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Section 15: Milks from Different Animals for Substituting Cow's Milk

Overview

The milks of goat, ewe, mare, donkey, or camel or formulas based on lamb or chicken, where available, have been proposed as substitutes in the management of CMA in infants and children. The nutritional value of a milk substitute must be taken into account less than 2 years of life when a substitute is needed. As human milk composition differs both in component ratios and structure from other milks, the composition of infant formula should serve to meet the particular nutritional requirements and to promote normal growth and development of the infants for whom they are intended. This is valid also for other milks, which are not currently fulfilling all human infants' nutritional requirements.

The DRACMA panel reviewed the literature on the tolerance of mammalian milks on the light of the existing cross-reactivity between mammalian proteins. The after clinical questions were asked for each milk considered in this section:

a. Is it tolerated by children with CMA?
b. How many children with CMA immediately react after ingestion?
c. How many children with CMA experience a delayed reaction after ingestion?

d. What about children with multiple food allergies?
e. Is it nutritionally safe?
f. Is it affordable?
g. Is it palatable?

Most of these questions have currently no answer for individual milks. It was concluded that the lack of suitable formulations for infant nutrition limits the use of alternative milks before the third year of life, when most children have outgrown their allergy, and where it persists, a substitute for CM is no longer needed. In particular, there is a consensus that:

1. In the developed world, other milks could be considered only in the impossibility to use another formula (eHF, SF, HRF, HSF, AAF) for a valid clinical reason.
2. The option of another milk rather than another formula should be weighed against allergy, clinical and nutritional considerations on an individual basis.
3. Goat's, ewe's and buffalo's milks should not be used for the treatment of CMA, as they can expose patients to severe reactions.
4. Camel's milk can be considered a valid substitute for children after 2 years.
5. Equine milks can be considered as valid CM substitutes, in particular (but not exclusively) for children with delayed-onset CMA.

Introduction

Milks from different animals (the goat, ewe, mare, donkey, or camel) or formulas based on lamb or chicken have been widely marketed as substitutes for CM in the management of CMA in infants and children. The substitute source reflects local culture, availability and costs but a comprehensive survey of substitutes for children with CMA is currently lacking. As described in CM Allergen section, cross-reactivity between mammalian proteins is in part explained by bovine taxonomy (Table 15-1)0064t25, with similarities and differences:

1. Human milk composition differs both in component ratios and structure from other milks.
2. The protein content of human milk is lower than that of ruminant dairy animals: cow, buffalo, yak, camel, goat, sheep, reindeer, but is closer to that of donkey's and mare's milk (1).
3. Human milk does not contain beta-lactoglobulin (BLG), one of the major allergens in cow milk, similarly to camel's and dromedary's milks (2).
4. BLG is a major whey protein of cow's, buffalo's, sheep's, goat's, mare's, and donkey's milks.
5. The proportion of casein within the total protein fraction is lower in whole human milk, serum proteins are higher than in cow's, buffalo's, and ewe's milks and more similar to donkey's and mare's milks.
6. The ratio of casein to whey protein is very similar among Bovidae (between 70:30 and 80:20).
7. Mare's and donkey's milks have a lower total protein content (similar to human milk) and a lower casein-to-whey protein ratio.
8. There is substantial homology between cow's, ewe's, or goat's milks protein fractions.
9. There is less structural similarity with the milk from swine, equines and camelids, and human milk (3).
10. Human milk, camel's and dromedary's milks do not contain beta-lactoglobulin.

Table 15-1 also shows the percentage of homology between individual CM protein and those from other animal species, including humans. Data were obtained from the Expasy Website, using the SIM alignment tool for protein sequences (4).

The use of other milks to manage CMA in children has been widely discussed. While there has been no significant breakthrough showing the efficacy of this dietary approach, it has been suggested that certain milks could benefit patients. This body of research has been reviewed by the Panel, using a search strategy similar to that described in the GRADE approach to milk substitutes and essentially aimed at the after clinical questions for each milk:

a. Is it tolerated by children with CMA?
b. How many children with CMA immediately react to ingestion?
c. How many children with CMA experience a delayed reaction to ingestion?
d. What about children with multiple food allergies?
e. Is it nutritionally safe?
f. Is it affordable?
g. Is it palatable?

Most of these questions have currently no answer for individual milks as there is a paucity of research in this particular field.

Goat's and Ewe's Milks

The most frequently suggested alternative to CM is goat's milk, although evidence of its tolerability is reported by only a few clinical studies. Goat's milk is in widespread use in Mediterranean and Middle Eastern countries, in Australia, New Zealand, and Taiwan (6). Similarly to CM, goat's milk is not suitable for infant use unless modified and fortified to meet infant formula regulations. In Australia and New Zealand, where the economical aspects of prescription have been surveyed, goat's milk is available at a cost which is similar to that of soy formulas, while both are typically 20–50% more expensive than standard cow milk-based formula. In New Zealand, the use of goat's milk now exceeds the use of soy-based formulas and comprises ~5% of infant formula purchased.

It has been surmised that goat's milk could be less allergenic than CM because of its lower alpha-casein content (7). Alpha-casein may act as a carrier for other CM allergens such as beta-lactoglobulin, which is tightly linked to casein micelles and therefore more difficult to digest. The lower alpha-casein content of goat's milk might allow a better digestion of beta-lactoglobulin and other allergens (8). In a murine model of food allergy, goat's milk given as a first source of protein after weaning was found less immunogenic than CM in pups in which it induced a weaker T_H2-biased response (9).

A 1997 clinical trial in France found that many children with CM allergy tolerated goat's milk for periods ranging from 8 days to 1 year (10), but several studies have since demonstrated that subjects with IgE-mediated CMA do not tolerate goat's and sheep's milk to this extent (6, 11). As 95% of children with CMA react to goat's milk, it has been suggested that a warning on the lack of safety of goat's milk for children with CMA should feature on the label of goat's milk formulas to prevent severe allergic reactions in infants with CMA- (6). Such reasonable suggestion remains to be complied with even in the parts of the world covered by labeling legislation. In one study of children with atopic dermatitis and IgE-mediated CMA which documented delayed reactions and excluded children with soy allergy, it was reported that goat's milk was tolerated by most of these patients (12). Furthermore, selective allergy to caprine or ovine, but not to bovine, milk has also been reported in patients with severe allergic reactions (13–18). The cross-reactivity between goat's and ewe's milk is incontrovertible (19). Allergy to ewe's milk can also evolve into allergy to CM (20).

From a nutritional point of view, the literature is almost silent. A major concern is the protein content, which is higher in goat's and ewe's milks than in human milk (Table 15-2). This could determine an excessive solute renal load (21). Goat's milk lacks vitamins B12 and B9 and must thus be enriched with these vitamins (22).

Data from a Malagasy report document that among malnourished children aged 1–5 years fed high-energy formulations made from goat's or CM weight gain does not differ between the 2 groups (23). Similarly, a study from New-Zealand shows that adequate grow this reached within the first semester in infants who are fed goat's milk (4).

