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Section 11: The Natural History of CMA

Overview

Cow's milk allergy (CMA) does not often persist into adulthood. Our current knowledge of its natural history suffers from a fragmentary epidemiology of risk and prognostic factors. CMA is often the first step of the allergic march. It can develop from the neonatal period and peaks during the first year of life, tending to remit in childhood.

In the 1990s, a Danish birth cohort study found that more than 50% of children outgrow their CMA at 1 year of age. Subsequent such studies have reported a longer duration of CMA with tolerance developing in 51% of cases within the 2 years after diagnosis.

Referral studies indicate that 80% of patients achieve tolerance within 3 to 4 years. In several studies, children with delayed reactions became tolerant faster than those with immediate reactions. In retrospective studies, the duration of CMA differs in different settings. In a population of breast-fed infants with cow's milk-induced allergic proctitis, tolerance developed between 6 and 23 months.

A universal natural history of CMA cannot be written at this time because the conditions described lack

uniformity. IgE status, genetics, method of evaluation, selection criteria, frequency of rechallenge, and standards of reporting and study designs vary. Children with respiratory symptoms at onset, sensitization to multiple foods and initial sensitization to respiratory allergens carry a higher risk of a longer duration of disease.

The onset of CMA is related to antigen exposure. A cow's milk avoidance diet, once thought of as the only treatment for CMA, has recently been challenged by opposite theories on the basis of human and animal studies.

A family history of progression to atopic asthma, rhinitis, eczema, early respiratory symptoms with skin and/or gastrointestinal symptoms, or severe symptoms are considered risk factors for persistent CMA. A larger wheal diameter at SPT with fresh milk significantly correlates with CMA persistence. Levels of specific IgE, especially to casein, and antibody binding to other ingestant and inhalant allergens, have also been linked to longer duration of CMA. However, in a population of children with a family history of atopy, sensitivity toward food and inhalant allergens during the first year of life were predictive of atopic disease by the age of six. A smaller eliciting dose at oral food challenge also correlates with duration of CMA.

Low milk-specific IgE levels correlate with earlier onset of tolerance and a 99% reduction in specific IgE concentrations more than 12 months translates into a 94% likelihood of achieving tolerance to cow's milk protein within that period.

It has been proposed that tolerance of cow's milk protein correlates with reduced concentrations of IgE- and IgG-binding casein epitopes, and an involvement of tertiary or linear casein epitope structures has been hypothesized. However, the maintenance of tolerance in atopic patients is associated with persistently elevated milk-specific IgG4 antibody concentrations.

Introduction

Pediatricians and allergists often have to face parents who are aware that CMA is not a lifelong condition and therefore wish to know how long CMA is likely to last. Adults who have been diagnosed with CMA are few and far between but the severity of disease is often more worri-

some. Answering these legitimate questions implies practical acquaintance with CMA in both age groups regardless of prevention and treatment effect. Our actual knowledge of the natural history of CMA, however, remains hampered by the fragmentary epidemiology of risk and prognostic factors that is the flip side of our extensive clinical literature.

When Does CMA Develop?

Food-linked hypersensitivity disorders are likely to have followed the general trend of allergic disease (1). Commonly, symptoms of CMA are seen during the first 2 months of life (2–4). According to a Japanese multicenter trial, the prevalence of CMA among newborns is 0.21 and 0.35% amid extremely low birth weight preemies (5). CMA prevalence peaks during the first 12 months of life and tends to subside with age in a time frame that seems to differ from other food allergies (6–10). Thus, egg allergy follows more or less a similar pattern, with a mean duration of about 3 years (11, 12), in fish and nut allergy the duration of disease is not predictable, and there are reports of reactions recurring even after tolerance has been documented (13–15). Cross-sectional studies indicate that infancy is the period when most milk allergy develops and suggest that the most pediatric patients will "outgrow CMA"(16).

The clinical symptoms of CMA follow a general age-related pattern, and infants allergic to cow's milk frequently develop an evolving pattern of allergic symptoms, the so-called "allergic march." This typical sequence begins with early sensitization to food allergens and progresses to atopic dermatitis and may go on to sensitization to inhalant allergens and asthma. Until recently, it seemed to provide a useful clinical model for describing the sequence of manifestations of the atopic phenotype. While it is still a useful paradigm for research and understanding the natural history of allergies, some findings have begun to cast doubts on the transition from manifestations of one organ-related allergy to another is actually sequential in terms of timing or dependent on diverse pathogenic mechanisms. Several trials have actually shown that different populations do not always display the same succession of allergic symptoms. The MAS study (7) reported that a subgroup of children with earlier or more severe atopic dermatitis (AD) had a higher prevalence of early-onset bronchospasm compared with those with AD or mild AD (46.3% vs. 32.1% (P = 0.001). These children had a characteristic and distinct sensitization pattern, and by the age of 7 their respiratory function was significantly more severely affected than that of other children. These observations suggest the possibility that a different disease phenotype may be at work, in which the allergic march does not develop, since AD and asthma can coexist from the earliest expression of atopic disease. Similarly, in a cohort of English children, atopic phenotypes were divided into several groups: never atopic (68%), early atopic (4.3%), late atopic (11.2%), and chronic atopic (16.5%), based on skin prick tests performed at age 4 and 10 (17). This again suggests that, at least in the chronic atopic group, the whole process may be set off quite early on (as suggested by the elevated IgE antibody levels found in cord blood from birth cohort patients) and persists over time, and the skin and airways are simultaneous organ targets. It is possible, therefore, that "chronic atopic" children with CMA develop a distinct clinical course consistent with a yet-to-be-described phenotype.

How Long Does CMA Last?

The average time span from diagnosis to resolution of CMA is the best (albeit approximate) measure of duration of disease (when inferred from prospective studies). Birth cohorts from the general population and clinical studies of selected patients presenting for referral are our best data sources for this purpose. The results obtained from these 2 kinds of sources is practical for the purpose of describing natural history, but referred patients are likely to present for, or to have undergone, treatment in some form such as prevention measures, special diets or therapy course(s), and birth cohort studies are expensive to conduct and consequently rare.

