta-LG</td>
<td>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)</td>
<td>Duchateau et al. 1998</td>
</tr>
<tr>
<td>Lactic Acid Fermentation
lactic acid fermentation of sterilized cow's milk with a mixed culture of meso- and thermophilic bacteria strains</td>
<td>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)</td>
<td>Jedrychowski & Wroblewska 1999</td>
</tr>
</table>

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)	(1) Gerrard & Shenassa 1983a, 1983b
"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
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)	(1) Jarmoc & Primack 1987 (2) Wüthrich et al. 1995 (3) Wüthrich et al. 1996

"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

12 Infant Formulas

[Application of Infant Formulas in CMA] [Allergenicity / Safety] [Prophylaxis of Atopic Disease]

12.1 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
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

12.2 Allergenicity / Safety of Infant Formulas

Reported Adverse Reactions	References
Human Milk	see 11 Allergen Sources Reported Adverse Reactions
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 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
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

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
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
Whey Hydrolyzed Formula 1 ultrafiltrated, extensively hydrolysed whey infant formula	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)	Van Hoeyveld et al. 1998
Casein Hydrolyzed Formula 10 children with CMA	Proliferative responses of PBMCs to hydrolysate formula: higher in 3 patients whose symptoms were not reduced by CAS hydrolysate formula	Nishida et al. 1995

Hydrolyzed Infant Formulas a) extensively hydrolyzed CAS formula b) extensively hydrolyzed whey formula c) partially hydrolyzed whey formula	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	Ragno et al. 1993
Hydrolyzed Infant Formulas a) non hydrolysed formula b) whey-based formula c) whey-based and ultra-filtrated formula d) CAS/whey-based formula	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)	Gortler et al. 1995
Hydrolyzed Infant Formulas 11 whey and 1 CAS hydrolysed formulas	Inhibition of IgE binding to **positive samples / inhibition** alpha-LA 12 18-93% beta-LG 12 2-84% BSA 6 2-75% bovine IgG 8 3-72% CAS 11 3-89% (RAST inhibition)	(1) van Beresteijn et al. 1995
Hydrolyzed Infant Formulas 9 whey or CAS hydrolysed formulas	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)	(1) Restani et al. 1995, 1996 (2) Plebani et al. 1997
Extensively Hydrolyzed Formulas children with CMA	IgE-binding to residual protein fractions less than 20 kDa in several extensively hydrolyzed cow milk- based formulae (RAST inhibition)	Hoffman & Sampson 1997
Infant Formulas a) partially hydrolysed whey formula b) partially hydrolysed whey/CAS formula c) soy/pork collagen hydrolysate d) amino acid formula	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	Niggemann et al. 1999a
Human Milk	Cow's milk proteins	see 11 Allergen Sources

12.3 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
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 cow's milk allergy: in a) 2.4%, b) 1.7%, c) 1.5%, d) 2.1% of infants	Saarinen et al. 1999a
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 !

13 References [Recent Reviews]

- Abernathy-Carver KJ, Sampson HA, Picker LJ, Leung DY (1995) **Milk-induced eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen** *J Clin Invest 95:913-8*
- Adams SL, Barnett D, Walsh BJ, Pearce RJ, Hill DJ, Howden ME (1991) **Human IgE-binding synthetic peptides of bovine beta-lactoglobulin and alpha- lactalbumin. In vitro cross-reactivity of the allergens** *Immunol Cell Biol 69(Pt 3):191-7*
- Alexander LJ, Stewart AF, Mackinlay AG, Kapelinskaya TV, Tkach TM, Gorodetsky SI (1988) **Isolation and characterization of the bovine kappa-casein gene** *Eur J Biochem 178:395-401*
- Alexander LJ, Hayes G, Pearse MJ, Beattie CW, Stewart AF, Willis IM, Mackinlay AG (1989) **Complete sequence of the bovine beta- lactoglobulin cDNA** *Nucleic Acids Res 17:6739*
- Alting AC, Meijer RJ, van Beresteijn EC (1997) **Incomplete elimination of the ABBOS epitope of bovine serum albumin under simulated gastrointestinal conditions of infants** *Diabetes Care 20:875-80*
- Alting AC, Meijer RJ, van Beresteijn EC (1998) **Selective hydrolysis of milk proteins to facilitate the elimination of the ABBOS epitope of bovine serum albumin and other immunoreactive epitopes** *J Food Prot 61:1007-12*
- Altintas D, Guneser S, Evliyaoglu N, Yuksel B, Atici A, Serbest M (1995) **A prospective study of cow's milk allergy in Turkish infants** *Acta Paediatr 84:1320-1*
- Amonette MS, Schwartz RH, Mattson L, Peers LB, Eldredge DM (1991) **Double- blind, placebo- controlled food challenges (DBPCFC) demonstrating acute IgE-mediated alleeergic reactions to Good Start, Ultrafiltered Good Start, Alfaré, Nutramigen, and Alimentum in a seven- year- old** *Pediatr Asthma Allergy Immunol 5:245-51*
- Amonette MS, Rosenfeld SI, Schwartz RH (1993) **Serum IgE antibodies to cow's milk proteins in children with differing degrees of IgE-mediated cow's milk allergy: analysis by immunoblotting***Pediatr Asthma Allergy Immunol 7:99-109*
- Andre F, Andre C, Colin L, Cacaraci F, Cavagna S (1994) **Role of new allergens and of allergens consumption in the increased incidence of food sensitizations in France** *Toxicology 93(1):77-83*
- Armisen Pedrejon A, Sancho Madrid B, Almaraz Garzon E, Prieto Bozano G, Polanco Allue I (1996) **Colitis induced by a food allergen. A report of 20 cases** *An Esp Pediatr 44:21-4* (in Spanish)
- Arruda LK, Vailes LD, Hayden ML, Benjamin DC, Chapman MD (1995) **Cloning of cockroach allergen, Bla g 4, identifies ligand binding proteins (or calycins) as a cause of IgE antibody responses** *J Biol Chem 270:31196-201*
- Ashkenazi A, Levin S, Idar D, Or A, Rosenberg I, Handzel ZT (1980) **In vitro cell- mediated immunologic assay for cow's milk allergy** *Pediatrics 66:399-402*
- Axelsson I, Jakobsson I, Lindberg T, Benediktsson B (1986) **Bovine beta- lactoglobulin in the human milk. A longitudinal study during the whole lactation period** *Acta Paediatr Scand 75:702-7*
- Bachman KD, Dees SC (1957) **Observations on incidence and symptoms in "well" babies** *Pediatr 20:393-406*
- Baehler P, Chad Z, Gurbindo C, Bonin AP, Bouthillier L, Seidman EG (1996) **Distinct patterns of cow's milk allergy in infancy defined by prolonged, two- stage double- blind, placebo- controlled food challenges** *Clin Exp Allergy 26:254-61*
- Baev AA, Smirnov IK, Gorodetskii SI (1987) **Primary structure of bovine beta-casein cDNA** *Mol Biol (Mosk) 21:214-22*
- Ball G, Shelton MJ, Walsh BJ, Hill D, Hosking CS, Howden MEH (1994) **A major continuous allergenic epitope of bovine {beta} lactoglobulin recognized by human IgE-binding** *Clin Exp Allergy 24:758-64*
- Barau E, Dupont C (1994) **Allergy to cow's milk proteins in mother's milk or in hydrolyzed cow's milk infant formulas as assessed by intestinal permeability measurements** *Allergy 49:295-8*
- Barman TE (1970) **Purification and properties of bovine milk glyco- alpha- lactalbumin** *Biochim Biophys Acta 214:242-4*
- Batt CA, Rabson LD, Wong DW, Kinsella JE (1990) **Expression of recombinant bovine beta-lactoglobulin in Escherichia coli** *Agric Biol Chem 54:949-55*
- Bauer A, Ekanayake Mudiyanselage S, Wigger-Alberti W, Elsner P (1999) **Oral rush desensitization to milk** *Allergy 54:894-5*
- Bell K, Hopper KE, McKenzie HA, Murphy WH, Shaw DC (1970) **A comparison of bovine alpha-lactalbumin A and B of Droughtmaster** *Biochim Biophys Acta 214:437-44*
- Bellioni-Businco B, Paganelli R, Lucenti P, Giampietro PG, Perborn H, Businco L (1999) **Allergenicity of goat's milk in children with cow's milk allergy** *J Allergy Clin Immunol 103:1191-4*
- Bengtsson U, Knutson TW, Knutson L, Dannaeus A, Hallgren R, Ahlstedt S (1996) **Increased levels of hyaluronan and albumin after intestinal challenge in adult patients with cow's milk intolerance** *Clin Exp Allergy 26:96-103*
- Bengtsson U, Knutson TW, Knutson L, Dannaeus A, Hallgren R, Ahlstedt S (1997) **Eosinophil cationic protein and histamine after intestinal challenge in patients with cow's milk intolerance** *J Allergy Clin Immunol 100:216-21*

- Benlounes N, Dupont C, Candalh C, Blaton MA, Darmon N, Desjeux JF, Heyman M (1996) **The threshold for immune cell reactivity to milk antigens decreases in cow's milk allergy with intestinal symptoms** *J Allergy Clin Immunol 98:781-9*
- Benlounes N, Dupont C, Candalh C, Blaton MA, Bloom M, Heyman M (1997) **Effect of terfenadine on TNF alpha release from peripheral blood mononuclear cells during cow's milk allergy** *Clin Exp Allergy 27:942-8*
- Benlounes N, Candalh C, Matarazzo P, Dupont C, Heyman M (1999) **The time- course of milk antigen- induced TNF-alpha secretion differs according to the clinical symptoms in children with cow's milk allergy** *J Allergy Clin Immunol 104(4Pt1):863-9*
- Bernard H, Creminon C, Yvon M, Wal JM (1998) **Specificity of the human IgE response to the different purified caseins in allergy to cow's milk proteins** *Int Arch Allergy Immunol 115:235-44*
- Bernaola G, Echechipia S, Urrutia I, Fernandez E, Audicana M, Fernandez de Corres L (1994) **Occupational asthma and rhinoconjunctivitis from inhalation of dried cow's milk caused by sensitization to alpha- lactalbumin** *Allergy 49:189-91*
- Bernhisel-Broadbent J, Yolken RH, Sampson HA (1991) **Allergenicity of orally administered immunoglobulin preparations in food- allergic children** *Pediatrics 87:208-14*
- Bishop JM, Hill DJ, Hosking CS (1990) **Natural history of cow milk allergy: clinical outcome** *J Pediatr 116(6):862-7* [comment J Pediatr 1991 118(4 Pt 1):655-6]
- Bjorksten B, Ahlstedt S, Bjorksten F, Carlsson B, Fallstrom SP, Juntunen K, Kajosaari M, Kober A (1983) **Immunoglobulin E and immunoglobulin G4 antibodies to cow's milk in children with cow's milk allergy** *Allergy 38:119-24*
- Bjornsson E, Janson C, Plaschke P, Norrman E, Sjoberg O (1996) **Prevalence of sensitization to food allergens in adult Swedes** *Ann Allergy Asthma Immunol 77:327-32*
- Blanco Quiros A, Garrote Adrados JA, Andion Dapena R, Alonso Franch M, Calvo Romero C, Bobillo del Amo H (1993) **Increased serum levels of soluble IL-2 receptor in food intolerance: possible mechanism of delayed immunity in milk intolerance** *An Esp Pediatr 38:330-6* (in Spanish)
- Bleck GT, Bremel RD (1993) **Sequence and single- base polymorphisms of the bovine alpha-lactalbumin 5' flanking region***Gene 126:213-8*
- Bock SA (1987) **Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life** *Pediatrics 79:683-8*
- Bock SA, Atkins FM (1990) **Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges** *J Pediatr 117(4):561-7*
- Bonifazi E, Garofalo L, Monterisi A, Meneghini CL (1978) **Food allergy in atopic dermatitis: experimental observations** *Acta Derm Venereol 58(4): 349-52*
- Bonsing J, Ring JM, Stewart AF, Mackinlay AG (1988) **Complete nucleotide sequence of the bovine beta-casein gene** *Aust J Biol Sci 41:527-37*
- Bottaro G, Failla P, Rotolo N, Azzaro F, Pennisi P, Pasqualetto A, Castiglione N, Patane R (1992) **Significance of milk antibodies in cow's milk protein intolerance** *Pediatr Med Chir 14:21-5*(in Italian)
- Brarda OA, Vanella LM, Greco CR (1989) **Lymphocyte blastogenesis in children with cow's milk hypersensitivity after its elimination from the diet** *Allergol Immunopathol (Madr) 17:45-8*
- Braunitzer G, Chen R, Schrank B, Stangl A (1973) **The sequence of beta- lactoglobulin** *Hoppe- Seyler's Z. Physiol. Chem. 354:867-878(1973)*
- Brew K, Castellino FJ, Vanaman TC, Hill RL (1970) **The complete amino acid sequence of bovine alpha-lactalbumin** *J Biol Chem 245:4570-82*
- Brignon G, Ribadeau-Dumas B (1973) **Localization of the Glu-Gln substitution differentiating B and D genetic variants in the peptide chain of bovine beta lactoglobulin** *FEBS Lett 33:73-76*
- Brignon G, Ribadeau-Dumas B, Mercier JC, Pelissier JP, Das BC (1977) **Complete amino acid sequence of bovine alphaS2-casein***FEBS Lett 76:274-9*
- Brown JR (1974) **Structure of serum albumin: disulfide bridges** *Fed Proc 33:1389*
- Brown JR (1975) **Structure of bovine serum albumin** *Fed Proc 34:591*
- Brownlow S, Morais Cabral JH, Cooper R, Flower DR, Yewdall SJ, Polikarpov I, et al. (1997) **Bovine {beta} lactoglobulin at 1.8Å resolution - still an enigmatic lipocalcin** *Structure 5:481-95*
- Buisseret PD (1978) **Common manifestations of cow's milk allergy in children** *Lancet 1(8059):304-5*
- Burks AW, James JM, Hiegel A, Wilson G, Wheeler JG, Jones SM, Zuerlein N (1998) **Atopic dermatitis and food hypersensitivity reactions** *J Pediatr 132(1):132-6*
- Businco L, Cantani A, Benincori N, Perlini R, Infussi R, De Angelis M, Businco E (1983a) **Effectiveness of oral sodium cromoglycate (SCG) in preventing food allergy in children** *Ann Allergy 1983 Jul;51(1 Pt 1):47-50*
- Businco L, Marchetti F, Pellegrini G, Perlini R (1983b) **Predictive value of cord blood IgE levels in 'at-risk' newborn**