No data are available on the palatability of goat's milk, but it is reasonable to expect that it is better than that of eHF, HSF, and HRF. Costs also vary, given that a global market for goat's milk does not exist.

Camel's Milk

In many parts of the world (North-East Africa (2), the Middle East (24), the Arabic Peninsula, and China (25)), camel's and dromedary's milks are used as human milk substitutes for bottle-fed infants.

Camel milk contains only 2% fat, consisting mainly of polyunsaturated fatty acids, and is rich in trace elements (26). Its protein composition makes it a possible alternative to CM for allergic subjects because of the low sequence homology of its protein fraction with that of CM and its lack of BLG (27).

Tolerance of camel milk has been anecdotally reported in a limited case series of children suffering from severe, not challenge-confirmed, CMA with immediate and delayed symptoms (28).

No comparative data are available on the palatability of camel's milk, but it is also reasonable to expect it to taste better than eHF, HSF, and HRF. In large geographical area of the world, camel's milk is used for the production of dairy and baked products, and an ingredient of prepackaged processed foods and there is a market for camel's and dromedary's milks.

Mare's and Donkey's Milks

Mare's and donkey's milks have a composition closer to human's than CM (29, 30). Their low protein content (1.3–2.8 g/100 mL) does not carry the risk of an excessive solute renal load.

Table 15-1. Mammalian Taxonomy: Milk Protein Composition and Homology **5**

Genus Species	Cow *Bos* *B. domesticus*	Buffalo *Bubalus* *B. bubalis*	Sheep *Ovis* *O. aries*	Goat *Capra* *C. aegagrus*	Pig *Sus* *S. domestico*	Dromedary *Camelus* *C. dromedarius*	Horse *Equus* *E.f. caballus*	Donkey *Equus* *E. asinus*	Human *Homo* *H. sapiens*
Protein (g percent)	3.2	4.5	4.9	4.3	4.8	3.6	2.14	2.2	1.25
Casein (percent)	80	82	84	84	58	74	56	58	40
Whey proteis (percent)	20	18	16	16	42	26	44	42	60
Homology									
α_{s1}-Casein	100	95.3	88.3	87.9	47.2	44.2	43.3	–	31.9
α_{s2}-Casein	100	95.0	89.2	88.3	62.8	58..3	–	60.0	–
β-Casein	100	97.8	92.0	91.1	67.0	69.2	60.5	–	56.5
κ-Casein	100	92.6	84.9	84.9	54.3	58.4	57.4	–	53.2
α-Lactalbumin	100	99.3	97.2	95.1	74.6	69.7	72.4 (A), 69.1(B/C)	71.5	73.9
β-Lactoglobulin	100	96.7	93.9	94.4	63.9	Absent	59.4 (1)	56.9 (1), 51.6 (2)	Absent
Serum albumin	100	–	92.4	71.2	79.9	–	74.5	74.1	76.6
Average	100	96.1	91.1	87.6	64.2	60.0	62.4	62.8	58.4

The protein fraction is rich in whey proteins (35–50%). Its Ca/P ratio of 1.7, which is close to the optimal value for calcium absorption and metabolism (31). Mare's milk also contains large amounts of linoleic and linolenic acids.

Table 15-2. Protein Content of Different Milks (in g/100 mL)

Milk	Total	Albumin	Casein
Human	1.03	0.4	0.4
Donkey	2.0	0.7	0.6
Mare	2.2	1.2	0.3
Cow	3.3	2.5	0.2
Goat	3.7	3.1	0.6
Ewe	5.3	4.5	1.7

Because of differences between the amino acid sequences of bovine and equine proteins, the epitopes relevant for IgE binding to CM are different or completely lacking and cross reactivity between equine and bovine milks is low (see *Allergens*). This explains why the use of mare's milk has proved useful for some patients. In a group of 25 children with severe IgE-mediated CMA, only one tested positive at DBPCFC with mare's milk (32). Thus, although appropriate modification in chemical composition and hygiene controls are necessary, equine milks are a possible alternative cows' milk substitute in CMA.

Donkey's milk is similar to mare's milk in composition and is easily available in some Mediterranean countries. Studies on its allergenicity and tolerability among patients with gastrointestinal symptoms concluded that this is a possible CM substitute in the dietary management of these delayed-onset, IgE and non-IgE mediated conditions (33, 34). In exquisite-contact acquired IgE-mediated CMA, an 82.6% tolerance of CM was reported in a cohort of children with CMA with heterogeneous symptoms (35). In this particular study, 21.2% of children with immediate CMA reacted to donkey's milk. Thus, the risk of potential cross-reactivity between cow's and donkey's milk proteins is far from theoretical, suggesting that more in vivo and in vitro studies are required before this milk can be recommended in this setting (36). In a population of children with atopic dermatitis and mild CMA most of whom tolerated goat's milk, donkey's milk was also tolerated by 88% of children (excluding those with immediate symptoms) (12).

Sow's, Yak's, and Reindeer CMs

The milks of these 3 species are probably only locally consumed, and the literature on the topic is non medical. However, an Israeli study suggested allergy to artiodactyls and ruminants such as cow, sheep, and goat to be because of the "kosher epitope." Patients allergic to CM tested positive to skin prick test with goat's, buffalo's, and deer's milk, but only one-fifth tested positive to sow's milk and 25% to camel's milk (37). Interestingly, although reindeer is also considered a ruminant only partial cross-reactivity exists between cow's and reindeer cow's milks BLG (38).

Conclusions

In the opinion of the DRACMA Panel, the types and methods of current studies on the use of other milks for the dietary management of CMA does not warrant a GRADE evaluation. So far, the lack of nutritionally suitable formulations for infant use limits alternative milk prescription before the second year of life, when most children have outgrown their allergy, and when it persists,

substituting CM is no longer an issue. However, there was a consensus that:

a. In the developed world, other milks can never constitute the treatment of choice for CMA. They may be considered only in the impossibility to use another formula (eHF, SF, HRF, HSF, AAF) for a valid clinical reason. The use of alternative milks remains an option for convenience, religious or economical considerations provided parental guidance is provided.
b. The option of an alternative milk rather than formula should always be weighed against allergy, clinical, and nutritional status and expectations on an individual basis. The generic consideration that an alternative milk is a "health food" should not be approved by physicians.
c. Goat's, ewe's, and ewe's milks should not be used for the treatment of CMA, as they can expose patients to severe reactions.
d. Camel's milk can be considered a valid substitute for children after 2 years.
e. Equine milks can be considered as valid CM substitutes, in particular, but not exclusively, for children with delayed-onset CMA. As their availability is limited and they are not used in the food industry, it is probably not economical to adapt them for infant use. However, given their protein quality, appropriately processed commercial products would probably make this protein source suitable for infants with CMA.

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Section 16: Nutritional Considerations in CMA Treatment

Overview

In previous sections it has been reported that diet therapy for the long-term management of CMA is fraught with nutritional risks. In this section such risks are re-evaluated through the few studies addressing these clinical issues.