In the earlier birth cohorts, CMA was estimated to run its course within 1 year (18). In these populations of children patients had grown out of their allergy at 1, 2, 3, 5, 10, and 15 years of age in 56, 77, 87, 92, 92, and 97% of cases, respectively (19). Subsequent birth cohort studies reported a longer duration of disease with tolerance developing in 44% of cases at 1.6 and in 51% of cases within the 2 years after diagnosis.

Referral studies indicate that in most cases (80%) tolerance is achieved within 3 to 4 years (20–22), but results vary according to the method of follow-up. Methodologically speaking, an oral food challenge to assess both disease at entry and development of tolerance during follow-up provides gold-standard information. In a Finnish

study, children with delayed reactions were found to develop tolerance sooner than those with immediate reactions (64, 92, and 96% compared with 31, 53 and 63%, respectively at study end point of 2, 3, and 4 years, respectively (23). Several studies report that among allergy clinic patients, 15% of children with IgE-mediated CMA were still allergic after 8.6 years whereas all children with non IgE-mediated disease reached tolerance earlier at an average of 5.0 years (19, 23, 24). In a cohort of pediatric patients referred to a tertiary center in Italy for DBPCFC to cow's milk, the median duration of CMA was 23 months while 23% of children acquired tolerance 13 months after diagnosis and 75% after 43 months (22).

In retrospective referral studies, the duration of CMA differs with settings. In a population of breast-fed infants less than 3 months presenting with CMA-linked allergic proctitis tolerance was achieved between the ages of 6 and 23 months (25). In an Israeli study, less than half of the children diagnosed with IgE-mediated CMA during the first 9 years of life outgrew it (26). A US study reported a duration of CMA far longer than that found in prospective studies, showing tolerance in only 54% of children after a median period of observation of 54 months, and that 80% of the children did not tolerate milk until 16 years of age (27). The authors acknowledged that several issues could lead to an overestimation of the duration of disease. Among them, children assumed to still have milk allergy could have had actually outgrown their allergy but had not undergone oral food challenge.

That the natural history of CMA appears to vary according to open or selective settings, IgE status, method of evaluation (open versus blinded experimental conditions) and frequency of rechallenge at follow-up, suggests that our understanding of the natural history of CMA remains fraught with procedural variability and requires further prospective studies of large unselected cohorts. Generalizing from these studies is further complicated by the adoption of different population selection criteria (21, 23, 28). Sometimes even the age of onset of symptoms is not reported (24). Overall, the diverse standards of reporting and the retrospective design of many of these studies provide information only for generating hypotheses about the natural history of CMA (26, 27).

Another possibly major influence on CMA outcomes for which there is a paucity of data are genetics. Children in whom respiratory symptoms develop at onset, with sensitization to multiple foods and initial sensitization to common respiratory allergens show a longer duration of disease (22). These results, echoing the findings of earlier epidemiological studies (7, 17), suggest that the influence of allergic phenotypes beyond immediate environmental factors may play a role in the onset of CMA. Taken together, these studies are consistent with the suspicion that the allergic march model might be applicable only in certain phenotypes rather than to all atopic individuals: in the case of CMA, there may be several different phenotypes that if identified, could lead to personalized medicine treatment strategies for different populations of atopic patients.

What Factors Can Alter the Course of CMA?

The onset of CMA is related to antigen exposure, with an increasingly recognized role of costimulating molecules at the level of the antigen-presenting cells of the mucous membranes (see *Mechanisms*) (29, 30). Milk allergy is the result of repeated exposure to a milk protein trigger and exclusion of this food, once identified, can prevent food allergy. Total exclusion of food allergens like peanut or milk, however, is difficult to obtain and repeated unintentional minor exposures via the cutaneous, respiratory or gastrointestinal barriers could be more likely to sensitize than providing larger quantities of the allergen by the oral route to induce tolerance. Animal studies have shown that, under certain circumstances, tolerance can develop via apoptosis on exposure to high antigen loads (31). Different studies have shown that the tendency of T-cells to become tolerant can be triggered by the ingestion of minimal quantities of the incriminated allergen (32, 33). The wide array of allergens that can be introduced in the diet is an obvious risk factor for developing allergy very early on, when the immune system is still functionally immature, and the jury is still out on whether early contact with potential antigen can modulate the response of the organism either way toward hyper-responsiveness or tolerance. Similarly, the impact of early or delayed introduction of solid foods on the development of allergy or CMA remains inconclusive (34). There is evidence that exposure to minute doses of milk in the neonatal period increases the likelihood of becoming sensitized to milk later in childhood (24, 35) and exposure to residual amounts of cow's milk proteins is associated with the risk of longer duration of CMA (36).

What Factors Predict the Duration of CMA?

A positive family history of atopic disease, clinical progression to asthma, rhinitis, and eczema (37), and early respiratory symptoms (asthma and rhinitis) with skin and/or gastrointestinal symptoms are considered risk factors for persistence through the involvement of several target organs and result in slower resolution of CMA (22, 27) Severe symptoms reported at the time of diagnosis are consistent with worse prognosis for duration of disease (22, 38–40).

In one cohort study of pediatric referrals, a larger weal diameter at SPT with fresh milk was significantly correlated with the failure to achieve tolerance (22), although this has not been seen in all studies. All patients with CMA and a negative SPT at 1 year of life had developed tolerance by their third year of life. However, 25% of 1-year-old infants with a positive skin prick test were still allergic at the same time. Cosensitization assessed by skin and specific serum antibody tests with, in particular, beef, eggs, wheat, and soy were also predictive of longer duration, as were cosensitization to common inhalant allergens and high levels of cow's milk IgE antibodies identified at diagnosis and during the course of disease.

It has been reported that a reduction in milk-specific IgE levels correlates with the development of tolerance (23) and that a 99% reduction in milk-specific IgE antibody concentrations more than 12 months translates into a 94% likelihood of achieving tolerance to cow's milk protein within that time span (28). Correspondingly, the time required to achieve tolerance to cow's milk protein can be predicted by the decrease in milk-specific IgE levels (28). However, other studies (41) conclude that this predictability applies only in those patients with atopic dermatitis, while the milk-specific IgE antibody levels may be useful a the time of first diagnosis, they cannot be reliably used for predicting tolerance in the general milk-allergic population.