babies and influence of type of feeding *Clin Allergy 13(6):503-8*
- Businco L, Benincori N, Cantani A, Tacconi L, Picarazzi A (1985) **Chronic diarrhea due to cow's milk allergy. A 4- to 10-year follow-up study** *Ann Allergy 55:844-7*
- Businco L, Cantani A, Longhi MA, Giampietro PG (1989) **Anaphylactic reactions to a cow's milk whey protein hydrolysate (Alfa-Re, Nestle) in infants with cow's milk allergy** *Ann Allergy 62:333-5*
- Businco L, Lucenti P, Arcese G, Ziruolo G, Cantani A (1994) **Immunogenicity of a so-called hypoallergenic formula in at-risk babies: two case reports** *Clin Exp Allergy 24:42-5*
- Buts JP, Di Sano C, Hansdorffer S (1993) **Clinical evaluation of the tolerance for a soy- based special milk formula in children with cow's milk protein intolerance/allergy** *Minerva Pediatr 45:209-13* (in Italian)
- Calvani M Jr, Alessandri C (1998) **Anaphylaxis to sheep's milk cheese in a child unaffected by cow's milk protein allergy** *Eur J Pediatr 157:17-9*
- Campbell DE, Ngamphaiboon J, Clark MM, Harris MC, Kolski GB, Douglas SD (1987) **Indirect enzyme- linked immunosorbent assay for measurement of human immunoglobulins E and G to purified cow's milk proteins: application in diagnosis of cow's milk allergy** *J Clin Microbiol 25:2114-9*
- Camponeschi B, Lucarelli S, Frediani T, Barbato M, Quintieri F (1997) **Association of HLA-DQ7 antigen with cow milk protein allergy in Italian children** *Pediatr Allergy Immunol 8:106-9*
- Cantani A, Ferrara M, Ragno V, Businco L (1990) **Efficacy and safety of a soy- protein- formula for feeding babies with atopic dermatitis and cow's milk hypersensitivity** *Riv Eur Sci Med Farmacol 12:311-8*
- Carroccio A, Cavataio F, Montalto G, Soresi M, Lorello D, Notarbartolo A, Iacono G (1997) **Evaluation of pancreatic function development after hydrolyzed protein- based and soy- based formulas in unweaned infants** *Scand J Gastroenterol 32:273-7*
- Casimir GJ, Duchateau J, Cuvelier P, Vis HL (1989) **Maternal immune status against beta- lactoglobulin and cow milk allergy in the infant** *Ann Allergy 63(6 Pt 1):517-9*
- Cavataio F, Iacono G, Montalto G, Soresi M, Tumminello M, Campagna P, Notarbartolo A, Carroccio A (1996) **Gastroesophageal reflux associated with cow's milk allergy in infants: which diagnostic examinations are useful?** *Am J Gastroenterol 91:1215-20*
- Challacombe DN, Wheeler EE, Campbell PE (1986) **Morphometric studies and eosinophil cell counts in the duodenal mucosa of children with chronic nonspecific diarrhoea and cow's milk allergy** *J Pediatr Gastroenterol Nutr 5:887-91*
- Chandra RK, Hamed A (1991) **Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas** *Ann Allergy 67(2 Pt 1):129-32*
- Chandra RK, Puri S, Hamed A (1989a) **Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants** *BMJ 299(6693): 228-30* [erratum in BMJ 299(6704):896]
- Chandra RK, Singh G, Shridhara B (1989b) **Effect of feeding whey hydrolysate, soy and conventional cow milk formulas on incidence of atopic disease in high risk infants** *Ann Allergy 63(2):102-6*
- Chandra RK (1997) **Five-year follow-up of high-risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas** *J Pediatr Gastroenterol Nutr 24(4):380-8*
- Chatel JM, Bernard H, Clement G, Frobert Y, Batt CA, Gavalchin J, Peltres G, Wal JM (1996) **Expression, purification and immunochemical characterization of recombinant bovine beta-lactoglobulin, a major cow milk allergen** *Mol Immunol 33:1113-8*
- Chatel JM, Adel-Patient K, Creminon C, Wal JM (1999) **Expression of a lipocalin in prokaryote and eukaryote cells: quantification and structural characterization of recombinant bovine beta- lactoglobulin** *Protein Expr Purif 16:70-5*
- Chen R, Wang B, Zhang Y, Liu W, Zhang J, Lao W (1992) **Cloning, mapping, and sequencing of 3' and its flanking region of bovine alpha-s1 casein gene** *Chin J Biotechnol 8:235-45*
- Chetty A (1982) **Extrinsic allergic alveolitis due to milk allergy: case report and review of the literature** *Ann Allergy 48:113-4*
- Chiancone E, Gattoni M (1993) **Selective removal of beta- lactoglobulin directly from cow's milk and preparation of hypoallergenic formulas: a bioaffinity method** *Biotechnol Appl Biochem 18(Pt1):1-8*
- Chirico G, Gasparoni A, Ciardelli L, De Amici M, Colombo A, Rondini G (1997) **Immunogenicity and antigenicity of a partially hydrolyzed cow's milk infant formula** *Allergy 52:82-8*
- Cho Y, Gu W, Watkins S, Lee SP, Kim TR, Brady JW, Batt CA (1994) **Thermostable variants of bovine beta-lactoglobulin** *Protein Eng 7:263-70*
- Chung HL, Hwang JB, Kwon YD, Park MH, Shin WJ, Park JB (1999) **Deposition of eosinophil- granule major basic protein and expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in the mucosa of the small intestine in infants with cow's milk- sensitive enteropathy** *J Allergy Clin Immunol 103:1195-201*
- Clein NW (1951) **Cow's milk allergy in infants** *Ann Allergy 9:195-204*
- Collins-Williams C (1956) **The incidence of milk allergy in pediatric practice** *J Pediatr 48:39-47*

- Crespo JF, Pascual C, Burks AW, Helm RM, Esteban MM (1995) **Frequency of food allergy in a pediatric population from Spain** *Pediatr Allergy Immunol 6:39-43*
- Dannaeus A, Johansson SG, Foucard T, Ohman S (1977) **Clinical and immunological aspects of food allergy in childhood. I. Estimation of IgG, IgA and IgE antibodies to food antigens in children with food allergy and atopic dermatitis** *Acta Paediatr Scand 66:31-7*
- Davidovits M, Levy Y, Avramovitz T, Eisenstein B (1993) **Calcium- deficiency rickets in a four- year- old boy with milk allergy** *J Pediatr 122:249-51*
- Davidson GP, Hill DJ, Townley RR (1976) **Gastrointestinal milk allergy in childhood: a rational approach** *Med J Aust 1(25):945-7*
- Dean T (1997) **Prevalence of allergic disorders in early childhood** *Pediatr Allergy Immunol 8(10 Suppl):27-31*
- Dean TP, Adler BR, Ruge F, Warner JO (1993) **In vitro allergenicity of cows' milk substitutes** *Clin Exp Allergy 23:205-10*
- de Boissieu D, Matarazzo P, Dupont C (1997) **Allergy to extensively hydrolyzed cow milk proteins in infants: identification and treatment with an amino acid- based formula** *J Pediatr 131:744-7*
- de Diego Lorenzo A, Robles Fornieles J, Herrero Lopez T, Cos Arregui E (1992) **Acute pancreatitis associated with milk allergy** *Int J Pancreatol 12:319-21*
- del Val G, Yee BC, Lozano RM, Buchanan BB, Ermel RW, Lee YM, Frick OL (1999) **Thioredoxin treatment increases digestibility and lowers allergenicity of milk** *J Allergy Clin Immunol 103:690-7*
- Docena GH, Fernandez R, Chirdo FG, Fossati CA (1996) **Identification of casein as the major allergenic and antigenic protein of cow's milk** *Allergy 51:412-6*
- Donzelli F, Da-Dalt L, Schiavon A, Baraldi E, Muraro MA (1990) **Clinical experience with a hydrolyzed soy formula in infants with protracted enteritis and atopic eczema** *Pediatr Med Chir 12(1):71-9* (in Italian)
- Duchateau J, Michils A, Lambert J, Gossart B, Casimir G (1998) **Anti- betalactoglobulin IgG antibodies bind to a specific profile of epitopes when patients are allergic to cow's milk proteins** *Clin Exp Allergy 28:824-33*
- Ebeler SE, Philips LG, Kinsella JE (1990) **Purification of {beta}- lactoglobulin: isolation of genetic variants and influence of purification method on secondary structure** *Milchwissenschaft 45:694-8*
- Eigenmann PA, Sampson HA (1998) **Interpreting skin prick tests in the evaluation of food allergy in children** *Pediatr Allergy Immunol 9(4):186-91*
- Eigenmann PA, Belli DC, Ludi F, Kahn JM, Polla BS (1995) **In vitro lymphocyte proliferation with milk and a casein-whey protein hydrolyzed formula in children with cow's milk allergy** *J Allergy Clin Immunol 96:549-57*
- Eigenmann PA, Tropia L, Hauser C (1999) **The mucosal adhesion receptor alpha4beta7 integrin is selectively increased in lymphocytes stimulated with beta- lactoglobulin in children allergic to cow's milk** *J Allergy Clin Immunol 103(5Pt1):931-6*
- Ellis MH, Short JA, Heiner DC (1991) **Anaphylaxis after ingestion of a recently introduced hydrolyzed whey protein formula** *J Pediatr 118:74-7*
- Endre L, Osvath P (1975) **Antigen- induced lymphoblast transformation in the diagnosis of cow's milk allergic diseases in infancy and early childhood** *Acta Allergol 30:34-42*