The major risk is rickets as a result of dietary manipulation. Poor growth has been found in children with CMA, possibly linked to the nutritional efficiency of substitute formula. Some nutritional aspects of the use of cow's milk hydrolysates and (to a lesser extent) soy formula in the first semester has been nutritionally evaluated in prevention studies, where the former have been found associated with normal growth. Few data are available for amino acid formula and no data for rice hydrolysates during the first months, but their use in the second semester onwards seem nutritionally warranted. Composition tables of the special formula are hereunder provided.

The dietary modulation of nutritional factors through pre, pro- and synbiotic preparations and polyunsaturated fatty acids (PUFA) represent a novel research hypothesis and a challenge for nutritionists and pediatric allergists. The modulation of the immune system using functional foods is a promising research hypothesis in the attempt to induce a tolerogenic immune environment. Some studies suggested a positive effect of probiotic interventions on atopic dermatitis, but meta-analyses have failed to confirm it. Another area of potential nutraceutical interest is the use of traditional Chinese herbal remedies.

Introduction

The use of diet therapy for the long-term management of CMA is fraught with nutritional risk. The growth and biochemical parameters of children with CMA should approach the standards of reference. Unfortunately, very few studies address these clinical issues. There is also an interest in the dietary modulation of nutritional factors through the use of pre, pro-, symbiotic preparations and polyunsaturated fatty acids (PUFA) representing a new research hypothesis for both nutritionists and pediatric allergists.

Meeting Nutrition Needs

Children with CMA have been described with vitamin D deficiency rickets as a result of dietary manipulation (1, 2), and the whole nutritional equilibrium of such children is at issue. Poor growth has been found in children with atopic dermatitis in the first years (3) and

in children with CMA at 6 months (4). Among the causes of growth limitation, the nutritional efficiency of substitute formula has been investigated (5).

Formulae designed for infant nutrition when human milk is not available should "achieve both an acceptable growth rate and blood proteins and amino acid profile that approach a reference standard, presumably that based on metabolic data from breast-fed infants." (6) Investigations about the nutritional adequacy of special formula used for CMA treatment have been known for a long time (7). Earlier studies indicated lower values of body mass index and higher blood urea nitrogen by infants fed extensively hydrolyzed formula (eHF), with differences in plasma amino acidograms showing higher essential amino acids (AA)/total AA ratio in soy formula (SF)- and eHF-fed compared with breast-fed infants. Also, a lower branch-chain AA/essential AA ratio was reported (8). More recently, clinical trials have investigated growth in infants with CMA fed different formula (eHF or SF), up to 48 months of age (9), suggesting that in general nutritional adequacy is guaranteed by these formula. Differences in the increase of standardized growth indices (weight-for-age, length-for-age, and weight-for-length z-scores) in infants with CMA have been found suggesting that infants fed hydrolyzed products (eHF, HRF) show a trend toward higher weight-for-age z-score increments than children fed SF in the 6 to 12 months period (10). Not only the total amount, but protein quality seems to be important for both symptomatic treatment and growth. Thus, the use of cow's milk or rice hydrolysates has not been explored during the first months, when breast- or formula-milk represent the only food source (11), but their use in the second semester onwards may have decreased local inflammatory responses, positively affecting the absorption of nutrients from the other solid foods. This is only an example of the potentially complex effects of substitute formula in nutrition of children with CMA.

Table 16-1 reports the most relevant nutritional parameters to be assessed in individual formula by the pediatrician when planning a special diet for CMA treatment. The nutritional parameters of the special formula currently available in the world are reported in the repository found on the WAO website.

Prebiotics, Probiotics, and Synbiotics for CMA Treatment

The modulation of the immune system using functional foods is a promising research hypothesis in the attempt to induce a tolerogenic immune environment. To skew the immune response toward a more T_H1/*Treg* polarized phenotype after the onset of CMA remains a clinical possibility for the future when we will have the know-how and the control over desensitization to ultimately induce oral tolerance. Although it is widely believed that intervention should begin as early in life as possible, several studies have shown that successful treatment of atopic dermatitis in children above the age of 2 may be possible further suggesting that the immune system is amenable to manipulation through functional foods later in childhood (12–14). In contrast, several other studies and some metanalysises failed to show a positive effect of a probiotic intervention on atopic dermatitis (15, 16). Currently, we may only conclude, with a review of the evidence, that "more RCTs need to be conducted to elucidate whether probiotics are useful for the treatment of AD" (17).

Polyunsaturated Fatty Acids (PUFAs) for the Treatment of CMA

Clinical trials focusing on the effect of gamma-linolenic acid and n-3 long-chain polyunsaturated fatty acids in patients suffering from atopic eczema have not lived to their expectation (18). Essential fatty acids (EFA) promote the renewal of the protective hydrolipidic film layer of the skin. An altered EFA metabolism has been associated with the pathogenesis of atopic dermatitis (AD). Reduced levels of gamma linolenic acid (18:3 n-6) and of dihomo-gamma-linolenic acid (20:3 n-6) have been found in the plasma phospholipids and in the erythrocyte membranes of patients with AD, supporting the hypothesis of a deficiency in delta-6 desaturase activity. The 20:3 n-6 chain is the direct precursor of prostaglandin (PGE1) and probably competes with PGE2, a potent inflammatory mediator derived from arachidonic acid. Both PGE1 and PGE2 may also be involved in more complex T-cell mediated regulatory mechanisms. In this context, treatment with gamma-linolenic acid has been successfully attempted (19) but has also been called into question (20). More recently, on the basis of new studies concerning the possible curative properties of PUFA supplements in allergic disease (21), the question has become topical again. This panel is of the opinion that the use of PUFA to treat CMA could be attempted in some well-defined cases but that there is a need for more and comprehensive (pre-clinical data for widespread recommendation).

Table 16-1. Nutritional Parameters to Be Assessed In Individual Formula By the Pediatrician When Planning a Special Diet In