The eliciting dose at oral food challenge has also been found to correlate with duration of CMA. In one cohort study, the smaller the dose of cow's milk sufficient to trigger a positive reaction at diagnosis, the longer the disease appears to last (22).

The levels of cow's milk-specific IgE antibodies vary over time and this has also been linked with duration of CMA (21, 27, 28). As is the case with SPTs, the association between tolerance achievement and antibody concentrations should be considered (especially for casein) and for other food (such as beef, soy, eggs, and wheat) (22, 27) and inhalant allergens (22). There is a significant correlation between initial IgE-antibody specific to the most common allergens and a delay in achieving tolerance to cow's milk protein, irrespective of family history. However, in a population of children with a family history of atopy, sensitivity toward common food and inhalant allergens during the first year of life were significant and predictive of developing atopic disease by the age of 6 (42).

Sensitization to α-1 casein (43), β-casein, and κ-casein has been associated with persistent milk allergy regardless of the age of the patient with allergic symptoms related to cow's milk protein ingestion. Several studies have suggested that milk-allergic patients that generate IgE antibodies to large numbers of sequential epitopes have more persistent allergy than those who generate antibodies primarily to conformational epitopes. Whether tolerance of cow's milk protein is correlated with reduced concentrations of T-cell epitopes of casein in either IgE-(44, 45) or non-IgE-mediated allergy is also unknown, although a different involvement of tertiary (IgE-mediated) or linear (non-IgE-mediated) (46) casein epitope structure with a consequent shift in predominance to milk-specific IgA antibodies could be involved. However, the maintenance of tolerance in atopic patients is known to be associated with persistently elevated milk-specific IgG4 antibody concentrations (47). On the basis of these observations, it remains to be seen whether patients with CMA can be screened for these milk epitope-specific IgE antibodies, with a positive result indicating persistent allergy, age notwithstanding, and whether these parameters make clinical sense in various patient subsets as knowledge of the natural history of the disease increases.

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Section 12: The Treatment of CMA According to Preceding Guidelines

The key principle in the treatment of cow's milk allergy (CMA) is the dietary elimination of cow's milk (CM) protein. During breast-feeding, and in children 2 years of age or older, a substitute formula may not be necessary. In nonbreastfed infants and in children less than 2 years, replacement with a substitute formula is mandatory. In this case, the choice of formula must take into account a series of considerations.

The following factors should be considered for the treatment of CMA:

1. The elimination diet must be effective and complete. Some children may tolerate some baked products.
2. Inhalation and skin contact should also be prevented.
3. Consumers' rights as to ingredients awareness should be reflected in adequate labeling legislation.
4. Beef allergy implies milk allergy in most cases but the reverse is not generally true.
5. All elimination diets should be nutritionally safe particularly in the first and the second semester of life.
6. Dietary compliance should be closely monitored throughout.
7. Periodical review through diagnostic challenge should be carried out to prevent unnecessarily prolonged elimination diets.

Table 12–1 summarizes the recommendations made by international scientific societies, as well as several consensus documents on the treatment of CMA.

As a food allergy, CM is not an exception to the general rule that "the management relies primarily on avoidance of exposure to the suspected or proven foods."(1) Thus, the key principle in the treatment of CMA, irrespective of the clinical type, is the dietary elimination of CMP.

Table 12-1. Treatment of Milk Allergy according to the Current Recommendations in Different Countries

	ESPACI/ESPGHAN 199919	AAP 200020	No. Scientific Society 200721 *	Australian Consensus Panel 200822
Breastfed	In exclusively breastfed infants, a strict elimination of the causal protein from the diet of the lactating mother should be tried	Elimination of cow's milk from the maternal diet may lead to resolution of allergic symptoms in the nursing infant	Breast-fed infants with proven CMA should be treated by CM avoidance	Breastfeeding may be continued, and recommendations are provided for eliminating maternal intake of CM protein
		If symptoms do not improve or mothers are unable to participate in a very restricted diet regimen, alternative formulas can be used to relieve the symptoms	Continue breastfeeding but avoid CMP in mother's diet	

Table 12-1. (Continued)

	ESPACI/ESPGHAN 199919	AAP 200020	No. Scientific Society 200721 *	Australian Consensus Panel 200822
Formula-fed	Allergen elimination is relatively easy in exclusively formula fed infants	eHF or SF (see infra)	(plus Ca^{++} supplement) Mild-to-moderate CMA: eHF When: • The child refuses to drink eHF, but accepts AAF • Symptoms do not improve on eHF after 2–4 weeks • Cost–benefit ratio favors the AAF AAF Severe CMA Refer to a paediatric specialist. In the meantime, an elimination diet should be started with AAF	
Partially hydrolyzed formula (pHF)	Not to be used for treatment of CMA	Not intended to be used to treat CMA		No place for pHF (known as HA) in treating CMA
Extensively hydrolyzed formula (eHF)	Extensively hydrolyzed protein are recommended for the treatment of infants with cows' milk protein allergy	At least 90% of CMA infants tolerate extensively hydrolyzed formulas	Some eHF based on whey and casein met the criteria to be considered a therapeutic formula: tolerated by at least 90% (with 95% confidence) of CMA infants	Appropriate for treating CMA
Soy formula (SF)	Formulas based on intact soy protein isolates are not recommended for the initial treatment of food allergy in infants	Although soy formulas are not hypoallergenic, they can be fed to infants with IgE-associated symptoms of milk allergy, particularly after the age of 6 months	• Are not hypoallergenic • Significantly cheaper, better acceptance than eHF and AAF, but high risk of soy allergy particularly <6 months • high concentration of phytate, aluminum and phyto-oestrogens (isoflavones), possible undesired effects	Appropriate for treating CMA
Other milks	CMA children should not be fed preparations based on unmodified milk of other species (such as goats' or sheep's milk) because of a high rate of cross reactivity	Milk from goats and other animals or formulas containing large amounts of intact animal protein are inappropriate substitutes for breast milk or cow's milk-based infant formula	The use of unmodified mammalian milk protein, including unmodified cow's, sheep, buffalo, horse or goats' milk, or unmodified soy or rice milk, is not recommended for infants	There is no place for other mammalian milks (such as goats milk) in treating CMA
Soy hydrolyzed formula (HSF)	Extensively hydrolyzed protein are recommended for the treatment of infants with cows' milk protein allergy (non specified if also HSF)		eHFs based on another protein source met the criteria to be considered a therapeutic formula: tolerated by at least 90% (with 95% CI) of CMA infants (HSF not expressly cited)	
Rice hydrolyzed formula (HRF)	At the time of recommendations, not extant	At the time of recommendations, not extant	eHFs based on another protein Source met the criteria to be considered a therapeutic formula: tolerated by at least 90% (with 95% CI) of CMA infants (HRF not expressly cited)	At the time of recommendations, not available in Australia
Amino Acid formula (AAF)	Are considered to be nonallergenic. Highly sensitive patients (ie, patients reacting to eHF) may require an amino acid based dietary product	Tolerated	AAF met the criteria to be considered a therapeutic formula: tolerated by at least 90% (with 95% CI) of CMA infants	Appropriate for treating CMA
Differentiation of recommendations by phenotype	No, only IgE mediated vs. non-IgE-mediated, but the recommendations do not differ	Infants with IgE-associated symptoms of allergy may benefit from a soy formula, after 6 months of age (eHF before 6 months)		