  Etesamifar M, Wüthrich B (1998) **IgE- mediated food allergies including oral allergy syndrome in 383 patients***Allergologie 21:451-7* (in German)
- European Commission (1998) **Reports on tasks for scientific cooperation. The occurrence of severe food allergies in the EU** *European Commission, Directorate-General III, Brussels*
- Falth-Magnusson K, Kjellman NI, Odelram H, Sundqvist T, Magnusson KE (1986) **Gastrointestinal permeability in children with cow's milk allergy: effect of milk challenge and sodium cromoglycate as assessed with polyethyleneglycols (PEG 400 and PEG 1000)** *Clin Allergy 16:543-51*
- Fiocchi A, Restani P, Decet E, Travaini M, Mirri GP, Bernardo L, Riva E (1999) **Evolution from ewe's milk to cow's milk allergy** *Allergy 54:401-2*
- Firer MA, Hosking CS, Hill DJ (1982) **Cow's milk allergy and eczema: patterns of the antibody response to cow's milk in allergic skin disease** *Clin Allergy 12:385-90*
- Firer MA, Hoskings CS, Hill DJ (1987) **Humoral immune response to cow's milk in children with cow's milk allergy. Relationship to the time of clinical response to cow's milk challenge** *Int Arch Allergy Appl Immunol 84:173-7*
- Forget P, Arends JW (1985) **Cow's milk protein allergy and gastro- oesophageal reflux** *Eur J Pediatr 144:298-300*
- Fossati G, Perri M, Careddu G, Mirra N, Carnelli V (1992) **Pulmonary hemosiderosis induced by cow's milk proteins: a discussion of a clinical case** *Pediatr Med Chir 14:203-7* (in Italian)
- Foucard T, Edberg U, Malmheden Yman I (1997) **Severe, even fatal reactions to food stuffs: peanuts and soya underestimated allergens** *J Swe Med Assoc 94:2635-8*
- Fredriksson (1972) **Scanning isoelectric focusing in small density gradient columns. II. Microfractionation of column contents. Evaluation of pH course. Isoelectric points of beta- lactoglobulins A and B** *Anal Biochem 50:575-85*

- Freier S, Lebenthal E, Freier M, Shah PC, Park BH, Lee PC (1983) **IgE and IgD antibodies to cow milk and soy protein in duodenal fluid: effects of pancreozymin and secretin** *Immunology 49(1):69-75*
- Fremont S, Kanny G, Bieber S, Nicolas JP, Moneret-Vautrin DA (1996) **Identification of a masked allergen, alpha-lactalbumin, in baby-food cereal flour guaranteed free of cow's milk protein** *Allergy 51:749-54*
- Gall H, Kalveram CM, Sick H, Sterry W (1996) **Allergy to the heat- labile proteins alpha- lactalbumin and beta-lactoglobulin in mare's milk** *J Allergy Clin Immunol 97:1304-7*
- Gern JE, Yang E, Evrard HM, Sampson HA (1991) **Allergic reactions to milk-contaminated "nondairy" products** *N Engl J Med 324:976-9*
- Gerrard JW, Lubos MC, Hardy LW, Holmlund BA,Webster D (1967) **Milk allergy: clinical picture and familial incidence** *Canad Mess Ass J 97:780-5*
- Gerrard JW, Shenassa M (1983a) **Food allergy: two common types as seen in breast and formula fed babies** *Ann Allergy 50:375-9*
- Gerrard JW, Shenassa M (1983b) **Sensitization to substances in breast milk: recognition, management and significance** *Ann Allergy 51:300-2*
- Gerrard JW, MacKenzie JW, Goluboff N, Garson JZ, Maningas CS (1973) **Cow's milk allergy: prevalence and manifestations in an unselected series of newborns** *Acta Paediatr Scand Suppl 234:1-21*
- Giampietro PG, Ragno V, Daniele S, Cantani A, Ferrara M, Businco L (1992) **Soy hypersensitivity in children with food allergy** *Ann Allergy 69(2):143-6*
- Gislason D, Björnsson E, Gislason T, Janson C, Sjöberg O, Elfman L, Boman G (1999) **Sensitization to airborne and food allergens in Reykjavic (Iceland) and Uppsala (Sweden) - a comparative study** *Allergy 54:1160-7*
- Gjesing B, Osterballe O, Schwartz B, Wahn U, Lowenstein H (1986) **Allergen- specific IgE antibodies against antigenic components in cow milk and milk substitutes** *Allergy 41:51-6*
- Gmoshinskii IV, Krzhechkovskaia VV, Zorin SN (1990) **Changes in the immunochemical properties of beta-lactoglobulin during proteolysis and exposure to various physico- chemical factors** *Vopr Med Khim 1990 Sep-Oct;36(5):11-5* (in Russian)
- Godovac-Zimmermann J, Krause I, Buchberger J, Weiss G, Klostermeyer H (1990) **Genetic variants of bovine beta-lactoglobulin. A novel wild- type beta- lactoglobulin W and its primary sequence** *Biol Chem Hoppe Seyler 371:255-60*
- Godovac-Zimmermann J, Krause I, Baranyi M, Fischer-Fruhholz S, Juszczak J, Erhardt G, Buchberger J, Klostermeyer H (1996) **Isolation and rapid sequence characterization of two novel bovine beta-lactoglobulins I and J** *J Protein Chem 15:743-50*
- Goh DLM, Lau YN, Chew FT, Shek LPC, Lee BW (1999) **Pattern of food-induced anaphylaxis in children of an Asian community** *Allergy 54:84-86*
- Goldman AS, Anderson Jr DW, Sellers WA, Saperstein S, Kniker WT, Halpern SR (1963a) **Milk allergy; I. Oral challenge with milk and isolated milk proteins in allergic children** *Pediatrics 32:425-43*
- Goldman AS, Sellars WA, Halpern SR, Anderson Jr DW, Furlow TE, Johnson Jr CH (1963b) **Milk allergy; II. Skin testing of allergic and normal children with purified milk proteins** *Pediatrics 32:572-9*
- Gorodetskii SI, Kaledin AS (1987) **Analysis of nucleotide sequence of bovine kappa-casein cDNA** *Genetika 23:398-404*
- Gorodetskii SI, Zakhar'ev VM, Kyarshulite DR, Kapelinskaya TV, Skryabin KG (1986) **Cloning and nucleotide sequence of cDNA for bovine alpha-S1-casein** *Biokhimiia 51:1402-9*
- Gortler I, Urbanek R, Forster J (1995) **Characterization of antigens and allergens in hypo- allergenic infant formulae** *Eur J Pediatr 154:289-94*
- Groenen MA, Dijkhof RJ, Verstege AJ, van der Poel JJ (1993) **The complete sequence of the gene encoding bovine alpha s2-casein** *Gene 123:187-93*
- Grosclaude F, Mahe MF, Mercier JC, Ribadeau-Dumas B (1972) **Localization of amino-acid substitutions that differenciate bovine kappa-casein variants A and B** *Ann Genet Sel Anim 4:515-21*
- Grosclaude F, Joudrier P, Mahe MF (1979) **A genetic and biochemical analysis of a polymorphism of bovine alpha S2-casein***J Dairy Res 46:211-3*
- Gruskay FL (1982) **Comparison of breast, cow, and soy feedings in the prevention of onset of allergic disease: a 15-year prospective study** *Clin Pediatr Phila 21(8):486-91*
- Gryboski JD (1993) **Ulcerative colitis in children 10 years old or younger** *J Pediatr Gastroenterol Nutr 17:24-31*
- Gryboski JD, Kocoshis S (1980) **Immunoglobulin deficiency in gastrointestinal allergies** *J Clin Gastroenterol 2(1):71-6*
- Haddad ZH, Kalra V, Verma S (1979) **IgE antibodies to peptic and peptic- tryptic digests of betalactoglobulin: significance in food hypersensitivity** *Ann Allergy 42:368-71*
- Halken S, Host A, Hansen LG, Osterballe O (1993a) **Safety of a new, ultrafiltrated whey hydrolysate formula in**

children with cow milk allergy: a clinical investigation *Pediatr Allergy Immunol 4:53-9*

- Halken S, Host A, Hansen LG, Osterballe O (1993b) **Preventive effect of feeding high-risk infants a casein hydrolysate formula or an ultrafiltrated whey hydrolysate formula. A prospective, randomized, comparative clinical study** *Pediatr Allergy Immunol 4:173-81*
- Hankard GF, Matarazzo P, Duong JP, Mougenot JF, Navarro J, Cezard JP, Peuchmaur M (1997) **Increased TIA1-expressing intraepithelial lymphocytes in cow's milk protein intolerance** *J Pediatr Gastroenterol Nutr 25:79-83*
- Hannuksela M (1987) **Diagnosis of dermatologic food allergy** *Ann Allergy 59:153-156*
- Harikul S, Haruehasavasin Y, Varavithya W, Chaicumpa W (1995) **Cow milk protein allergy during the first year of life: a 12 year experience at the children's hospital, Bangkok** *Asian Pac J Allergy Immunol 13(2):107-11*
- Harris MJ, Petts V, Penny R (1977) **Cow's milk allergy as a cause of infantile colic: immunofluorescent studies on jejunal mucosa** *Aust Paediatr J 13:276-81*
- Hattevig G, Kjellman B, Johansson SG, Bjorksten B (1984) **Clinical symptoms and IgE responses to common food proteins in atopic and healthy children** *Clin Allergy 14(6):551-9*
- Hauer AC, Breese EJ, Walker-Smith JA, MacDonald TT (1997) **The frequency of cells secreting interferon- gamma and interleukin-4, -5, and -10 in the blood and duodenal mucosa of children with cow's milk hypersensitivity** *Pediatr Res 42:629-38*
- Hayashi N, Owa K, Yoshijima S, Hatanaka T, Suehiro Y, Shinomiya K (1993) **A case of severe milk allergy. Relationship with type I and Type III allergic reactions** *Arerugi 42:57-63* (in Japanese)
- Heinzmann A, Blattmann S, Spuergin P, Forster J, Deichmann KA (1999) **The recognition pattern of sequential B cell epitopes of beta- lactoglobulin does not vary with the clinical manifestations of cow's milk allergy** *Int Arch Allergy Immunol 120:280-6*
- Heyman M, Grasset E, Ducroc R, Desjeux JF (1988) **Antigen absorption by the jejunal epithelium of children with cow's milk allergy** *Pediatr Res 24:197-202*
- Heyman M, Darmon N, Dupont C, Dugas B, Hirribaren A, Blaton MA, Desjeux JF (1994) **Mononuclear cells from infants allergic to cow's milk secrete tumor necrosis factor alpha, altering intestinal function** *Gastroenterology 106:1514-23*
- Hide DW, Guyer BM (1983) **Cows milk intolerance in Isle of Wight infants** *Br J Clin Pract 37:285-7*
- Higuchi R, Noda E, Koyama Y, Shirai T, Horino A, Juri T, Koike M (1996) **Biotin deficiency in an infant fed with amino acid formula and hypoallergenic rice** *Acta Paediatr 85:872-4*
- Hill DJ, Milla PJ (1990) **Colitis caused by food allergy in infants** *Arch Dis Child 65:132-3*
- Hill DJ, Davidson GP, Cameron DJ, Barnes GL (1979) **The spectrum of cow's milk allergy in childhood. Clinical, gastroenterological and immunological studies** *Acta Paediatr Scand 68:847-52*
- Hill DJ, Firer MA, Shelton MJ, Hosking CS (1986) **Manifestations of milk allergy in infancy: clinical and immunologic findings** *J Pediatr 109:270-6*
- Hill DJ, Firer MA, Ball G, Hosking CS (1989) **Recovery from milk allergy in early childhood: antibody studies** *J Pediatr 114:761-6*
- Hill DJ, Ball G, Hosking CS, Wood PR (1993a) **Gamma-interferon production in cow milk allergy** *Allergy 48:75-80*
- Hill DJ, Firer MA, Ball G, Hosking CS (1993b) **Natural history of cows' milk allergy in children: immunological outcome over 2 years** *Clin Exp Allergy 23:124-31*
- Hill DJ, Bannister DG, Hosking CS, Kemp AS (1994) **Cow milk allergy within the spectrum of atopic disorders** *Clin Exp Allergy 24:1137-43*
- Hill DJ, Cameron DJ, Francis DE, Gonzalez-Andaya AM, Hosking CS (1995) **Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance** *J Allergy Clin Immunol 96(3):386-94*
- Hill DJ, Hosking CS, Zhie CY, Leung R, Baratwidjaja K, Iikura Y et al. (1997) **Frequency of food allergy in Australia and Asia** *Environ Toxicol Pharmacol 4:101-10*
- Hill DJ, Hosking CS, Heine RG (1999) **Clinical spectrum of food allergy in children in Australia and South-East Asia: identification and targets for treatment** *Ann Med 31:272-81*
- Hiraoka Y, Segawa T, Kuwajima K, Sugai S, Murai N (1980) **alpha- Lactalbumin: a calcium metalloprotein** *Biochem Biophys Res Commun 95:1098-104*
- Hitchin E, Stevenson EM, Clark AJ, McClenaghan M, Leaver J (1996) **Bovine beta- casein expressed in transgenic mouse milk is phosphorylated and incorporated into micelles** *Protein Expr Purif 7:247-52*
- Hoffman KM, Sampson HA (1997) **Serum specific-IgE antibodies to peptides detected in a casein hydrolysate formula** *Pediatr Allergy Immunol 8:185-9*
- Hoffman KM, Ho DG, Sampson HA (1997) **Evaluation of the usefulness of lymphocyte proliferation assays in the diagnosis of allergy to cow's milk** *J Allergy Clin Immunol 99:360-6*
- Hofman T (1994) **Specific IgE antibodies for nuts in infants** *Pol Tyg Lek 49:328-9* (in Polish)