Labeling indications	e.g. treatment of CMA in children with gastrointestinal symptom		
Age from which the product may be used			
Protein source	e.g. whey, casein, soy, rice		
Technological processing of the protein source	hydrolysis, heating, . . .		
Carbohydrate source			
Lipid source			
Formulation	Powder or liquid		
Proteins	g/L		
Amino acids (AA)	Alanine, Arginine, . . . Tyrosine, Valine.		
Essential AA/total AA	%		
Peptide molecular weight (Daltons)/100 total proteins	< 1000, 1000–2000, . . . >10000		
Free amino acids/100 total proteins			
Carbohydrates	g/L		
Glucose, galactose, fructose			
Saccharose, lactose, maltose			
Oligosaccharides			
Fructo-oligosaccharides (FOS)			
Galacto-oligosaccharides (GOS)			
Mannan-oligosaccharides (MOS)			
Inulin			
Maltodestrin			
Mannose			
Starch			
Total dietary fiber			
Lipids	mg/L		
Saturated fat			
Monounsaturated fat			
Polyunsaturated fat			
Medium-chain triglycerides			
Total *trans* fatty acids			
Conjugated linoleic acid			
Erucic acid			
Total omega-3 fatty acids			
Alpha-linolenic acid			
Eicosatrienoic acid (ETE)			
Eicosatetraenoic acid (ETA)			
Eicosapentaenoic acid (EPA)			
Docosapentaenoic acid (DPA)			
Docosahexaenoic acid (DHA)			
Total omega-6 fatty acids			
Linoleic acid			
Gamma-linolenic acid			
Arachidoinic acid			
Total phospholipids			
Fatty acid profile			
Vitamin			
A	IU/L		
B1	mcg/L		
B2	mcg/L		
B3	mcg/L		
B5	mcg/L		
B6	mcg/L		
B9	mcg/L		
B12	mcg/L		
C	mg/L		
D	IU/L		
E	IU/L		
H	mcg/L		
K	mcg/L		
Choline	mg/L		
Betaine	mcg/L		
Other vitamins			
Minerals			
Calcium	mg/L		
Phosphorus	mg/L		
Magnesium	mg/L		
Iron	mg/L		
Zinc	mg/L		
Copper	mcg/L		
Manganese	mcg/L		
Iodine	mcg/L		
Selenium	mcg/L		
Sodium	mg/L		
Potassium	mg/L		
Chloride	mg/L		
Molybdenum	mcg/L		
Chromium	mcg/L		
Fluoride	mcg/L		
Other minerals			
Nucleotides			
Cytidine 5`-monophosphate			
Uridine 5`-monophosphate			
Adenosine 5`-monophosphate			
Guanosine 5`-monophosphate			
Inosine 5`-monophosphate			
Other nutrients			
Taurine			
Carnitine			
Inositol			
Histidine			
Functional nutrients			
Probiotics		Genus, species	CFU/g powder
Lactoferrin			
Others			
Caloric information	Kcalories/L		
From carbohydrates	%		
From lipids	%		
From proteins	%		
From fibers	%		
Osmolarity			
Potential renal solute load	mOsm/L		
Osmolality	mOsm/kg water		
Osmolarity	mOsm/L		

Chinese Herbal Medicines

Complementary and alternative medicine has raised interest in the field of allergic asthma treatment. Additional scientific evidence for the treatment of food allergy is also accruing (22, 23). Studies are in the preclinical stage to treat food allergy with a traditional Chinese herbal remedy (24–26). Two different formula have been tested. The FA herbal formula (FAHF)-1 and FAHF-2 mix 9 to11 different herbs. Traditionally, these herbs have been prescribed for gastrointestinal disorders such as diarrhea and vomiting and therefore ought to be effective in food allergy. The safety of these compounds has been investigated in a phase I clinical trial in humans (27).

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Section 17: Choosing the Appropriate Substitute Formula in Different Presentations

The DRACMA recommendations about the most appropriate choice of the substitute formula when breastfeeding is not available (7.1–7.5) are all conditional, i.e. they should be interpreted with special attention to patient's preferences, individual clinical circumstances and cost. It is not possible for any guideline to take into consideration all of the often compelling individual clinical circumstances or patient characteristics because recommendations in guidelines are for typical patients. The DRACMA guideline panel made recommendations for use of substitute formulas specifically for patients with IgE-mediated CMA. However, the choice of the formula may be different for patients with non IgE-mediated CMA or in patients with other specific presentations such as allergic eosinophilic oesophagitis or food protein-induced enterocolitis syndrome (FPIES). The use of formulas in patients with these conditions will be addressed in the future updates of the DRACMA guidelines.

Table 17-1. Reference Guide to the Recommendations

Clinical presentation	Possible options (refer to recommendations 7.1–7.5)		
Anaphylaxis	AAF[¬]	eHF[#§]	SF
Acute urticaria or angioedema	eHF[§□]	AAF^/SF°	
Atopic dermatitis	eHF[§□]	AAF^/SF°	
Immediate gastrointestinal allergy	eHF[§□]	AAF^/SF°	
Allergic eosinophilic oesophagitis	AAF		
Gastroesophageal reflux disease			

Table 17-1. (Continued)

Clinical presentation	Possible options (refer to recommendations 7.1–7.5)		
(GERD)	eHF[μ]	AAF	
Cow's milk protein-induced enteropathy	eHF[¶]	AAF	
Food protein-induced enterocolitis syndrome (FPIES)	eHF*	AAF	
CM protein-induced gastroenteritis and proctocolitis	eHF	AAF	
Severe irritability (colic)	eHF	AAF	
Constipation	eHF	AAF	Donkey milk
Milk-induced chronic pulmonary disease (Heiner's syndrome) **	AAF	eHF	SF

Against this background, Table 17-1 reports a quick reference guide to the recommendations.

Section 18: Grade Recommendations on Immunotherapy for CMA

Should oral immunotherapy be used in patients with cow's milk allergy?

Population: patients with cow's milk allergy (CMA)

Intervention: immunotherapy (specific oral tolerance induction) and elimination diet

Comparison: usual care and elimination diet

Outcomes, Oral Immunotherapy

Outcomes	Importance
Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis)	8
Allergic reaction to cow's milk protein during immunotherapy	7
Duration of CMA	7
Chronic symptoms (eczema)	7
Quality of life of a patient	7
Moderate symptoms of CMA (mild laryngeal edema, mild asthma)	6
Quality of life of caregivers	6
Resource utilization (cost, hospital visits, availability of trained personnel, availability of resuscitation equipment)	6
Mild symptoms of CMA (erythema, urticaria, angioedema, pruritus, vomiting, diarrhoea, rhinitis, conjunctivitis)	4

Summary of Findings

We did not find any systematic review of immunotherapy for CMA. We found 3 randomized trials (1–3) and 3 observational studies (4–6) that examined specific tolerance induction to cow's milk in children with cow's milk allergy.

Two randomized trials (1, 3) included children (mean age 9 years; range 5–17) with CMA confirmed with a blinded placebo-controlled food challenge test. One study used oral immunotherapy with whole milk for 12 months in children with a history of at least 1 severe allergic reaction and milk-specific IgE levels greater than 85 kUA/L (assessed with Phadia CAP System FEIA) who were not able to tolerate more than 0.8 mL of milk during the challenge test (1). The other study used preparation of dry nonfat powdered milk for 6 months in children with a history of IgE-mediated milk allergy (no history of anaphylaxis requiring hospitalization, intubation, or severe asthma), a positive skin prick test (SPT) result to milk extract or milk-specific IgE level greater than 0.35 kU/L (assessed with Phadia CAP System FEIA) who were not able to tolerate more than 75 mL of milk during the challenge test (3). We used information from these studies to prepare summaries of evidence for immunotherapy in patients with CMA.

A third study included children aged 2.2 years (range: 1–6.5) of whom 90% had atopic eczema and were able to tolerate at least 60 mL of milk; diagnosis was established based on the results of food challenge test, SPT or serum milk-specific IgE determination (2). We did not combine the results of this study with the results of the other 2 studies, because the diagnosis of CMA in included children was uncertain.