Table 12-1. (Continued)

	ESPACI/ESPGHAN 199919	AAP 200020	No Scientific Society 200721 *	Australian Consensus Panel 200822
Non-IgE-associated syndromes such as enterocolitis, proctocolitis, malabsorption syndrome or esophagitis eHF >6 months: SF for immediate reactions, GI symptoms or atopic dermatitis in the absence of failure to thrive AAF 1st choice in anaphylaxis and eosinophilic oesophagitis		<6 months: eHF for immediate CMA (nonanaphylactic), FPIES, atopic eczema, gastrointestinal symptoms and food protein-induced proctocolitis		
Formula to be given during the diagnostic elimination phase			Mild-to-moderate CMA: eHF or AAF	
Anaphylaxis	eHF	SF (no specific indication for anaphylaxis, only for IgE-mediated CMA)		AAF
Immediate GI reactions	eHF	SF 1st, eHF 2nd		eHF <6 months, AAF >6 months
IgE-mediated respiratory reactions	eHF	SF 1st, eHF 2nd		eHF <6 months, AAF >6 months
IgE-mediated cutaneous reactions	eHF	SF 1st, eHF 2nd		eHF <6 months, AAF >6 months
Atopic dermatitis	eHF	SF 1st, eHF 2nd ? no specific recommendation		eHF <6 months, AAF >6 months
Delayed GI reactions	eHF	eHF: "In infants with adverse reactions to food proteins and malabsorptive enteropathy, the use of a formula with highly reduced allergenicity (extensively hydrolyzed formula or amino acid mixture) without lactose and with medium chain triglycerides might be useful until normal absorptive function of the mucosa is regained"		eHF < 6 months, AAF >6 months. AAF in eosinophilic oesophagitis
Heiner Syndrome	eHF	eHF? No specific recommendation		eHF? AAF? No. specific recommendation
Follow-up	Controlled rechallenges should be performed at regular intervals to avoid unnecessarily prolonged avoidance diets			

*Company-supported guidelines intended for general pediatricians and/or GPs. Recommendations valid for mild to moderate CMA. In case of suspicion of severe CMA, refer to a specialist.

In breast-fed infants, and in children after 2 years of age, a substitute formula may not be necessary. In infants and children less than 2 years of age, replacement with a substitute formula is mandatory. In this case, the choice of formula must take into account a series of considerations (see GRADE evaluation). Basically, in all cases the factors to be considered are the after:

1. To avoid untoward effects of persistent symptoms, elimination diet must be effective and complete (2). Thus, to inform the choices of parents, lists of acceptable foods and suitable substitutes must be provided with the help of a dietician.

2. As CM proteins may be encountered in inhalant or contact forms, either of which are able to trigger severe reactions (3–5), such exposures must be monitored to avoid accidental exposure.
3. As CM proteins may be accidentally ingested in food preparations, legislation ensuring that unambiguous labeling is clearly detailed for processed or prepackaged foods is needed worldwide.
4. As cross-reactivity between CM proteins and beef is not the rule, avoidance of other bovine proteins should be evaluated on a case by case basis: while practically all children allergic to beef are allergic to milk (6), the opposite is not true (7).
5. Particular attention must be paid to the prescription of a nutritionally safe diet. Low intake of energy, fat and protein has been reported in CMA children on cows' milk-free diets (8). As cases of severe malnutrition have been reported in children treated with milk elimination for different reasons (9–11), this is not just a theoretical issue. Thus, CMA elimination diets need to be formally assessed for their nutritional adequacy with regard to protein, energy, calcium, vitamin D, and other micronutrient contents.
6. Good quality alternative protein sources must be found, both from the allergy and the nutritional point if view. Particular attention must be paid to data assessing the nutritional safety of CM substitutes in vulnerable periods as the first (12) and the second (13) years of life.
7. Compliance with dietetic advice should be verified throughout the therapeutic phase. In some cultural contexts, full compliance with elimination diets are not always feasible for CM (14), and alternative strategies used for children with severe CMA unable to avoid accidental exposures to CM have been based on this observation (15).
8. When the diagnostic challenge indicates that the child is tolerating small doses of CM, complete milk avoidance may not always be required. Milk-limited diets, including limited, extensively heated milk have been reported not to induce acute milk-induced allergic reactions (16). Such an approach could provide a substantial improvement to the quality of life of milk-allergic individuals (17), but studies with baked-milk products are still in their early stages and it is premature to suggest this as a general recommendation.
9. As the natural history shows that many CMA children outgrow their condition, a periodical re-evaluation of CM tolerance through diagnostic challenges is mandatory to prevent children with this condition from continuing unnecessary elimination diets.

Table 12-1 reports the recommendations so far issued by official documents of international scientific societies (18–20) and largely circulated consensuses on CMA treatment (21, 22). These are not the only documents in the field. National position papers and guidelines have been produced in Germany (23, 24), the Netherlands (25), Finland (26), and Argentina (27), reflecting general and local needs and visions. As the decision strategies in the management of CMA include locally changing issues (indicators of human well-being for the country, prevalence of the condition in that population, methods of diagnosis, local availability of formula, and their price, availability of potential milk substitutes differ from the products available worldwide, reimbursements by the healthcare providers), these documents are not only possible, but necessary.