- Hopper KE, McKenzie (1973) **Minor components of bovine alpha- lactalbumin A and B** *Biochim Biophys Acta 295:352-63*
- Host A, Halken S (1990) **A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction** *Allergy 45(8):587-96*
- Host A, Samuelsson EG (1988) **Allergic reactions to raw, pasteurized, and homogenized/pasteurized cow milk: a comparison. A double- blind placebo- controlled study in milk allergic children** *Allergy 43:113-8*
- Host A, Husby S, Osterballe O (1988) **A prospective study of cow's milk allergy in exclusively breast-fed infants. Incidence, pathogenetic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk** *Acta Paediatr Scand 77:663-70*
- Host A, Husby S, Gjesing B, Larsen JN, Lowenstein H (1992) **Prospective estimation of IgG, IgG subclass and IgE antibodies to dietary proteins in infants with cow milk allergy. Levels of antibodies to whole milk protein, BLG and ovalbumin in relation to repeated milk challenge and clinical course of cow milk allergy** *Allergy 47:218-29*
- Hurley WL, Schuler LA (1987) **Molecular cloning and nucleotide sequence of a bovine alpha- lactalbumin cDNA***Gene 61:119-22*
- Husby S, Host A, Teisner B, Svehag SE (1990) **Infants and children with cow milk allergy/intolerance. Investigation of the uptake of cow milk protein and activation of the complement system** *Allergy 45:547-51*
- Hyttinen JM, Korhonen VP, Hiltunen MO, Myohanen S, Janne J (1998) **High-level expression of bovine beta-lactoglobulin gene in transgenic mice** *J Biotechnol 61:191-8*
- Iacono G, Carroccio A, Montalto G, Cavataio F, Bragion E, Lorello D, Balsamo V, Notarbartolo A (1991) **Severe infantile colic and food intolerance: a long- term prospective study** *J Pediatr Gastroenterol Nutr 12:332-5*
- Iacono G, Carroccio A, Cavataio F, Montalto G, Soresi M, Balsamo V (1992) **Use of ass' milk in multiple food allergy** *J Pediatr Gastroenterol Nutr 14:177-81*
- Iacono G, Carroccio A, Cavataio F, Montalto G, Cantarero MD, Notarbartolo A (1995a) **Chronic constipation as a symptom of cow milk allergy** *J Pediatr 126:34-9*
- Iacono G, Carroccio A, Cavataio F, Montalto G, Lorello D, Kazmierska I, Soresi M (1995b) **IgG anti- betalactoglobulin (betalactotest): its usefulness in the diagnosis of cow's milk allergy** *Ital J Gastroenterol 27:355-60*
- Iacono G, Carroccio A, Cavataio F, Montalto G, Kazmierska I, Lorello D, Soresi M, Notarbartolo A (1996) **Gastroesophageal reflux and cow's milk allergy in infants: a prospective study** *J Allergy Clin Immunol 97:822-7*
- Iacono G, Cavataio F, Montalto G, Carroccio A (1998a) **Cow's milk-protein allergy as a cause of anal fistula and fissures: a case report** *J Allergy Clin Immunol 101(1Pt1):125-7*
- Iacono G, Cavataio F, Montalto G, Florena A, Tumminello M, Soresi M, Notarbartolo A, Carroccio A (1998b) **Intolerance of cow's milk and chronic constipation in children** *N Engl J Med 339:1100-4*
- Iacono G, Cavataio F, Montalto G, Soresi M, Notarbartolo A, Carroccio A (1998c) **Persistent cow's milk protein intolerance in infants: the changing faces of the same disease** *Clin Exp Allergy 28:817-23*
- Iida S, Kondo N, Agata H, Shinoda S, Shinbara M, Nishida T, Fukutomi O, Orii T (1995) **Differences in lymphocyte proliferative responses to food antigens and specific IgE antibodies to foods with age among food-sensitive patients with atopic dermatitis** *Ann Allergy Asthma Immunol 74:334-40*
- Isolauri E, Turjanmaa K (1996) **Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis** *J Allergy Clin Immunol 97(1Pt1):9-15*
- Isolauri E, Virtanen E, Jalonen T, Arvilommi H (1990) **Local immune response measured in blood lymphocytes reflects the clinical reactivity of children with cow's milk allergy** *Pediatr Res 28:582-6*
- Isolauri E, Suomalainen H, Kaila M, Jalonen T, Soppi E, Virtanen E, Arvilommi H (1992) **Local immune response in patients with cow milk allergy: follow-up of patients retaining allergy or becoming tolerant** *J Pediatr 120:9-15*
- Isolauri E, Sutas Y, Makinen-Kiljunen S, Oja SS, Isosomppi R, Turjanmaa K (1995) **Efficacy and safety of hydrolyzed cow milk and amino acid- derived formulas in infants with cow milk allergy** *J Pediatr 1995 Oct;127(4):550-7*
- Isolauri E, Sutas Y, Salo MK, Isosomppi R, Kaila M (1998) **Elimination diet in cow's milk allergy: risk for impaired growth in young children** *J Pediatr 132:1004-9*
- Ivady G, Torma I, Baranyai P, Jezerniczky J, Madarasz J, Bitvai K (1978) **Iron deficiency anemia caused by occult intestinal bleeding due to milk allergy** *Monatsschr Kinderheilkd 126:627-30* (in German)
- Iwanczak F, Mozrzymas R, Heimrath Z, Koszewicz P (1995) **Clinical evaluation of food allergy and food intolerance dietary treatment in children** *Rocz Akad Med Bialymst 40:588-94*
- Iwasaki E, Yamaura M, Masuda K, Miyabayashi Y, Yamaguchi K, Zaitsu M, Fujimaki K, Baba M (1994) **Diagnostic value of glass microfibre-based basophil histamine release test in food allergic children. Comparison with specific IgE antibody and skin scratch test***Arerugi 43(5):609-18* (in Japanese)
- Iyngkaran N, Yadav M, Boey CG, Kamath KR, Lam KL (1989) **Causative effect of cow's milk protein and soy protein on progressive small bowel mucosal damage** *J Gastroenterol Hepatol 4:127-36*
- Iyngkaran N, Yadav M, Boey CG (1995) **Mucosal and serum alkaline phosphatase activities in milk allergy** *Med J*

Malaysia 50:21-4

- Jakobsson I, Lindberg T (1978) **Cow's milk as a cause of infantile colic in breast- fed infants** *Lancet 2(8087):437-9*
- Jakobsson I, Lindberg T (1979) **A prospective study of cow's milk protein intolerance in swedish infants** *Acta Paediatr Scand 68:853-9*
- Jakobsson I, Lindberg T, Benediktsson B (1982) **In vitro digestion of cow's milk proteins by duodenal juice from infants with various gastrointestinal disorders** *J Pediatr Gastroenterol Nutr 1:183-91*
- Jakobsson I, Borulf S, Lindberg T, Benediktsson B (1983) **Partial hydrolysis of cow's milk proteins by human trypsins and elastases in vitro** *J Pediatr Gastroenterol Nutr 2:613-6*
- Jakobsson I, Lindberg T, Benediktsson B, Hansson BG (1985) **Dietary bovine beta-lactoglobulin is transferred to human milk** *Acta Paediatr Scand 74:342-5*
- Jalonen T (1991) **Identical intestinal permeability changes in children with different clinical manifestations of cow's milk allergy** *J Allergy Clin Immunol 88:737-42*
- James JM, Sampson HA (1992) **Immunologic changes associated with the development of tolerance in children with cow milk allergy** *J Pediatr 121:371-7*
- Jamieson AC, Vandeyar MA, Kang YC, Kinsella JE, Batt CA (1987) **Cloning and nucleotide sequence of the bovine beta- lactoglobulin gene** *Gene 61:85-90*
- Jarmoc LM, Primack WA (1987) **Anaphylaxis to cutaneous exposure to milk protein in a diaper rash ointment** *Clin Pediatr (Phila) 26:154-5*
- Jarvinen KM, Aro A, Juntunen-Backman K, Suomalainen H (1998) **Large number of CD19+/CD23+ B cells and small number of CD8+ T cells as early markers for cow's milk allergy (CMA)** *Pediatr Allergy Immunol 9:139-42*
- Jarvinen KM, Juntunen-Backman K, Suomalainen H (1999a) **Relation between weak HLA-DR expression on human breast milk macrophages and cow milk allergy (CMA) in suckling infants** *Pediatr Res 45:76-81*
- Jarvinen KM, Makinen-Kiljunen S, Suomalainen H (1999b) **Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy** *J Pediatr 135:506-12*
- Jedrychowski L, Wroblewska B (1999) **Reduction of antigenicity of whey proteins by lactic acid fermentation** *Food Agric Immunol 11:91-9*
- Jeng SY, Bleck GT, Wheeler MB, Jimenez-Flores R (1997) **Characterization and partial purification of bovine alpha-lactalbumin and beta- casein produced in milk of transgenic mice** *J Dairy Sci 80:3167-75*
- Jimenez-Flores R, Kang YC, Richardson T (1987) **Cloning and sequence analysis of bovine beta-casein cDNA** *Biochem Biophys Res Commun 142:617-21*
- Jones EA Jr (1985) **Oral cromolyn sodium in milk induced anaphylaxis** *Ann Allergy 54:199-201*
- Jones RT, Squillace DL, Yunginger JW (1992) **Anaphylaxis in a milk- allergic child after ingestion of milk-contaminated kosher- pareve-labeled "dairy- free" dessert** *Ann Allergy 68:223-7*
- Jonkhoff-Slok TW, Veenhoven RH, de Graeff-Meeder ER, Buller HA (1997) **An immunocompetent infant with cow's milk allergy and cytomegalovirus colitis** *Eur J Pediatr 156:528-9*
- Julge K, Vasar M, Bjorksten B (1997) **The development of atopic sensitization in Estonian infants** *Acta Paediatr 86(11):1188-94*
- Juvonen P, Månsson M, Kjellman NIM, Björkstén B, Jakobsson I (1999) **Development of immunoglobulin G and immunoglobulin E antibodies to cow's milk proteins and ovalbumin after a temporary neonatal exposure to hydrolyzed and whole cow's milk proteins** *Pediatr Allergy Immunol 10:191-8*
- Kaczmarski M, Lisiecka M, Kurpatkowska B, Jastrzebska J (1989) **Quantitative estimation of cellular infiltration of the small intestinal mucosa in children with cow's milk and gluten intolerance** *Acta Med Pol 30:129-39*
- Kahn A, Mozin MJ, Casimir G, Montauk L, Blum D (1985) **Insomnia and cow's milk allergy in infants** *Pediatrics 76:880-4*
- Kahn A, Rebuffat E, Blum D, Casimir G, Duchateau J, Mozin MJ, Jost R (1987) **Difficulty in initiating and maintaining sleep associated with cow's milk allergy in infants** *Sleep 10:116-21*
- Kaila M, Isolauri E (1997) **Diagnosis of cow's milk allergy: open or blinded ?** *J Allergy Clin Immunol 100:714-5*
- Kaiser C, Reibisch H, Fölster-Holst R, Sick H (1990) **Cow's milk protein allergy - results of skin- prick test with purified milk proteins** *Z Ernährungswiss 29:122-8*
- Kaiserlian D, Lachaux A, Grosjean I, Graber P, Bonnefoy JY (1995) **CD23/FC epsilon RII is constitutively expressed on human intestinal epithelium, and upregulated in cow's milk protein intolerance** *Adv Exp Med Biol 371B:871-4*
- Kajosaari M (1982) **Food allergy in Finnish children aged 1 to 6 years** *Acta Paediatr Scand 71:815-9*
- Kang YC, Richardson T (1988) **Molecular cloning and expression of bovine kappa- casein in Escherichia coli** *J Dairy Sci 71:29-40*
- Kanny G, de Hauteclocque C, Moneret-Vautrin DA (1998) **Food anaphylaxis to bovine serum albumin** *J Allergy Clin Immunol 101(1Pt1):137-9*
- Kapel N, Matarazzo P, Haouchine D, Abiola N, Guerin S, Magne D, Gobert JG, Dupont C (1999) **Fecal tumor necrosis**