Three observational studies reported by the same group of investigators used oral milk immunotherapy in children aged 3 to 14 years with CMA confirmed by a blinded placebo-controlled food challenge test (4–6). No study measured the quality of life of children or their parents.

Benefits

Two randomized trials showed that the probability of tolerating at least 150 mL of milk and eat any dairy and milk-containing products) was 17 times higher (95% CI: 2.4–123.2) in children receiving immunotherapy compared with placebo or no immunotherapy (1, 3). The probability of achieving partial tolerance (being able to tolerate between 5 and 150 mL of milk) was also higher with immunotherapy (relative benefit: 20.7; 95% CI: 2.9–147.0). These effects were similar in observational studies (the relative benefit of achieving full tolerance was 8.7; 95% CI: 1.9–40.6) (4–6).

One study in children with atopic eczema who initially were able to tolerate up to 60 mL of milk showed a very modest effect of

immunotherapy (relative benefit of achieving full tolerance: 1.44; 95% CI: 0.98–2.11) (2).

Downsides

Local symptoms were the most frequent adverse effects of immunotherapy occurring during the administration of 16% of doses (rate ratio: 4.5; 95% CI: 3.9–5.2). Lip and/or mouth pruritus was more than 800 times more frequent in children receiving immunotherapy than in children not receiving it (rate ratio: 880.1; 95% CI: 54.6–14, 185.8). Other adverse effects were also more frequent in children receiving immunotherapy included the after: perioral urticaria (rate ratio: 9.9; 95% CI: 4.3–22.9), generalized erythema or urticaria (rate ratio: 16.8; 95% CI: 4.5–63.4), abdominal pain and/or vomiting (rate ratio: 25.8; 95% CI: 5.9–113.3), rhinoconjunctivitis (rate ratio: 15.5 95% CI: 3.7–64.7), mild laryngospasm (rate ratio: 40.9; 95% CI: 2.5–671.8), mild bronchospasm (rate ratio: 11.0; 95% CI: 0.97–124.0), the need for oral glucocorticosteroids (rate ratio: 50.9; 95% CI: 7.0–368.7), need for nebulised epinephrine (rate ratio: 62.8; 95% CI: 3.8–1032.8), and the need for intramuscular epinephrine (rate ratio: 6.4; 95% CI: 1.2–34.1).

Severe reactions occur rarely, however, once they develop they may pose a serious problem, since they may occur at home. Immunotherapy for CMA requires long-term compliance and a significant commitment of the child's family, availability of medical support 24-hour a day, and resources to treat adverse effects immediately.

Other Considerations

The immunologic mechanism of immunotherapy for CMA is not known. It has not been established whether this is a true tolerance induction with a long-lasting effect on IgE production or a desensitization with a temporary reduction of milk-specific IgE levels (similar to tolerating antibiotics or aspirin). Long-term observations are needed to elucidate this and estimate the safety of immunotherapy for CMA.

Conclusions

The net clinical benefit of oral immunotherapy for CMA is very uncertain. Potentially large benefit seems counter-balanced by frequent and serious adverse reactions. There is a need for rigorously designed and executed randomized

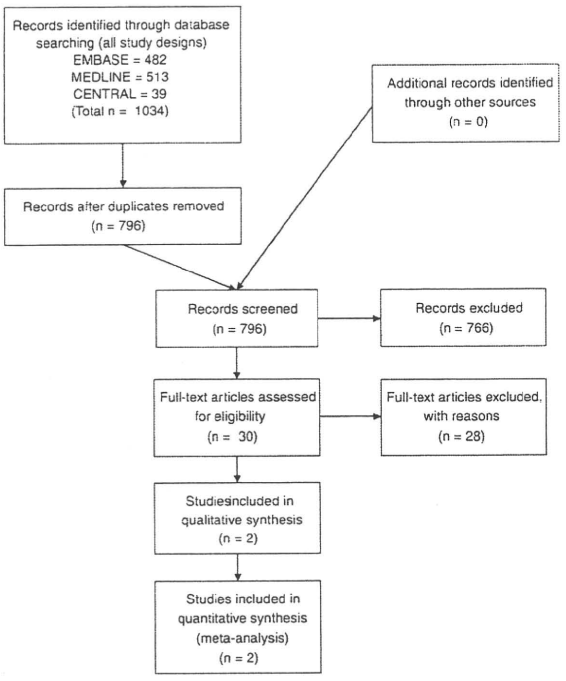

Fig. 18. PRISMA diagram, immunotherapy. Should immunotherapy be used in patients with cow's milk allergy?

trials of immunotherapy in children and adults with cow's milk allergy that measure and properly report (7, 8) patient-important outcomes and adverse effects. Further research, if done, will have important impact on this recommendation.

Clinical Recommendation

In patients with IgE-mediated CMA, we recommend that clinicians do not administer oral immunotherapy with cow's milk, unless this is done in the context of formal clinical research (strong recommendation/very low quality evidence).

Underlying Values and Preferences. This recommendation places a relatively high value on avoiding serious adverse effects of oral immunotherapy, and a relatively low value on the increased probability of desensitization to milk.

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Section 19: Unmet needs, recommendations for research, implementation of DRACMA

In the opinion of this panel, research into new formula and diagnostic tools is entering a new phase with the advent of international initiatives to promote the growth of translational research bringing to the average pediatrician and practitioner a like the benefits of ten years of CMA research as synthesized in the present document. However, much work remains to be done and many multidisciplinary approaches await the exploration of an emergent international field in allergy medicine. The present section offers in outline some relevant questions for future discussion. This panel believes that the after are important areas for the development of research in CMA.

Epidemiology

- An assessment of symptomatic, clinician-diagnosed, and self-reported prevalence of CMA and its time-trends worldwide, reproducible over time, similar to the International Study of Asthma and Allergies in Childhood (ISAAC)1
- More studies on the prevalence of self-reported CMA (relevant for the food industry, the tertiary level of care and other stakeholders) versus challenge-confirmed CMA (relevant for patients and clinicians)
- Studies on prevalence of challenge-confirmed CMA in southern Europe, the U.S., the Middle East, the Asian, African, and Australian regions based on shared challenge methods. These studies should aim at clarifying the geographical trends of CMA
- Birth cohorts studies carried out outside the European context
- Studies expressly addressing the prevalence of non-IgE-mediated CMA based on shared challenge procedures
- Repeated cross-sectional or birth cohort studies aimed at clarifying the time trends of CMA
- Studies on the prevalence of CMA in adulthood

Genetics

- Family clustering of food and respiratory allergies suggests a genetic basis for the disease
- The specific genetic study of CMA remains largely *terra incognita*
- The disease genotypes are still unknown
- The prevalence of susceptibility genes and their distribution across various populations remains unspecified
- Even the clinical impact of family history is still unexplored
- The genetic basis of the variability in individual responses to CM would be an important breakthrough