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Section 13: When can Milk Proteins be Eliminated from the Diet Without Substituting Cow's Milk?

Overview

The simplest way to deal with cow's milk allergy (CMA) is avoidance of cow's milk proteins. A CM-based diet is necessary until 2 years of age. Before this time, a CM substitute of adequate nutritional value is necessary:

- For breast-fed infants, mothers should been advised to continue breast-feeding while avoiding dairy products. The mother will require calcium supplements while on a dairy-free diet.
- For nonbreastfed infants, available substitutes include extensively hydrolyzed cow's milk whey and/or casein formula, soy formula, soy and rice hydrolysates, and amino acid-based formula. The value of such formula is subjected to GRADE evaluation in the relevant sections. Alternative milks will not be GRADE-evaluated and can be used on an individual basis.

In either case, lists of acceptable foods and suitable substitutes congruent with national context and clinical setting must be drawn from various sources and adapted to the individual patient's needs and values.

It is DRACMA contention that all dietary interventions and avoidance strategies be re-evaluated with patients and their families on a yearly basis ideally through an oral food challenge carried out under medical supervision (see *Diagnosis* section). Convincing symptoms after accidental ingestion can be considered equivalent to positive oral food challenge and the follow-up procedure can be rescheduled accordingly.

Introduction

Fully breast-fed infants and toddlers more than 2 years may not need to substitute cow's milk if an adequate supply of calcium (600-800 mg/day) is provided. From these patients' perspective, avoidance means meeting obstacles unshared by their nonallergic peers, thereby curtailing their quality of life; from the physician's outlook, patient and parent education, encouraging compliance, and receptiveness in both patient and caregiver are the major didactic concerns. The cues for a successful avoidance phase result from a dialectical assessment of these competing factors in concert with all parties concerned.

Prescribing an Effective DIET

A successful avoidance strategy planned with the patient's family rests on achieving the absolute avoidance of contact with cow's milk proteins. For breast-fed infants, this entails to provide mothers with the advice to continue breast-feeding while avoiding dairy products altogether (1). Milk proteins are found in breast milk and may cause adverse reactions during exclusive breast-feeding in sensitized infants (2). The mother will also require calcium supplements (1000 mg/day divided into several doses) while after a milk-free diet.

For the nonbreastfed infants, a substitute formula will be proposed. Current guidelines define a therapeutic formula as one that is tolerated by at least 90% (with 95% CI) of CMPA infants (3). These criteria are met by some extensively hydrolyzed cow's milk whey and/or casein formula, soy and rice hydrolysates, and by amino acid-based formula (AAF). To maximize the diagnostic significance of the elimination phase, the least allergenic substitute should be proposed. Children may react to residual allergens in eHF, with a risk of failure up to 10% of children with CMA (4). The residual allergens in eHF account for failure of therapy in this setting (5), and such formula are more likely to produce gastrointestinal and other non-IgE-associated manifestations compared with AAF (6, 7). However, immediate reactions have also been reported in connection with eHF treatment (8). In such cases, clinicians should consider either rice hydrolyzed formula (HRF) or AAF, the safety of which is well documented (9, 10) and that provide adequate nutrition (8, 11), promote weight gain, and foster growth.

Planning a dietary regimen avoiding all cow's milk proteins from dairy or processed food products for these infants and children is a collaborative consensus between scientific societies, primary care physicians and caregivers that goes beyond office procedures. For infant foods in particular, lists of acceptable foods and suitable substitutes congruent with national context and clinical setting must be drawn from various sources and adapted to the individual patient's needs and values (12). A dietician can be of help and specific lists are available to inform the everyday choices of parents and patients. For children and adolescents, who are major consumers of prepackaged industrially processed foods, recognizing the danger signals can be more difficult than in adult populations. Inadvertent milk contamination is difficult and costly to consistently eliminate from the food chain and, for infants and children, good quality alternative protein sources must be found that are also attractive. To compound the problem, milk allergen inhalant, ingestant, or skin contact forms are all liable to trigger severe reactions (13, 14).

Prevention of Accidental Exposure

In an effort to meet the needs of food allergic patients, regulators have come up with legislation ensuring that unambiguous labeling for the main categories of food allergens is clearly detailed for processed or prepackaged foods. Since 2005 (after the review of a labeling directive issued in September 2001 by the European Union), 12 foods, including dairy milk, are required to seem as disclosure of content on the label of all processed or prepackaged foods. Similar legislation is in effect in the US, where the Food Allergen Labeling and Consumer Protection Act provides that all milk products require an ingredient statement. Thus, hidden allergens previously not requiring labeling because found in ingredients/additives exempt from specific indication (ie, colors and flavorings, etc.) must now be disclosed.

On both the sides of Atlantic, however, these regulatory efforts have raised the concern of a labeling overkill, which could restrict even further the range of potentially safe choices for allergic consumers. The threshold concept, on which avoidance should be objectively predicated is elusive and the issue of eliciting dose, either for diagnosis or for real-life situations is likely to rely on individual intrinsic and extrinsic factors (15). Current legislation does not enforce disclosure of potential contaminants, but many manufacturers include a "may contain..." warning of hypothetical contamination during food processing to

ward off litigation. Even in the case of contaminants, blanket eliminations should be avoided if one is to maintain a wide range of food options especially with the cow's milk allergic consumer in mind. A case in point is lactose, which textbooks (16), reviews (17), and position papers (18, 19) single out as a possible cause of adverse reactions in children with CMA. The literature does not report a single case of an adverse reaction to lactose ingestion among children with CMA, and a prospective study of the allergenicity of whey-derived lactose investigated by serology and DBPCFC did not document such reactions (20). Thus, even if lactose ingestion may per se carry risks of cow's milk protein contamination (as seen from incidents after inhalation of lactose-containing drugs (21)), the total elimination of lactose from the diet of children with CMA is not warranted. Some of the products intended for use by milk-allergic children may contain lactose (22).