factor alpha, eosinophil cationic protein and IgE levels in infants with cow's milk allergy and gastrointestinal manifestations *Clin Chem Lab Med 37:29-32*

- Karjalainen J, Martin JM, Knip M, Ilonen J, Robinson BH, Savilahti E, Akerblom HK, Dosch HM (1992) **A bovine albumin peptide as a possible trigger of insulin-dependent diabetes mellitus** *N Engl J Med 327:302-7 (erratum 327:1252)*
- Kekki OM, Turjanmaa K, Isolauri E (1997) **Differences in skin- prick and patch- test reactivity are related to the heterogeneity of atopic eczema in infants** *Allergy 52:755-9*
- Keller KM, Burgin-Wolff A, Lippold R, Wirth S, Lentze MJ (1996) **The diagnostic significance of IgG cow's milk protein antibodies re-evaluated** *Eur J Pediatr 155:331-7*
- Kim HHY, Jiminzez-Flores R (1994) **Comparison of milk proteins using preparative isoelectric focusing followed by polyacrylamide gel electrophoresis** *J Dairy Sci 77:2177-90*
- Kim TR, Goto Y, Hirota N, Kuwata K, Denton H, Wu SY, Sawyer L, Batt CA (1997) **High- level expression of bovine beta- lactoglobulin in Pichia pastoris and characterization of its physical properties** *Protein Eng 10:1339-45*
- Koers WJ, van der Elst AM, van Dijk AG, Berrens L (1986) **Cow's milk allergy in an adult patient** *Ann Allergy 56:267-9*
- Kohno Y, Honma K, Saito K, Shimojo N, Tsunoo H, Kaminogawa S, Niimi H (1994) **Preferential recognition of primary protein structures of alpha- casein by IgG and IgE antibodies of patients with milk allergy** *Ann Allergy 73:419-22*
- Kondo N, Shinoda S, Agata H, Nishida T, Miwa Y, Fujii H, Orii T (1992) **Lymphocyte responses to food antigens in food sensitive patients with allergic tension- fatigue syndrome** *Biotherapy 5:281-4*
- Kondo N, Fukutomi O, Agata H, Motoyoshi F, Shinoda S, Kobayashi Y, Kuwabara N, Kameyama T, Orii T (1993) **The role of T lymphocytes in patients with food- sensitive atopic dermatitis** *J Allergy Clin Immunol 91:658-68*
- Kongpanichkul A, Vichyanond P, Tuchinda M (1997) **Allergen skin test reactivities among asthmatic Thai children** *J Med Assoc Thai 80(2):69-75*
- Korol D, Cudowska B, Kaczmarski M (1995) **Effectiveness of Nutramigen and Prosobee in children with cow's milk protein intolerance** *Rocz Akad Med Bialymst 40:595-601*
- Kosnai I, Kuitunen P, Savilahti E, Sipponen P (1984) **Mast cells and eosinophils in the jejunal mucosa of patients with intestinal cow's milk allergy and celiac disease of childhood** *J Pediatr Gastroenterol Nutr 3:368-72*
- Koczan D, Hobom G, Seyfert HM (1991) **Genomic organization of the bovine alpha-S1 casein gene** *Nucleic Acids Res 19:5591-6*
- Kronman MJ, Sinha SK, Brew K (1981) **Characteristics of the binding of Ca2+ and other divalent metal ions to bovine alpha- lactalbumin** *J Biol Chem 256:8582-7*
- Kuitunen P, Savilahti E, Verkasalo M (1985) **Intestinal cow's milk allergy** *Klin Padiatr 197:355-9*
- Kuitunen M, Savilahti E, Sarnesto A (1994) **Human alpha- lactalbumin and bovine beta- lactoglobulin absorption in infants** *Allergy 49:354-60*
- Kuwata K, Hoshino M, Era S, Batt CA, Goto Y (1998) **alpha-->beta transition of beta-lactoglobulin as evidenced by heteronuclear NMR** *J Mol Biol 283:731-9*
- Lake AM (1991) **Food protein-induced gastrenteropathy in infants and children** in: *Food Allergy* (Metcalfe DD, Sampson HA, Simon RA eds) Blackwell Scientific Publications pp174-85
- Laoprasert N, Wallen ND, Jones RT, Hefle SL, Taylor SL, Yunginger JW (1998) **Anaphylaxis in a milk-allergic child following ingestion of lemon sorbet containing trace quantities of milk** *J Food Prot 61:1522-4*
- Larsen JN, Lowenstein H (1999) **Official list of allergens: IUIS Allergen Nomenclature Subcommittee** *ftp://biobase.dk / pub / who-iuis / allergen.list*
- Lefranc-Millot C, Vercaigne-Marko D, Wal JM, Lepretre A, Peltre G, Dhulster P, Guillochon D (1996) **Comparison of the IgE titers to bovine colostral G immunoglobulins and their F(ab')2 fragments in sera of patients allergic to milk** *Int Arch Allergy Immunol 110:156-62*
- Lessof MH, Wraith DG, Merrett TG, Merrett J, Buisseret PD (1980) **Food allergy and intolerance in 100 patients - local and systemic effects** *Q J Med 49(195):259-71*
- Levy FS, Bircher AJ, Buchner SA (1996a) **Delayed- type hypersensitivity to cow's milk protein in Melkersson-Rosenthal syndrome: coincidence or pathogenetic role?** *Dermatology 192:99-102*
- Levy FS, Bircher AJ, Gebbers JO (1996b) **Adult onset of cow's milk protein allergy with small- intestinal mucosal IgE mast cells** *Allergy 51:417-20*
- Liappis N, Starke A (1999) **In vitro allergy screening in serum of children. Distribution of specific IgE antibodies in SX1 and fx5 positive sera** *Allergologie 22:388-91* (in German)
- Lifschitz CH, Hawkins HK, Guerra C, Byrd N (1988) **Anaphylactic shock due to cow's milk protein hypersensitivity in a breast- fed infant** *J Pediatr Gastroenterol Nutr 7:141-4*
- Lin HY, Shyur SD, Fu JL, Lai YC (1998) **Whey and casein specific IgE and the cow's milk challenge test for atopic**