Allergens

- Diagnostic and prognostic values of the sensitization to each specific CM allergen (mainly *Bos d 4*, *Bos d 5*, *Bos d 6*, *Bos d 7*)
- Sensitization patterns versus single epitopes and their diagnostic and prognostic values
- Molecular studies of cross-reactivity

Mechanisms

- Development of animal models of CMA
- Basic immunology of the innate and adaptive immune response to ingested CM allergens

- The whole area of CD4 $^{+}$ CD25 $^{+}$ T regulatory cells remains to be investigated in the context of CMA
- Whether CD4 $^{+}$ CD25 + Foxp3 + T regulatory cells can be harnessed for immunotherapy remains to be investigated
- Role of exposure to CM allergens in the development of allergy
- Role of exposure to CM allergens in the development of tolerance

Clinical Presentations

- Identification of patient profiles (disease pehnotypes) in CMA
- CMA in adulthood
- Studies on QoL of children with CMA
- Comorbidities in CMA and cognate diseases
- Role/impact/interactions in cognate conditions such as infantile colic, gastro-esophageal reflux disease, constipation, etc
- Role/impact/interactions in other inflammatory conditions such as inflammatory bowel diseases

Diagnosis

- Accuracy of the atopy patch test in non-IgE mediated CMA
- Proteomics (component-resolved diagnosis and microarray technologies) and their value in CMA
- Diagnostic markers for non-IgE-mediated CMA
- Comparative studies between different challenge protocols
- Assessing the economical consequences of a positive or negative challenge
- Studies on the risks of diagnostic challenge in office settings
- Studies on eliciting thresholds for cow's milk allergen

Natural History

- Prospective assessment of tolerance to cow's milk through periodic oral challenge procedures
- Natural history of non-IgE-mediated CMA
- Natural history of the different CMA phenotypes, incorporating risk factors for longer duration of disease

Formulae

- Extensively hydrolyzed versus soy or hydrolyzed rice formula comparative studies
- Soy and hydrolyzed rice formula comparative studies
- Amino acid formula studies
- Extensive hydrolysate studies
- Amino acid-based formula versus soy formula or rice hydrolysate comparative studies
- Rice hydrolysate in non IgE-mediated CMA
- Studies on growth and nutritional indices in infants less than 6 months fed vegetable-based formula
- Comparative studies of the palatabilty and acceptability of various formula in infants and children with CMA
- Studies of other animals' milks
- Detailed proteomic analysis: insight into its hypoallergenicity
- Impact of dietary regimen on the duration of CMA
- Epidemiological and clinical studies on compliance to dietetic advice

Induction of Tolerance

- Strategies to induce tolerance development in children with CMA
- Identification of CMA phenotypes with high probability to respond to SOTI
- Probiotic supplementation in CMA treatment
- Immunotherapy (anti-IgE antibody therapy) for CMA

Recommendation for the Implementation of the DRACMA Guidelines: Periodical Update of DRACMA

Special attention must be given to overcoming barriers to the implementation of CMA management programs in developing countries where resources are limited.

1. DRACMA publication: *WAO Journal*, April 2010
2. Milan Meeting proceedings: JACI 2010
3. GLORIA educational modules
4. World allergy societies endorsement and input sought
5. World sister societies endorsement and input sought
6. DRACMA symposia during allergy and nutrition society meetings

7. Outreach toward patient organizations
8. Creation of an international bureau for dissemination and update

Reference, Section 19

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Conflicts of interest

A. Fiocchi has participated on advisory boards for Ordesa Spain and Phadia Sweden. He has also received research and travel grants from Heinz Baby Food. A. von Berg has received research support from Nestlé, and speaker's fees from Nestlé, Mead Johnson and SHS.

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H.A. Sampson has received consultancy fees from Allertein Therapeutics LLC and Schering Plough, and research support from Phadia. He serves on the National Institutes of Health's NIAID Expert Panel to write Guidelines for the Diagnosis and Management of Food Allergy. He is also immediate-past president of the American Academy of Allergy, Asthma and Immunology, which is one of the sponsoring organizations for these guidelines. He may be called upon to discuss and defend the guidelines once finally accepted and released.

H. Schunemann, S.L. Bahna, J. Brozek, E. Compalati, M. Ebisawa, M.A. Guzman, H. Li, P.K. Keith, M. Landi, A. Martelli, F. Rancé, A.T. Stein, L. Terracciano and S. Vieths have no potential conflicts of interest to declare.

Appendix 1. COW'S MILK ALLERGY *LITERATURE SEARCH ALGORITHMS*

Electronic searches

The following electronic databases were searched:

- NCBI PubMed (1999 onwards);
- EMBASE (1999 onwards);
- UKCRN (the UK Clinical Research Network Portfolio Database);
- WHO ICTRP (the World Health Organization International Clinical Trials Registry Platform);
- *m*RCT (the *meta*Register of Controlled Trials);
- The Cochrane Central Register of Controlled Trials;
- ISI Web of Science;
- Google Scholar.

Search strategy

- Searches were undertaken from January 1999 to July 2008.
- References were checked and *.pdf* copies were provided.
- Restrictions: Humans, English language, Age [*see Section 3 'Epidemiology of CMA' for details*]. No publication restrictions were applied.
- Panellists were required to apply their clinical experience to compile a draft list of suitable articles for the topic within their purview.

Epidemiology of CMA

NCBI PubMed; ISI Web of Science; Google Scholar	LIMITATIONS
Cow's milk allergy	0-18
Cow's milk protein allergy	childhood infant*
Cow's milk hypersensitivity	preschooler* school age
Cow's milk protein hypersensitivity	adolescence young adults
Cow's milk IgE-mediated reaction*	adults elderly

NCBI PubMed; ISI Web of Science; Google Scholar		
Cow's milk allergy	AND	Prevalence; incidence; epidemiology; survey
Cow's milk protein allergy		Risk factor; social impact; burden
Cow's milk hypersensitivity		Health-related quality of life; Health-related quality of life questionnaire
Cow's milk protein hypersensitivity		Perception; parental perception; consumer*; hidden allergen
Cow's milk IgE-mediated reaction*		Hospitali#ation; length of stay; outpatient*; medical visits
		[Anaphylaxis; adrenaline; epinephrine] AND ["school environment" OR "work environment"]

Allergens of cow's milk

NCBI PubMed; ISI Web of Science; Google Scholar	Terms successively entered in Position 1
1. Cow's milk allergy.mp.	• α-lactalbumin
2. Cow's milk protein allergy.mp.	• alpha-lactalbumin
3. Cow's milk protein hypersensitivity$.mp.	• β-lactoglobulin
4. Cow's milk hypersensitivity$.mp.	• beta-lactoglobulin
5. IgE-mediated react$.mp.	• c-type lysozyme*
6. anaphylactic react$.mp.	• serum albumin*
7. anaphylactic shock$.mp.	• P02769
8. anaphylactic syndrome$.mp.	• bovine serum albumin
9. anaphylactoid react$.mp.	• P00711 1HFZ
10. anaphylactoid shock$.mp.	• bovine lactalbumin
11. anaphylactoid syndrome$.mp.	• P04421
12. acute systemic allergic react$.mp.	• bovine lysozyme
13. idiopathic anaphylaxis.mp.	• lipocalin*
14. systemic anaphylaxis.mp.	• P02754 1BEB
15. or/1–14	• bovine lactoglobulin