Awareness of Cross-Reactive Foods

While the need for casual contact avoidance is easy enough to grasp, this is not the case with the phenomenon of cross-reactivity among seemingly unrelated food families where cultural habits interfere. Multiple food allergies are actually rare in the general population and oral food challenge confirms allergy to no more than one or 2 foods, while a dozen foods or so account for most food-induced hypersensitivities (23). It follows that, as extensive elimination diets are seldom necessary, so are avoidance strategies based on presumed cross-reactions between different proteins (24). In the context of CMA, a case in point is beef, as dairy products and meat contain common antigenic protein (25) and cross-reactivity could be alleged in favor of elimination because of amino acid sequence homology (26). Nutritionally and economically, dairy products and beef are important protein sources in the western diet (30 kg of beef per person are consumed in the US annually (27)) but CMA is more frequent than hypersensitivity to beef, with point prevalence of 10% in one study of children with CMA (28). While almost all children allergic to beef are also allergic to milk (29), industrial treatment, more than home cooking, may modify the allergic reactivity of this meat in beef-sensitive children (30), thus making industrially freeze-dried or homogenized beef safe alternatives to butcher's meat cooked at home. Thus, total avoidance of beef by all cow's milk-allergic children is not justified. In this setting, an allergist's evaluation of cross-sensitization makes sense during the diagnostic work-up of CMA.

Prescribing a Nutritionally Adequate Diet

Formulating the diet of infants and children during the CMA work-up requires a careful evaluation of all nutritional aspects and requirements on a strictly individual patient basis. There has long been a consensus is in the food allergy literature that "extensive [elimination] diets should be used as a diagnostic tool only for a short period of time" (31) and that "it is crucial to provide a balanced diet which contains sufficient proteins, calories, trace elements, and vitamins." (32) This is particularly relevant for infants with CMA, since their nutritional requirements demand a balanced calorie-protein ratio, amino-acid composition and an adequate calcium source (33). Ignoring these principles can lead to inappropriate diets, sometimes with dramatic effects (34). As far as cow's milk substitutes are concerned, studies demonstrating their nutritional safety even in the first (35) and the second (36) semester of life are part of the body of evidence underlying the consensus treatment of CMA.

Compliance with Avoidance Measures

A Dutch study of children who had followed an avoidance diet from birth for primary prevention of CMA has brought into question the very feasibility of enforcing absolute compliance (37). The main lessons to be drawn for diagnostic diets from such a study include the difficulty of enforcement and the need for epidemiological and clinical studies on compliance breakdown in the context of CMA.

Periodic Re-evaluation of CMA

As a prognostic index is currently lacking, remission of CMA should be periodically reviewed (see *Natural history* section). It is the consensus of this panel that all dietary interventions and avoidance strategies should be re-evaluated with patients and their families on a yearly basis. In practice, this reappraisal takes the form of an oral food challenge under medical supervision (see *Diagnosis* section). Challenges may be carried out earlier if inadvertent cow's milk ingestion without symptoms is reported. Convincing symptoms after accidental ingestion can be considered equivalent to positive oral food challenge and the follow-up procedure can be rescheduled accordingly.

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Section 14: Guidelines for Choosing A Replacement Formula

Introduction

Treating cow's milk allergy (CMA) entails a nutritional risk, as milk is a staple food in particular for children less than 2 years of age. When a replacement formula is needed, the allergist can avail themselves with different types of formula:

1. Amino acid formula (AAF)
2. Extensively hydrolyzed formula of cow's milk proteins (eHF)
3. Soy formula (SF)
4. Rice extensively hydrolyzed formula (RHF)
5. Soy hydrolyzed formula (SHE)
6. Other mammal's milks.

After an evaluation of the literature, the DRACMA panel decided to commend to the GRADE specialists the analysis of the formula 1–4. For SHF and other mammal's milks, it was decided not to go into similar analysis given the paucity of information. DRACMA will deal with mammal's milks in section 13. Thus, this section reports the guidelines for the use of AAF, eHF, SF, and RHF as replacement formula in infants confirmed to have CMA. After the complete evaluation of randomized trials, 1,579 of which were screened (Fig. 14-1), the panel asked the GRADE group to analyze also the observational studies. For this analysis, 2,954 studies were assessed (Fig. 14-2). This supplementary investigation did not change the recommendations.

Question 7

Should amino acid formula, extensively hydrolyzed whey or casein formula, soy formula or rice formula be used in children with IgE-mediated CMA?

Population: children with CMA
Interventions (management options):

1. Amino acid-based formula
2. Extensively hydrolyzed whey or casein formula
3. Soy formula
4. Rice extensively hydrolyzed formula

Outcomes of Interest, Question 7

Importance	
Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis)	9
Allergic reaction to protein in the formula	7
Moderate symptoms of CMA (mild laryngeal edema, mild asthma)	7
Failure to thrive	7
Enteropathy, entero/proctocolitis	7
Protein and fats deficiency	7
Iron, calcium, vitamin D, and other minerals and vitamins deficiency	7
Weight/height	7
Mild symptoms of CMA (erythema, urticaria, angioedema, pruritus, vomiting, diarrhoea, rhinitis, conjunctivitis)	7
Quality of life of a patient	6
Duration of CMA	6
Unpleasant taste (child may refuse to take the formula)	6
Quality of life of caregivers	6
Anthropometric values	6
Resource utilization (cost)	5
Cross-reactivity with cow's milk	5
Development of secondary sensitization to proteins present in a formula	5
Excessive weight gain	5
Skin fold thickness	5
Burden for parents: need to change from bottles to beakers (milk hydrolyzed, rice, and amino acid formulas are high in sugar)	5
Sexual maturation (development of secondary and tertiary sexual traits)	4

Summary of Findings

Systematic Reviews. One systematic review assessed the efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy (1). We could not use this review to directly inform these recommendations since it did not assess the methodological quality of included studies, did not combine the results of individual studies, and included studies done in children without confirmed CMA (2, 3). We assessed all the studies identified in this review and used those that met our prespecified criteria (see description of individual studies below). We identified one additional randomized trial of amino acid versus extensively hydrolyzed formula (4) that appeared after Hill and colleagues' review was published.[1]

We did not identify any systematic review assessing the relative benefits and downsides of using extensively hydrolyzed formula compared with soy formula or rice formula 0064t24or comparing soy to rice formula in children with CMA.