children *Chung Hua Min Kuo Hsiao Erh Ko I Hsueh Hui Tsa Chih 39:99-102*

- Little CH, Georgiou GM, Shelton MJ, Cone RE (1998) **Production of serum immunoglobulins and T cell antigen binding molecules specific for cow's milk antigens in adults intolerant to cow's milk** *Clin Immunol Immunopathol 89:160-70*
- Lothe L, Lindberg T, Jakobsson I (1982) **Cow's milk formula as a cause of infantile colic: a double-blind study** *Pediatrics 70:7-10*
- Lucarelli S, Frediani T, Zingoni AM, Ferruzzi F, Giardini O, Quintieri F, Barbato M, D'Eufemia P, Cardi E (1995) **Food allergy and infantile autism** *Panminerva Med 37:137-41*
- Machtinger S, Moss R (1986) **Cow's milk allergy in breast-fed infants: the role of allergen and maternal secretory IgA antibody** *J Allergy Clin Immunol 77:341-7*
- Maciejewski Z, Milewska-Bobula B, Rowecka-Trzebicka K, Piatosa B, Dobrzanska A, Ganowicz J (1995) **Development conditions and principles for identification of cow's milk protein hypersensitivity in infants** *Rocz Akad Med Bialymst 40:433-8*
- Maeda S, Morikawa A, Tokuyama K, Kuroume T (1993) **The concentration of bovine IgG in human breast milk measured using different methods** *Acta Paediatr 82:1012-6*
- Majamaa H, Isolauri E (1997) **Probiotics: a novel approach in the management of food allergy** *J Allergy Clin Immunol 99:179-85*
- Majamaa H, Miettinen A, Laine S, Isolauri E (1996) **Intestinal inflammation in children with atopic eczema: faecal eosinophil cationic protein and tumour necrosis factor- alpha as non- invasive indicators of food allergy** *Clin Exp Allergy 26:181-7*
- Majamaa H, Moisio P, Holm K, Kautiainen H, Turjanmaa K (1999) **Cow's milk allergy: diagnostic accuracy of skin prick and patch tests and specific IgE** *Allergy 54:346-51*
- Makinen-Kiljunen S, Sorva R (1993) **Bovine beta- lactoglobulin levels in hydrolysed protein formulas for infant feeding** *Clin Exp Allergy 23:287-91*
- Malmheden Yman I, Eriksson A, Everitt G, Yman L, Karlsson T (1994) **Analysis of food proteins for verification of contamination or mislabelling** *Food Agric Immunol 6:167-72*
- Martin-Esteban M, Garcia-Ara MC, Banque-Molas M, Boyano-Martinez MT, Martin-Munoz F, Diaz-Pena JM (1998) **Evaluation of an extensively hydrolyzed casein- whey protein formula in immediate cow's milk protein hypersensitivity** *J Pediatr Gastroenterol Nutr 26:398-401*
- Maynard F, Jost R, Wal JM (1997) **Human IgE binding capacity of tryptic peptides from bovine alpha- lactalbumin** *Int Arch Allergy Immunol 113:478-88*
- Mercier JC, Grosclaude F, Ribadeau-Dumas B (1971) **Primary structure of bovine alpha-s1 casein. Complete sequence***Eur J Biochem 23:41-51*
- Mercier JC, Grosclaude F, Ribadeau-Dumas B (1973) **Primary structure of alpha casein and of bovine beta casein. Correction** *Eur J Biochem 40:323*
- Merritt RJ, Carter M, Haight M, Eisenberg LD (1990) **Whey protein hydrolysate formula for infants with gastrointestinal intolerance to cow milk and soy protein in infant formulas** *J Pediatr Gastroenterol Nutr 11(1):78-82* [comments J Pediatr Gastroenterol Nutr 1991 13(3):315-6]
- Michaud L, Gottrand F, Dubar G, Turck D, Farriaux JP (1993) **Cow's milk proteins intolerance disclosed by ulcero-necrotizing enterocolitis in a full-term infant** *Arch Fr Pediatr 50:693-5* (in French)
- Miller I, Gemeiner M (1993) **Peculiarities in electrophoretic behavior of different serum albumins** *Electrophoresis 14(12):1312-7*
- Moneret-Vautrin DA (1999) **Cow's milk allergy** [review] *Allerg Immunol (Paris) 31:201-10*
- Moneret-Vautrin DA, Kanny G (1995) **Food-induced anaphylaxis. A new French multicenter survey** *Ann Gastroenterol Hepatol (Paris) 31:256-263* (article in French)
- Mueller et al. (1963) **The incidence of milk sensitivity and the development of allergy in infants** *N Engl J Med 268:1220-4*
- Mylek D (1992) **Migraine as one of the symptoms of food allergy** *Pol Tyg Lek 47:89-91 erratum 47:557* (in Polish)
- Nagao M, Maki M, Sasaki R, Chiba R (1984) **Isolation and sequence analysis of bovine alpha-s1-casein cDNA clone** *Agric Biol Chem 48:1663-7*
- Nakajima H, Hachimura S, Nishiwaki S, Katsuki T, Shimojo N, Ametani A, Kohno Y, Kaminogawa S (1996) **Establishment and characterization of alpha s1-casein-specific T-cell lines from patients allergic to cow's milk: unexpected higher frequency of CD8+ T-cell lines** *J Allergy Clin Immunol 97:1342-9*
- Nakajima-Adachi H, Hachimura S, Ise W, Honma K, Nishiwaki S, Hirota M, Shimojo N, Katsuki T, Ametani A, Kohno Y, Kaminogawa S (1998) **Determinant analysis of IgE and IgG4 antibodies and T cells specific for bovine alpha(s)1-casein from the same patients allergic to cow's milk: existence of alpha(s)1-casein-specific B cells and T cells characteristic in cow's-milk allergy** *J Allergy Clin Immunol 101:660-71*

- Niggemann B, Binder C, Klettke U, Wahn U (1999a) **In vivo and in vitro studies on the residual allergenicity of partially hydrolysed infant formulae** *Acta Paediatr 88:394-8*
- Niggemann B, Sielaff B, Beyer K, Binder C, Wahn U (1999b) **Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis** *Clin Exp Allergy 29(1):91-96*
- Nishida T, Kondo N, Agata H, Fukutomi O, Shinoda S, Shinbara M, Orii T (1995) **Evaluation of lymphocyte proliferative responses to casein hydrolysate formula in cow's milk- sensitive children: response of peripheral blood mononuclear cells to hydrolysate formula** *J Investig Allergol Clin Immunol 5:86-90*
- Nitta K, Sugai S (1989) **The evolution of lysozyme and alpha- lactalbumin** *Eur J Biochem 182:111-8*
- Norgaard A, Bindslev-Jensen C (1992) **Egg and milk allergy in adults. Diagnosis and characterization** *Allergy 47:503-9*
- Norgaard A, Bindslev-Jensen C, Skov PS, Poulsen LK (1995) **Specific serum IgE in the diagnosis of egg and milk allergy in adults** *Allergy 50:636-47*
- Norgaard A, Bernard H, Wal JM, Peltre G, Skov PS, Poulsen LK, Bindslev-Jensen C (1996) **Allergenicity of individual cow milk proteins in DBPCFC-positive milk allergic adults**[abstract 218] *J Allergy Clin Immunol 97(1Pt3):237*
- Novembre E, Cianferoni A, Bernardini R, Mugnaini L, Caffarelli C, Cavagna G, Giovane A, Vierucci A (1998) **Anaphylaxis in children: clinical and allergological features** *Pediatrics 101(4):e8*
- Odelram H, Vanto T, Jacobsen L, Kjellman NI (1996) **Whey hydrolysate compared with cow's milk- based formula for weaning at about 6 months of age in high allergy- risk infants: effects on atopic disease and sensitization** *Allergy 51:192-5*
- Ogle KA, Bullock JD (1980) **Children with allergic rhinitis and/or bronchial asthma treated with eliminationdiet: a five-year follow-up** *Ann Allergy 44:273-8*
- Oldaeus G, Bjorksten B, Einarsson R, Kjellman NIM (1991) **Antigenicity and allergenicity of cow milk hydrolysates intended for infant feeding** *Pediatr Allergy Immunol 2:156-64*
- Oldaeus G, Bradley CK, Bjorksten B, Kjellman NIM (1992) **Allergenicity of some milk based infant formulas as assessed by skin prick test** *J Allergy Clin Immunol 90:133-5*
- Oldaeus G, Anjou K, Bjorksten B, Moran JR, Kjellman NIM (1997) **Extensively and partially hydrolysed infant formulas for allergy prophylaxis** *Arch Dis Child 77:4-10*
- Oldaeus G, Bjorksten B, Jenmalm MC, Kjellman NI (1999) **Cow's milk IgE and IgG antibody responses to cow's milk formulas** *Allergy 54:352-7*
- Olsder NK, van Elburg RM, van Rijn M, van Voorst Vader PC, de Monchy JG, Heymans HS (1995) **Standardized multidisciplinary diagnosis of cow's milk protein allergy in children. Work Group Cow's Milk Protein Allergy of the Groningen Academic Hospital***Ned Tijdschr Geneeskd 139:1690-4* (in Dutch)
- Oranje AP, Aarsen RS, Mulder PG, van Toorenenbergen AW, Liefaard G, Dieges PH (1992) **Food immediate-contact hypersensitivity (FICH) and elimination diet in young children with atopic dermatitis. Preliminary results in 107 children** *Acta Derm Venereol Suppl Stockh 176:41-4*
- Österlund P, Järvinen KM, Laine S, Suomalainen H (1999) **Defective tumor necrosis factor-alpha production in infants with cow's milk allergy** *Pediatr Allergy Immunol 10:186-90*
- Osvaath P, Kerese I, Szendrey A (1976) **Use of chestnut in the feeding of infants allergic to cow's milk or intolerant to lactose** *Allergol Immunopathol (Madr) 4:413-8*
- Otani H, Dong XY, Hara T, Kobayashi M, Kayahara H, Hosono A (1989) **Specifities to cow milk protiens of human serum antibodies from clinically allergic patients** *Milchwissenschaft 44:267-70*
- Paganus A, Juntunen-Backman K, Savilahti E (1992) **Follow-up of nutritional status and dietary survey in children with cow's milk allergy***Acta Paediatr 81:518-21*
- Papadopoulos NG, Syrigou EI, Bossios A, Manou O, Gourgiotis D, Saxoni-Papageorgiou P (1999) **Correlation of lymphocyte proliferating cell nuclear antigen expression with dietary cow's milk antigen load in infants with allergy to cow's milk** *Int Arch Allergy Immunol 119:64-8*
- Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB (1998) **Food allergy in children: results of a standardized protocol for oral desensitization** *Hepatogastroenterology 45(19):52-8*
- Paranos S, Nikolic G (1996) **Antibodies to cow's milk proteins in chronic urticaria** *Allergy 51:273-5*
- Piastra M, Stabile A, Fioravanti G, Castagnola M, Pani G, Ria F (1994) **Cord blood mononuclear cell responsiveness to beta- lactoglobulin: T-cell activity in 'atopy-prone' and 'non-atopy-prone' newborns** *Int Arch Allergy Immunol 104:358-65*
- Pike ACW, Brew K, Acharya KR (1996) **Crystal structures of guinea-pig, goat and bovine alpha- lactalbumin highlight the enhanced conformational flexibility of regions that are significant for its action in lactose synthase** *Structure 4:691-703*
- Plebani A, Albertini A, Scotta S, Ugazio AG (1990) **IgE antibodies to hydrolysates of cow milk proteins in children with cow milk allergy** *Ann Allergy 64:279-80*

- Plebani A, Restani P, Naselli A, Galli CL, Meini A, Cavagni G, Ugazio AG, Poiesi C (1997) **Monoclonal and polyclonal antibodies against casein components of cow milk for evaluation of residual antigenic activity in 'hypoallergenic' infant formulas** *Clin Exp Allergy 27:949-56*
- Podleski WK, Panaszek BA, Schmidt JL, Burns RB (1984) **Inhibition of eosinophils degranulation by Ketotifen in a patient with milk allergy, manifested as bronchial asthma - an electron microscopic study** *Agents Actions 15:177-81*
- Prahl P, Krasilnikof F, Stahl Skov P, Norn S (1988) **Basophil histamine release in children with adverse reactions to cow milk. Comparison with RAST and skin prick test** *Allergy 43:442-8*
- Prinzenberg EM, Anglade P, Ribadeau-Dumas B, Erhardt G (1998) **Biochemical characterization of bovine alpha s1-casein F and genotyping with sequence-specific primers** *J Dairy Res 65:223-31*
- Pumphrey RS, Stanworth SJ (1996) **The clinical spectrum of anaphylaxis in north-west England** *Clin Exp Allergy 26:1364-70*
- Ragno V, Giampietro PG, Bruno G, Businco L (1993) **Allergenicity of milk protein hydrolysate formulae in children with cow's milk allergy** *Eur J Pediatr 152:760-2*
- Rance F, Dutau G (1997) **Labial food challenge in children with food allergy** *Pediatr Allergy Immunol 8(1):41-4*
- Rance F, Juchet A, Bremont F, Dutau G (1997) **Correlations between skin prick tests using commercial extracts and fresh foods, specific IgE, and food challenge** *Allergy 52:1031-5*
- Rance F, Kanny G, Dutau G, Moneret-Vautrin DA (1999a) [no title available] *Arch Pediatr 6 Suppl 1:61S-66S* (in French)
- Rance F, Kanny G, Dutau G, Moneret-Vautrin DA (1999b) **Food hypersensitivity in children: Clinical aspects and distribution of allergens** *Pediatr Allergy Immunol 10:33-8*
- Rasanen L, Lehto M, Reunala T (1992) **Diagnostic value of skin and laboratory tests in cow's milk allergy/intolerance** *Clin Exp Allergy 22:385-90*
- Reekers R, Beyer K, Niggemann B, Wahn U, Freihorst J, Kapp A, Werfel T (1996) **The role of circulating food antigen-specific lymphocytes in food allergic children with atopic dermatitis** *Br J Dermatol 135:935-41*
- Renz H, Vestner R, Petzoldt S, Brehler C, Prinz H, Rieger CH (1990) **Elevated concentrations of salivary secretory immunoglobulin A anti-cow's milk protein in newborns at risk of allergy** *Int Arch Allergy Appl Immunol 92:247-53*
- Resano A, Crespo E, Fernandez Benitez M, Sanz ML, Oehling A (1998) **Atopic dermatitis and food allergy** *J Investig Allergol Clin Immunol 8(5):271-6*
- Restani P, Velona T, Plebani A, Ugazio AG, Poiesi C, Muraro A, Galli CL (1995) **Evaluation by SDS-PAGE and immunoblotting of residual antigenicity in hydrolysed protein formulas** *Clin Exp Allergy 25:651-8*
- Restani P, Plebani A, Velona T, Cavagni G, Ugazio AG, Poiesi C, Muraro A, Galli CL (1996) **Use of immunoblotting and monoclonal antibodies to evaluate the residual antigenic activity of milk protein hydrolysed formulae** *Clin Exp Allergy 26:1182-7*
- Restani P, Gaiaschi A, Plebani A, Beretta B, Cavagni G, Fiocchi A, Poiesi C, Velona T, Ugazio AG, Galli CL (1999) **Cross- reactivity between milk proteins from different animal species** *Clin Exp Allergy 29:997-1004*
- Ribadeau-Dumas B, Brignon G, Grosclaude F, Mercier JC (1972) **Primary structure of bovine beta casein. Complete sequence** *Eur J Biochem 25:505-14*
- Rijnkels M, Kooiman PM, Platenburg GJ, van Dixhoorn M, Nuijens JH, de Boer HA, Pieper FR (1998) **High-level expression of bovine alpha s1-casein in milk of transgenic mice** *Transgenic Res 7:5-14*
- Rizk C, Valdes L, Ogier de Baulny H, Saudubray JM, Olivier C (1999) **Severe lactic acidosis disease disclosing milk-protein intolerance to cows' milk** *Arch Pediatr 6:427-9* (in French)
- Roger A, Pena M, Botey J, Eseverri JL, Marin A (1994) **The prick test and specific IgE (RAST and MAST-CLA) compared with the oral challenge test with milk, eggs and nuts** *J Investig Allergol Clin Immunol 4:178-81*
- Rossi GL, Corsico A, Moscato G (1994) **Occupational asthma caused by milk proteins: report on a case** *J Allergy Clin Immunol 93:799-801*
- Rugo E, Wahn U (1992) **In vivo studies of residual allergen activity of hydrolysate feeding** *Monatsschr Kinderheilkd 1992 Aug;140(8):472-5* (in German)
- Saalman R, Dahlgren UI, Fallstrom SP, Hanson LA, Wold AE, Ahlstedt S (1995) **ADCC- mediating capacity in children with cow's milk protein intolerance in relation to IgG subclass profile of serum antibodies to beta-lactoglobulin** *Scand J Immunol 42:140-6*
- Saarinen KM, Juntunen-Backman K, Jarvenpaa AL, Kuitunen P, Lope L, Renlund M, Siivola M, Savilahti E (1999a) **Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: A prospective study of 6209 infants** *J Allergy Clin Immunol 104(2Pt1):457-61*
- Saarinen KM, Vaarala O, Klemetti P, Savilahti E (1999b) **Transforming growth factor-{beta}1 in mothers' colostrum and immune responses to cows' milk proteins in infants with cows' milk allergy** *J Allergy Clin Immunol 104:1093-8*
- Sabbah A, Drouet M, Lauret MG (1996) **Western blotting or immunoblotting: application of the Alastat-Alablot to the study of cross reactions between cow's milk and goat's milk***Allerg Immunol (Paris) 28:335-9* (in French)