NCBI PubMed; ISI Web of Science, Google Scholar	Terms successively entered in Position 1
	• P18902 1ERB • bovine plasma retinol-binding protein* • Q28133 1BJ7 • S1- casein • alpha S1-casein • S2-casein • alpha S2-casein • -casein • beta-casein • -casein • kappa-casein • -casein • gamma-casein • bovine allergen* • Bos d 1 • Bos d 2 • Bos d 3 • Bos d 4 • Bos d 5 • Bos d 6 • Q95182 1EW3 • equine allergen • Equ c 1 • P02769 • bovine serum albumin • threshold* • structural biology • Antibod# • IgE antibod# • IgA antibod# • IgM antibod# • Bioinformatics* • characterisation • cross-reactivity • epitope* • B cell epitope* • T cell epitope* • protein folding

Immunological mechanisms of CMA

NCBI PubMed; ISI Web of Science; Google Scholar		
Cow's milk allergy Cow's milk protein allergy Cow's milk hypersensitivity Cow's milk protein hypersensitivity Cow's milk IgE-mediated reaction*	AND	Immune reaction*; immune mechanism; adaptive immunity; Cow's milk IgE-mediated reaction*; immediate reaction*; delayed reaction*; biphasic reaction*; inflammation; neutrophilia; specific IgE antibody; specific IgA antibody; tumor necrosis factor alpha; (cow's milk [protein]) sensitisation.

The clinical history and symptoms of CMA

NCBI PubMed; ISI Web of Science; Google Scholar		
Cow's milk allergy Cow's milk protein allergy Cow's milk hypersensitivity Cow's milk protein hypersensitivity Cow's milk IgE-mediated reaction*	AND	Spectrum; atopic dermatitis, atopic eczema; atopic eczema and dermatitis syndrome; erythematous reaction*; urticaria, pruritus; labial #edema; asthma, wheezing, cough; angioedema; hoarseness; laryngospasm; oro-pahryngeal #edema; anaphylaxis; anaphylactoid reaction*; enteropathy; coeliac disease; cystic fibrosis; Crohn's disease; inflammatory bowel disease; irritable colon syndrome; constipation; colic; vomiting; abdominal pain; bloating; diarrh#ea; respiratory symptoms; gastrointestinal symptoms; oral allergy syndrome; failure to thrive, stunted growth; irritability; crying; autism.

NCBI PubMed; ISI Web of Science; Google Scholar		
Cow's milk allergen Cow's milk protein	AND	1. ANAPHYLAXIS/ 1. anaphylactic react$.mp. 2. anaphylactic shock$.mp. 3. anaphylactic syndrome$.mp. 4. anaphylactoid react$.mp. 5. anaphylactoid shock$.mp. 6. anaphylactoid syndrome$.mp. 7. acute systemic allergic react$.mp. 8. idiopathic anaphylaxis.mp. 9. systemic anaphylaxis.mp. 10. or/1–10

NCBI PubMed; ISI Web of Science; Google Scholar	AND	OR	OR
Cow's milk allergy Cow's milk protein allergy Cow's milk hypersensitivity Cow's milk protein hypersensitivity Cow's milk IgE-mediated reaction*	symptom*	presentation	phenotype

Elimination diet in the diagnostic work-up of cow's milk allergy

Literature search

Anaphylaxis
Oral allergy syndrome
Asthma
Rhinitis
Urticaria and/or angioedema
Atopic dermatitis
Gastro-oesophageal reflux
Pyloric stenosis
Eosinophilic oesophagitis
Enteropathy
Constipation
Colic
Food protein-induced gastroenteritis and/or proctocolitis
Heiner's syndrome

NCBI PubMed; ISI Web of Science; Google Scholar ←		
Cow's milk allergy Cow's milk protein allergy Cow's milk hypersensitivity Cow's milk protein hypersensitivity Cow's milk IgE-mediated reaction*	AND	Cow's milk allergy Cow's milk protein allergy Cow's milk hypersensitivity Cow's milk protein hypersensitivity Cow's milk IgE-mediated reaction*

NCBI PubMed; ISI Web of Science; Google Scholar	AND	OR	OR
Cow's milk allergy Cow's milk protein allergy Cow's milk hypersensitivity Cow's milk protein hypersensitivity Cow's milk IgE-mediated reaction*	History	Clinical presentation	Clinical examination

NCBI PubMed; ISI Web of Science; Google Scholar	AND	OR	OR
Cow's milk allergy Cow's milk protein allergy Cow's milk hypersensitivity Cow's milk protein hypersensitivity Cow's milk IgE-mediated reaction*	(Skin/prick)[$] test	Elimination diet	Fresh food (skin/prick)[$] test

NCBI PubMed; ISI Web of Science; Google Scholar	AND	OR	OR
Cow's milk allergy Cow's milk protein allergy Cow's milk hypersensitivity Cow's milk protein hypersensitivity Cow's milk IgE-mediated reaction*	Specific immunoglobulin E antibody tit[$]	Elimination diet	Specific immunoglobulin E antibody level*

Oral food challenges procedures

NCBI PubMed; ISI Web of Science; Google Scholar ←		
Cow's milk allergy Cow's milk protein allergy Cow's milk hypersensitivity Cow's milk protein hypersensitivity Cow's milk IgE-mediated reaction*	AND	Cow's milk allergy Cow's milk protein allergy Cow's milk hypersensitivity Cow's milk protein hypersensitivity Cow's milk IgE-mediated reaction*

INDICATION
- Diagnosis of cow's milk allergy
- Double blind placebo-controlled food challenge
- SPT endpoint titration
- Elimination diet

DOSAGE
- Starting dose
- Time between steps
- Dilution
- Threshold dosage
- Titration
- Concentration
- Drops

INTERVENTION
- Schedule
- Scheme
- Protocol
- Patient information
- Parent information
- Ethics Committee Review
- ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
- placebos.sh.
- placebo$.ti,ab.
- random$.ti,ab.
- research design.sh.
- comparative study.sh.
- exp evaluation studies/
- follow up studies.sh.
- prospective studies.sh.
- (control$ or prospectiv$ or volunteer$).ti,ab.

When can milk proteins be eliminated from the diet without substituting cow's milk?

1. cow's milk formula
2. randomized controlled trial.pt.
3. controlled clinical trial.pt.
4. open trials.sh.
5. random allocation.sh.
6. double blind method.sh.
7. single blind method.sh.
8. or/1-7
9. (HUMAN not ANIMALS).sh.