Individual Studies. Altogether we identified 3 randomized trials comparing amino acid-based formula to an extensively hydrolyzed whey formulas (4–6). All studies used Neocate (SHS International) amino acid-based formula and 3 different whey hydrolyzed formulas: Pep-

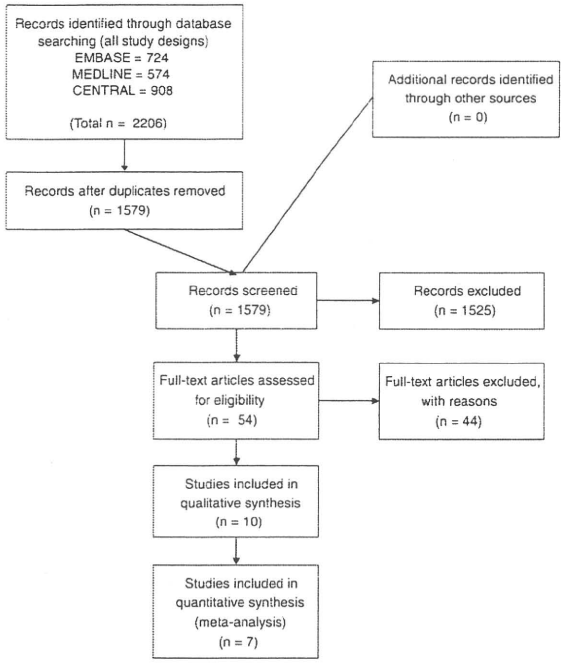

Fig. 14.1. PRISMA diagram, randomized trials. Should extensively hydrolyzed milk, soy, amino acid or extensively hydrolyzed rice formula be used in patients with cow's milk allergy?

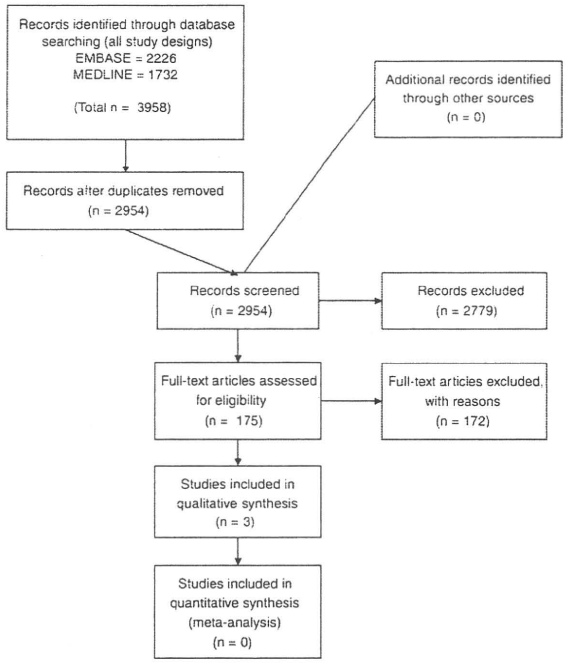

Fig. 14.2. PRISMA diagram, observational studies. Should extensively hydrolyzed milk, soy, amino acid or extensively hydrolyzed rice formula be used in patients with cow's milk allergy?

tidi-Nutteli (Valio), (5, 6) Alfare (Nestlé), (6) and Althera (Nestlé). (4) All studies had methodological limitations, none reported a method of randomization, concealment of allocation, and only one reported blinding (it was not blinded and only results of per protocol analysis were reported). Studies did not measure or report most outcomes of interest (see evidence profile Appendix 3).

We also identified 2 randomized short-term food challenge trials that compared amino acid-based formula to extensively hydrolyzed casein formula (7, 8) and to soy formula (7). Sampson and colleagues enrolled 28 children (aged 11 months to 12 years) with confirmed CMA and allergy to several other foods (8). Children were challenged with an amino acid formula (Neocate) and an extensively hydrolyzed casein formula (Nutramigen). There were no reactions during the challenge with amino acid formula and one child reacted to extensively hydrolyzed formula with vomiting, erythema, rhinitis, laryngeal edema, and wheezing. Caffarelli and colleagues enrolled twenty children (aged 11 months to 9 years) with confirmed CMA fed with soy formula with no symptoms (7). This study suffered from major limitations with 20% of children not being challenged with extensively hydrolyzed formula and 50% not being challenged with amino acid formula. Two children challenged with amino acid formula developed a delayed eczema, one child receiving extensively hydrolyzed casein formula had immediate diarrhea, and 3 children challenged with extensively hydrolyzed whey formula developed symptoms of allergy: vomiting and diarrhea (one), urticaria (one), and delayed eczema (one).

No study using amino acid formula reported laryngeal edema, severe asthma, anaphylaxis, enteropathy, or entero/proctocolitis. No study measured protein and nutrients deficiency, and quality of life of both children and parents. We did not identify any study comparing amino acid-based formula to soy formula or rice hydrolysate.

We identified 2 studies that compared extensively hydrolyzed cow's milk formula to soy formula (9, 10). Extensively hydrolyzed formulas used were Nutramigen regular (Mead Johnson) (9) and Peptidi-Tutteli (Valio) (10) and the soy formulas were Isomil-2 (Ross Abbott) (9) and Soija Tutteli (Valio) (10). All studies had methodological limitations, none reported a method of randomization, concealment of allocation, and they were not blinded. In one study only results of per protocol analysis were reported (9). Most outcomes of interest did not occur in the studies (see evidence profile, Table A3-3 in Appendix 3).

Only one randomized trial compared extensively hydrolyzed formula to rice formula (9). A extensively hydrolyzed rice formula used in one study was Risolac (Heinz) (see evidence profile, Table A3-2 in Appendix 3).

We found 2 randomized trials comparing soy formula to rice formula published by the same group of investigators, one was the abovementioned study by Agostoni and colleagues (9) and the other was a study by D'Auria and colleagues (11) (see evidence profile, Table A3-4 in Appendix 3).