- Saito T, Itoh T (1992) **Variations and distributions of O-glycosidically linked sugar chains in bovine kappa- casein** *J Dairy Sci 75:1768-74*
- Salo OP, Makinen-Kiljunen S, Juntunen K (1986) **Milk causes a rapid urticarial reaction on the skin of children with atopic dermatitis and milk allergy** *Acta Derm Venereol 66:438-42*
- Sampson HA, Cooke SK (1990)**Food allergy and the potential allergenicity- antigenicity of microparticulated egg and cow's milk proteins** *J Am Coll Nutr 9:410-7*
- Sampson HA, Cooke S (1992) **The antigenicity and allergenicity of microparticulated proteins: Simplesse** *Clin Exp Allergy 22:963-9*
- Sampson HA, Ho DG (1997) **Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents** *J Allergy Clin Immunol 100(4):444-51*.
- Sampson HA, Scanlon SM (1989) **Natural history of food hypersensitivity in children with atopic dermatitis** *J Pediatr 115(1):23-7*
- Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM (1991) **Safety of casein hydrolysate formula in children with cow milk allergy** *J Pediatr 118(4Pt1):520-5*
- Sampson HA, Mendelson L, Rosen JP (1992) **Fatal and near-fatal anaphylactic reactions to food in children and adolescent** *N Engl J Med 327:380-384*
- Savilahti E (1981) **Cow's milk allergy** [review] *Allergy 36:73-88*
- Savilahti E, Tainio VM, Salmenpera L, Arjomaa P, Kallio M, Perheentupa J, Siimes MA (1991) **Low colostral IgA associated with cow's milk allergy** *Acta Paediatr Scand 80:1207-13*
- Saylor JD, Bahna SL (1991) **Anaphylaxis to casein hydrolysate formula** *J Pediatr 118:71-4*
- Schafer T, Kramer U, Dockery D, Vieluf D, Behrendt H, Ring J (1999) **What makes a child allergic? Analysis of risk factors for allergic sensitization in preschool children from East and West Germany** *Allergy Asthma Proc 20:23-7*
- Schmidt DG, Meijer RJ, Slangen CJ, van Beresteijn EC (1995) **Raising the pH of the pepsin- catalysed hydrolysis of bovine whey proteins increases the antigenicity of the hydrolysates** *Clin Exp Allergy 25:1007-17*
- Schrander JJ, Oudsen S, Forget PP, Kuijten RH (1992) **Follow up study of cow's milk protein intolerant infants** *Eur J Pediatr 151:783-5*
- Schrander JJ, Dellevoet JJ, Arends JW, Forget PP, Kuijten R (1993a) **Small intestinal mucosa IgE plasma cells and specific anti-cow milk IgE in children with cow milk protein intolerance** *Ann Allergy 70:406-9*
- Schrander JJ, van den Bogart JP, Forget PP, Schrander-Stumpel CT, Kuijten RH, Kester AD (1993b) **Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study** *Eur J Pediatr 152:640-4*
- Schwartz RH (1991) **IgE-mediated reactions to cow's milk** in: *Immunology and Allergy Clinics Of North America 11:717-41* (Anderson J, ed) W.B. Saunders Company
- Schwartz RH, Amonette MS (1991) **Cow milk protein hydrolysate infant formulas not always "hypoallergenic"**. [letter to the editor] *J Pediatr 119:839*
- Schwartz RH, Kubicka M, Dreyfuss EM, Nikaein A (1987) **Acute urticarial reactions to cow's milk in infants previously fed breast milk or soy milk** *Pediatr Asthma Allergy Immunol 1:81-93*
- Schwartz RH, Keefe MW, Harris N, Witherly S (1989) **The spectrum of IgE- mediated acute allergic reactions to cow's milk in children as determined by skin testing with cow's milk protein hydrolysate formulas** *Pediatr Asthma Allergy Immunol 3:207-15*
- Schwartz RH, Peers LB, Amonette MS, Witherly SA (1991) **Usefulness of a cow's milk whey infant formula (Good Start) in the management of children with Group 1A (Topical Reactors) IgE-mediated cow's milk allergy** *Pediatr Asthma Allergy Immmunol 5:305-12*
- Selo I, Negroni L, Creminon C, Yvon M, Peltre G, Wal JM (1998) **Allergy to bovine beta-lactoglobulin: specificity of human IgE using cyanogen bromide- derived peptides** *Int Arch Allergy Immunol 117:20-8*
- Selo I, Clement G, Bernard H, Chatel JM, Cremion C, Peltre G, Wal JM (1999) **Allergy to bovine {beta}- lactoglobulin: specificity of human IgE to tryptic peptides** *Clin Exp Allergy 29:1055-63*
- Sicherer SH, Sampson HA (1999) **Cow's milk protein- specific IgE concentrations in two age groups of milk- allergic children and in children achieving clinical tolerance** *Clin Exp Allergy 29:507-12*
- Sicherer SH, Eigenmann PA, Sampson HA (1998) **Clinical features of food protein-induced enterocolitis syndrome***J Pediatr 133(2):214-9*
- Sieniawska M, Szymanik-Grzelak H, Kowalewska M, Wasik M, Koleska D (1992) **The role of cow's milk protein intolerance in steroid- resistant nephrotic syndrome** *Acta Paediatr 81:1007-12*
- Shimojo N, Kohno Y, Katsuki T, Honma K, Yamaguchi K, Tsunoo H, Takahashi T, Kaminogawa S, Niimi H (1997) **Comparison of specificity between IgG, IgE and T cells to three casein components: implication for the role of circulating allergen- specific T cells in food allergy** *Acta Paediatr Jpn 39:416-21*
- Shiner M, Ballard J, Smith ME (1975) **The small- intestinal mucosa in cow's milk allergy** *Lancet 1(7899):136-4*
- Simons G, van den Heuvel W, Reynen T, Frijters A, Rutten G, Slangen CJ, Groenen M, de Vos WM, Siezen RJ (1993)

Overproduction of bovine beta-casein in Escherichia coli and engineering of its main chymosin cleavage site *Protein Eng 6:763-70*