The following search arguments were entered in position 1 on successive searches:

ELIMINATION DIET
COW'S MILK FORMULA
HYDROLY#ED COW'S MILK FORMULA
WHEY HYDROLY#ATE FORMULA
CASEIN HYDROLY#ATE FORMULA
AMINO ACID FORMULA
CAMEL MILK
MARE'S MILKS
DONKEY'S MILK
GOAT'S MILK
EWE'S MILK
SOY FORMULA
RICE HYDROLY#ATE FORMULA

Boolean syntax used in the search for supporting literature used in the narrative sections

NB: MeSH terms limited to searches of databases supporting this linking format.

Keywords: prevalence, cow's milk allergy, children [*N* = 120]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English, 0-18 years.

{(``epidemiology''[Subheading] OR ``epidemiology''[All Fields] OR ``prevalence''[All Fields] OR ``prevalence''[MeSH Terms]) AND cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields])} AND (``humans''[MeSH Terms] AND English[lang] AND (``infant''[MeSH Terms] OR ``child''[MeSH Terms] OR ``adolescent''[MeSH Terms]) AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: prevalence, cow's milk allergy, adults [*N* = 15]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English, Adults

{(``epidemiology''[Subheading] OR ``epidemiology''[All Fields] OR ``prevalence''[All Fields] OR ``prevalence''[MeSH Terms]) AND cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields])} AND (``adult''[MeSH Terms] OR ``adult''[All Fields] OR ``adults''[All Fields])} AND (``humans''[MeSH Terms] AND English[lang] AND (``infant''[MeSH Terms] OR ``child''[MeSH Terms] OR ``adolescent''[MeSH Terms]) AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, spectrum, symptoms [*N* = 11]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``Spectrum''[Journal] OR ``spectrum''[All Fields]) OR ``symptoms''[All Fields] OR ``symptoms''[MeSH Terms] OR ``symptoms''[All Fields])} AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, diagnosis [*N* = 392]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``diagnosis''[Subheading] OR ``diagnosis''[All Fields] OR ``diagnosis''[MeSH Terms])} AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, laboratory techniques and procedures [*N* = 115]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``skin''[MeSH Terms] OR ``skin''[All Fields]) AND prick[All Fields] AND (``laboratory techniques and procedures''[MeSH Terms] OR (``laboratory''[All Fields] AND ``techniques''[All Fields] AND ``procedures''[All Fields]) OR ``laboratory techniques and procedures''[All Fields] OR ``tests''[All Fields])} AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, ``skin prick test'' [*N* = 57]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields])} AND ``skin prick test''[All Fields] AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, ``atopy patch test'' [*N* = 57]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields])) AND ``atopy patch test''[All Fields] AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, ``microarray'' [*N* = 4]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields])) AND ``microarray''[All Fields] AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, ``natural history'' [*N* = 18]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``natural history''[MeSH Terms] OR (``natural''[All Fields] AND ``history''[All Fields]) OR ``natural history''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, prognosis [*N* = 45]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``prognosis''[MeSH Terms] OR ``prognosis''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, etiology [*N* = 515]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``etiology''[Subheading] OR ``etiology''[All Fields] OR ``causality''[MeSH Terms] OR ``causality''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, risk factors [*N* = 50]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields])) AND ``risk factors''[All Fields] AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, anaphylaxis [*N* = 33]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``anaphylaxis''[MeSH Terms] OR ``anaphylaxis''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, asthma [*N* = 67]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``asthma''[MeSH Terms] OR ``asthma''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, atopic dermatitis [*N* = 120]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``dermatitis, atopic''[MeSH Terms] OR (``dermatitis''[All Fields] AND ``atopic''[All Fields]) OR ``atopic dermatitis''[All Fields] OR (``atopic''[All Fields] AND ``dermatitis''[All Fields]))) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, allergic rhinitis [*N* = 31]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND allergic[All Fields] AND (``rhinitis''[MeSH Terms] OR ``rhinitis''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, urticaria [*N* = 32]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``urticaria''[MeSH Terms] OR ``urticaria''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, angioedema [N = 14]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``angioedema''[MeSH Terms] OR ``angioedema''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, eosinophilic esophagitis [N = 7]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND eosinophilic[All Fields] AND (``oesophagitis''[All Fields] OR ``esophagitis''[MeSH Terms] OR ``esophagitis''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk allergy, gastroesophageal reflux [N = 23]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``gastro oesophageal reflux''[All Fields] OR ``gastroesophageal reflux''[MeSH Terms] OR (``gastroesophageal''[All Fields] AND ``reflux''[All Fields]) OR ``gastroesophageal reflux''[All Fields] OR (``gastro''[All Fields] AND ``esophageal''[All Fields] AND ``reflux''[All Fields]) OR ``gastro esophageal reflux''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk, allergen [N = 188]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk, human''[MeSH Terms] OR (``milk''[All Fields] AND ``human''[All Fields]) OR ``human milk''[All Fields] OR ``milk''[All Fields] OR ``milk''[MeSH Terms]) AND (``allergens''[MeSH Terms] OR ``allergens''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk, epitope [N = 42]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk, human''[MeSH Terms] OR (``milk''[All Fields] AND ``human''[All Fields]) OR ``human milk''[All Fields] OR ``milk''[All Fields] OR ``milk''[MeSH Terms]) AND (``epitope''[MeSH Terms] OR ``epitope''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk, immunology [N = 409]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``immunology''[Subheading] OR ``immunology''[All Fields] OR ``allergy and immunology''[MeSH Terms] OR (``allergy''[All Fields] AND ``immunology''[All Fields]) OR ``allergy and immunology''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk, immunopathology [N = 9]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND immunopathology[All Fields]) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk, management [N = 65]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``organization and administration''[MeSH Terms] OR (``organization''[All Fields] AND ``administration''[All Fields]) OR ``organization and administration''[All Fields] OR ``management''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk, clinical management [N = 30]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND clinical[All Fields] AND (``organization and administration''[MeSH Terms] OR (``organization''[All Fields] AND ``administration''[All Fields]) OR ``organization and administration''[All Fields] OR ``management''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))

Keywords: cow's milk, therapy OR treatment [N = 242]

Limits: Published between 1st January 1999 and 30th June 2009, Humans, English

(cow's[All Fields] AND (``milk hypersensitivity''[MeSH Terms] OR (``milk''[All Fields] AND ``hypersensitivity''[All Fields]) OR ``milk hypersensitivity''[All Fields] OR (``milk''[All Fields] AND ``allergy''[All Fields]) OR ``milk allergy''[All Fields]) AND (``therapy''[Subheading] OR ``therapy''[All Fields] OR ``therapeutics''[MeSH Terms] OR ``therapeutics''[All Fields]) AND (``therapy''[Subheading] OR ``therapy''[All Fields] OR ``treatment''[All Fields] OR ``therapeutics''[MeSH Terms] OR ``therapeutics''[All Fields])) AND (``humans''[MeSH Terms] AND English[lang] AND (``1999/01/01''[PDAT] : ``2009/06/30''[PDAT]))