- Slangen CJ, Visser S (1999) **Use of mass spectrometry to rapidly characterize the heterogeneity of bovine alpha-lactalbumin** *J Agric Food Chem 47:4549-56*
- Sorva R, Makinen-Kiljunen S, Juntunen-Backman K (1994) **Beta- lactoglobulin secretion in human milk varies widely after cow's milk ingestion in mothers of infants with cow's milk allergy** *J Allergy Clin Immunol 93:787-92*
- Soulier S, Stinnakre MG, Lepourry L, Mercier JC, Vilotte JL (1994) **Use of doxycycline- controlled gene expression to reversibly alter milk- protein composition in transgenic mice** *Eur J Biochem 260:533-9*
- Spuergin P, Mueller H, Walter M, Schiltz E, Forster J (1996) **Allergenic epitopes of bovine alpha S1-casein recognized by human IgE and IgG** *Allergy 51:306-12*
- Spuergin P, Walter M, Schiltz E, Deichmann K, Forster J, Mueller H (1997) **Allergenicity of alpha- caseins from cow, sheep, and goat** *Allergy 52:293-8*
- Stewart AF, Willis IM, Mackinlay AG (1984) **Nucleotide sequences of bovine alpha S1- and kappa-casein cDNAs** *Nucleic Acids Res 12:3895-907*
- Stewart AF, Bonsing J, Beattie CW, Shah F, Willis IM, MacKinlay AG (1987) **Complete nucleotide sequences of bovine alpha S2- and beta-casein cDNAs: comparisons with related sequences in other species** *Mol Biol Evol 4:231-41*
- Stintzing G, Zetterstrom R (1979) **Cow's milk allergy, incidence and pathogenetic role of early exposure to cow's milk formula** *Acta Paediatr Scand 68:383-7*
- Stoger P, Wüthrich B (1993) **Type I allergy to cow milk proteins in adults. A retrospective study of 34 adult milk- and cheese- allergic patients** *Int Arch Allergy Immunol 102:399-407*
- Strange ED, Malin EL, Van Hekken DL, Basch JJ (1993) **Chromatographic and electrophoretic methods used for analysis of milk proteins** [review] *J Chromatogr 624:81-102*
- Suomalainen H, Isolauri E, Kaila M, Virtanen E, Arvilommi H (1992) **Cow's milk provocation induces an immune response to unrelated dietary antigens** *Gut 33:1179-83*
- Suomalainen H, Soppi E, Laine S, Isolauri E (1993a) **Immunologic disturbances in cow's milk allergy, 2: Evidence for defective interferon-gamma generation** *Pediatr Allergy Immunol 4:203-7*
- Suomalainen H, Soppi E, Isolauri E (1993b) **Immunologic disturbances in cow's milk allergy, 1: Delayed maturation of suppressor activity** *Pediatr Allergy Immunol 4:196-202*
- Suomalainen H, Soppi E, Isolauri E (1994a) **Lymphocyte response to cow's milk proteins in patients with cow's milk allergy: relationship to antigen exposure** *Pediatr Allergy Immunol 5:20-6*
- Suomalainen H, Soppi E, Isolauri E (1994b) **Evidence for eosinophil activation in cow's milk allergy** *Pediatr Allergy Immunol 5:27-31*
- Sutas Y, Hurme M, Isolauri E (1997) **Oral cow milk challenge abolishes antigen- specific interferon- gamma production in the peripheral blood of children with atopic dermatitis and cow milk allergy** *Clin Exp Allergy 27:277-83*
- Szepfalusi Z, Ebner C, Urbanek R, Ebner H, Scheiner O, Boltz-Nitulescu G, Kraft D (1993) **Detection of IgE antibodies specific for allergens in cow milk and cow dander** *Int Arch Allergy Immunol 102:288-94*
- Szepfalusi Z, Nentwich I, Gerstmayr M, Jost E, Todoran L, Gratzl R, Herkner K, Urbanek R (1997) **Prenatal allergen contact with milk proteins** *Clin Exp Allergy 27:28-35*
- Tabar AI, Alvarez MJ, Echechipia S, Acero S, Garcia BE, Olaguibel J (1996) **Anaphylaxis from cow's milk casein** *Allergy 51:343-5*
- Tainio VM, Savilahti E (1990) **Value of immunologic tests in cow milk allergy** *Allergy 45:189-96*
- Tarim O, Anderson VM, Lifshitz F (1994) **Fatal anaphylaxis in a very young infant possibly due to a partially hydrolyzed whey formula** *Arch Pediatr Adolesc Med 148:1224-9*
- Taylor B, Fergusson DM, Mahoney GN, Hartley WA, Abbott J (1982) **Specific IgA and IgE in childhood asthma, eczema and food allergy** *Clin Allergy 12:499-505*
- Teuber SS, Vogt PJ (1999) **An unproven technique with potentially fatal outcome: provocation / neutralization in a patient with systemic mastocytosis** *Ann Allergy Asthma Immunol 82:61-5*
- Tiainen JM, Nuutinen OM, Kalavainen MP (1995) **Diet and nutritional status in children with cow's milk allergy** *Eur J Clin Nutr 49:605-12*
- Totsuka M, Katakura Y, Shimizu M, Kumagai I, Miura K, Kaminogawa S (1990) **Expression and secretion of bovine beta- lactoglobulin in Saccharomyces cerevisiae** *Agric Biol Chem 54:3111-6*
- Totsuka M, Furukawa S, Sato E, Ametani A, Kaminogawa S (1997) **Antigen- specific inhibition of CD4+ T-cell responses to beta-lactoglobulin by its single amino acid-substituted mutant form through T-cell receptor antagonism** *Cytotechnology 25:115-26*
- Troncone R, Caputo N, Florio G, Finelli E (1994) **Increased intestinal sugar permeability after challenge in children**

with cow's milk allergy or intolerance *Allergy 49:142-6*
- Umpierrez A, Quirce S, Maranon F, Cuesta J, Garcia-Villamuza Y, Lahoz C, Sastre J (1999) **Allergy to goat and sheep cheese with good tolerance to cow cheese** *Clin Exp Allergy 29:1064-8*
- Vaarala O, Saukkonen T, Savilahti E, Klemola T, Akerblom HK (1995) **Development of immune response to cow's milk proteins in infants receiving cow's milk or hydrolyzed formula** *J Allergy Clin Immunol 96(6Pt1):917-23*
- Vanaman TC, Brew K, Hill RL (1970) **The disulfide bonds of bovine alpha- lactalbumin** *J Biol Chem 245:4583-90*
- van Beresteijn EC, Meijer RJ, Schmidt DG (1995) **Residual antigenicity of hypoallergenic infant formulas and the occurrence of milk-specific IgE antibodies in patients with clinical allergy** *J Allergy Clin Immunol 96:365-74*
- Vandenplas Y, Sacre L (1986) **Influences of neonatal serum IgE concentration, family history and diet on the incidence of cow's milk allergy** *Eur J Pediatr 145:493-5*
- Vandenplas Y, Hauser B, Van den Borre C, Clybouw C, Mahler T, Hachimi-Idrissi S, Deraeve L, Malfroot A, Dab I (1995) **The long- term effect of a partial whey hydrolysate formula on the prophylaxis of atopic disease** *Eur J Pediatr 154:488-94*
- Van Elburg RM, Heymans HS, De Monchy JG (1993) **Effect of disodiumcromoglycate on intestinal permeability changes and clinical response during cow's milk challenge** *Pediatr Allergy Immunol 4:79-85*
- Van Hoeyveld EM, Escalona-Monge M, de Swert LF, Stevens EA (1998) **Allergenic and antigenic activity of peptide fragments in a whey hydrolysate formula** *Clin Exp Allergy 28:1131-7*
- Vanto T, Smogorzewska EM, Viander M, Kalimo K, Koivikko A (1987) **Leukocyte migration inhibition test in children with cow milk allergy** *Allergy 42:612-8*
- Vanto T, Juntunen-Backman K, Kalimo K, Klemola T, Koivikko A, Koskinen P, Syvanen P, Valovirta E, Varjonen E (1999) **The patch test, skin prick test, and serum milk- specific IgE as diagnostic tools in cow's milk allergy in infants** *Allergy 54:837-42*
- Vargiu A, Vargiu G, Locci F, Del Giacco S, Del Giacco GS (1994) **Hypersensitivity reactions from inhalation of milk proteins** *Allergy 49:386-7*
- Ventura A, Greco L (Italian Working Group on CMPA) (1988) **Cow's milk allergy in the first year of life. An Italian Collaborative Study** *Acta Paediatr Scand Suppl 348:1-14*
- Vergesslich KA, Gotz M, Granditsch G, Ponhold W (1985) **Allergic alveolitis in cow milk allergy** *Monatsschr Kinderheilkd 1985 Aug;133(8):545-7* (in German)
- Verwimp JJ, Bindels JG, Barents M, Heymans HS (1995) **Symptomatology and growth in infants with cow's milk protein intolerance using two different whey-protein hydrolysate based formulas in a Primary Health Care setting** *Eur J Clin Nutr 49 (Suppl 1):S39-48*
- Viaene A, Volckaert G, Joniau M, De Baetselier A, Van Cauwelaert F (1991) **Efficient expression of bovine alpha-lactalbumin in Saccharomyces cerevisiae** *Eur J Biochem 202:471-7)*
- Vila Sexto L, Sanchez Lopez G, Sanz Larruga ML, Dieguez Lopez I (1998) **Delayed reaction to cow's milk proteins: a case study** *J Investig Allergol Clin Immunol 8:249-52*
- Vilotte JL, Soulier S, Mercier JC, Gaye P, Hue-Delahaie D, Furet JP (1987) **Complete nucleotide sequence of bovine alpha-lactalbumin gene: comparison with its rat counterpart***Biochimie 69:609-20*
- Visser S, Slangen CJ, Lagerwerf FM, Van Dongen WD, Haverkamp J (1995) **Identification of a new genetic variant of bovine beta- casein using reversed- phase high- performance liquid chromatography and mass spectrometric analysis** *J Chromatogr A 711:141-50*
- Wahn U, Wahl R, Rugo E (1992) **Comparison of the residual allergenic activity of six different hydrolyzed protein formulas** *J Pediatr 121(5 Pt 2):S80-4*
- Wal JM (1998) **Cow's milk allergens** [review] *Allergy 53:1013-22*
- Wal JM, Bernard H, Creminon C, Hamberger C, David B, Peltre G (1995a) **Cow's milk allergy: the humoral immune response to eight purified allergens** *Adv Exp Med Biol 371B:879-81*
- Wal JM, Bernard H, Yvon M et al. (1995b) **Enzyme immunoassay of specific human IgE to purified cow's milk allergens** *Food Agric Immunol 7:175-87*
- Walsh BJ, Elliott C, Baker RS, Barnett D, Burley RW, Hill DJ & Howden MEH (1987) **Allergenic cross-reactivity of egg-white and egg-yolk proteins** *Int Arch Allergy Immunol 84:228-232*
- Wang MG, Scott WA, Rao KR, Udey J, Conner GE, Brew K (1989) **Recombinant bovine alpha-lactalbumin obtained by limited proteolysis of a fusion protein expressed at high levels in E.coli** *J Biol Chem 264:21116-21*
- Watson WTA, Becker ML, Simons FER, Peng Z, Becker AB (1995) **Cow's milk protein in lactose** [abstract 650] *J Allergy Clin Immunol 95(1Pt2):303*
- Weisselberg B, Dayal Y, Thompson JF, Doyle MS, Senior B, Grand RJ (1996) **A lamb- meat- based formula for infants allergic to casein hydrolysate formulas** *Clin Pediatr (Phila) 35:491-5*
- Werfel T, Ahlers G, Schmidt P, Boeker M, Kapp A (1996) **Detection of a kappa- casein- specific lymphocyte response in milk- responsive atopic dermatitis** *Clin Exp Allergy 26:1380-6*

- Werfel SJ, Cooke SK, Sampson HA (1997a) **Clinical reactivity to beef in children allergic to cow's milk** *J Allergy Clin Immunol 99:293-300*
- Werfel T, Ahlers G, Schmidt P, Boeker M, Kapp A, Neumann C (1997b) **Milk- responsive atopic dermatitis is associated with a casein- specific lymphocyte response in adolescent and adult patients** *J Allergy Clin Immunol 99(1Pt1):124-33*
- Wilson NW, Hamburger RN (1988) **Allergy to cow's milk in the first year of life and its prevention** *Ann Allergy 61(5):323-7*
- Wilson NW, Self TW, Hamburger RN (1990) **Severe cow's milk induced colitis in an exclusively breast-fed neonate. Case report and clinical review of cow's milk allergy** *Clin Pediatr (Phila) 29:77-80*
- Wüthrich B (1993) **Nahrungsmittelallergie** *Allergologie 16:280-287* (in German)
- Wüthrich B, Hofer T (1986) **Food allergies. III. Therapy: elimination diet, symptomatic drug prophylaxis and specific hyposensitization** *Schweiz Med Wochenschr 116:1401-10* (in German)
- Wüthrich B, Johansson SGO (1995) **Allergy to cheese produced from sheep's and goat's milk but not to cheese produced from cow's milk** *J Allergy Clin Immunol 96:270-3*
- Wuthrich B, Stern A, Johansson SG (1995) **Severe anaphylactic reaction to bovine serum albumin at the first attempt of artificial insemination** *Allergy 50:179-83*
- Wuthrich B, Bianchi-Kusch E, Johansson SG (1996) **Allergic urticaria and angioedema caused by a hemostatic sponge of bovine fibrin used in tooth extraction** *Allergy 51:49-51*
- Ylitalo L, Makinen-Kiljunen S, Turjanmaa K, Palosuo T, Reunala T (1999) **Cow's milk casein, a hidden allergen in natural rubber latex gloves** *J Allergy Clin Immunol 104:177-80*
- Zeiger RS, Sampson HA, Bock SA, Burks AW Jr, Harden K, Noone S, Martin D, Leung S, Wilson G (1999) **Soy allergy in infants and children with IgE-associated cow's milk allergy** *J Pediatr 134:614-22*

Recent Reviews

- Moneret-Vautrin DA (1999) **Cow's milk allergy** *Allerg Immunol (Paris) 31:201-10*
- Wal JM (1998) **Cow's milk allergens** *Allergy 53:1013-22*
- Halken S, Host A (1997) **How hypoallergenic are hypoallergenic cow's milk- based formulas ?** *Allergy 52:1175-83*
- Cantani A (1999) **Hidden presence of cow's milk proteins in foods** *Invest Allergol Clin Immunol 9:141-5*