Because the information from randomized trials was sparse, we searched for observational studies with an independent control group that compared different formula in children with cow's milk allergy. We identified 5 observational studies (12–16). Two of them reported comparing different extensively hydrolyzed milk formula only (12, 15). One study described 51 children with immediate allergic reactions to cow's milk protein in whom extensively hydrolyzed milk, soy or amino acid formula were used (13). The formula were selected by the clinician and the selection was not described. Allergic reaction to selected formula was observed in 3 of the 8 children receiving extensively hydrolyzed milk formula, and none of the children receiving either soy (29 children) or amino acid formula (6 children). Another study described a cohort of 25 children "sensitized to cow's milk proteins" (authors did not report the criteria for diagnosis) that received either soy formula or extensively hydrolyzed casein formula for 12 months (14). Authors measured body height, mass and upper arm circumference and found no difference between the groups. The third study described 58 children with atopic eczema and CMA, who received a rice hydrolysate formula, soy formula or an extensively hydrolyzed casein formula (16). The choice of the formula was reported as being "based on allergometric tests, clinical features at the beginning of the diet and age." Authors measured weight of the children and observed no difference in the weight-for-age z-score among the groups.

Amino Acid Formula Versus Extensively Hydrolyzed Whey or Casein Formula

(Table A3-1 in Appendix 3)

Benefits

In children with atopic eczema extensively hydrolyzed whey formula had similar impact on the severity of eczema compared with amino acid-based formula (mean difference in SCORAD score: 1.39 point higher; 95% CI: 1.08 lower to 3.86 higher). Growth, as measured by relative length and weight, were similar in both groups, although the results were imprecise (see evidence profile, Table A3-1 in Appendix 3).

Downsides

Vomiting was noted in fewer children receiving extensively hydrolyzed whey formula compared with amino acid formula (relative risk: 0.12 [95% CI: 0.02–0.88]; risk difference: 235 fewer per 1000 [from 32 fewer to 261 fewer]), however, this estimate is based on 9 events only. One study estimated the cost treatment. The use of extensively hydrolyzed whey formula was associated with direct cost of £E149 per child per month and amino acid formula £E318 per child per month (difference: £E169 less per child per month). However, this estimate can only serve as a rough guide for decisions in other settings. Direct cost measured in one country and jurisdiction at some point in time will likely not be applicable to different settings. Direct cost may be estimated considering that the children in the study (mean age 8 months) consumed about 600 mL (±200) of formula daily.

Conclusions

Net clinical benefit of substituting cow's milk with amino acid formula compared with extensively hydrolyzed whey formula is uncertain. Most outcomes of interest were not measured in clinical studies and the estimates of outcomes that were measured are very imprecise. The direct cost of amino acid formula is higher than extensively hydrolyzed whey formula. There is no information from controlled clinical studies about the relative benefits and downsides of using amino acid formula compared with soy or rice formula (1). Further research, if done, will have important impact on this recommendation.

Extensively Hydrolyzed Whey or Casein Formula Versus Soy Formula

Benefits

Growth, as measured by length and weight for age z-score, were similar in both groups, although there was a trend toward improved growth in the group receiving extensively

hydrolyzed formula compared with soy formula (length for age z-score - mean difference: 0.27 SD higher; 95% CI: 0.19 lower to 0.73 higher, and weight for age z-score, mean difference: 0.23 SD higher; 95% CI: 0.01–0.45 higher). However, the results were again imprecise and it is not certain to what extent these measures of child's growth relate to outcomes that are important to patients.

Downsides

Fewer children with CMA experienced allergic reaction to extensively hydrolyzed formula than to soy formula (relative risk: 0.18; 95% CI: 0.05–0.71) and developed secondary sensitization confirmed by the presence of specific IgE in serum (relative risk: 0.14; 95% CI: 0.03–0.76). However, very few events occurred in both groups, thus the results are imprecise.

Quality of life was not measured in these studies, but investigators recorded "acceptance" of a formula (9). All 37 children receiving soy formula accepted it well, but 4 of 35 children receiving extensively hydrolyzed formula accepted it poorly (relative risk: 0.89; 95% CI: 0.75–1.02).

Conclusions

Net clinical benefit of substituting cow's milk with extensively hydrolyzed formula compared with soy formula is uncertain. Most outcomes of interest were not measured in clinical trials and the estimates of the outcomes that were measured are very imprecise. Further research, if done, will have important impact on this recommendation.

Extensively Hydrolyzed Whey or Casein Formula Versus Extensively Hydrolyzed Rice Formula

(Table A3-2 in Appendix 3).

Benefits

Growth, as measured by length and weight for age z-score, was similar in the group receiving extensively hydrolyzed casein formula compared with hydrolyzed rice formula (length for age z-score, mean difference: 0.33 SD higher; 95% CI: 0.13 lower to 0.79 higher, and weight for age z-score; mean difference: 0.04 SD higher; 95% CI: 0.53 lower to 0.45 higher). The results were imprecise and it is not certain to what extent these measures of child's growth relate to outcomes that are important to patients.

Downsides

No allergic reaction to extensively hydrolyzed formula or to rice formula occurred in this study (9). Acceptance of extensively hydrolyzed whey formula and extensively hydrolyzed rice formula was similar (relative benefit: RR 1.06; 95% CI: 0.86–1.32), but the results were very imprecise not excluding appreciable benefit or appreciable harm. Hydrolyzed rice formulas are not available in many countries.

Conclusions

Net clinical benefit of substituting cow's milk with extensively hydrolyzed formula compared with rice formula is uncertain. Only one relatively small randomized trial is available that did not report most outcomes of interest and the estimates of the outcomes that were measured are very imprecise. Further research, if done, will have important impact on this recommendation.

Soy Formula Versus Extensively Hydrolyzed Rice Formula

(Table A3-4 in Appendix 3).

Benefits

There was no apparent difference in length and weight for age z-scores between children receiving soy formula compared with rice formula (length for age z-score, mean difference: 0.33 SD higher; 95% CI: 0.13 lower to 0.79 higher, and weight for age z-score, mean difference: 0.04 SD lower; 95% CI: 0.53–0.45 higher). In a study that enrolled children with atopic eczema its severity was similar in both groups both at baseline and at the end of the study, but 11/16 children had SCORAD scores <20 at baseline (9, 11).

Downsides

Fewer children with CMA experienced allergic reaction to hydrolyzed rice formula that to soy formula (0/43 versus 5/44; relative risk: 0.08; 95% CI: 0.00–1.52). However, very few events occurred, thus the results are imprecise.

Conclusions

Net clinical benefit of substituting cow's milk with soy formula compared with extensively hydrolyzed rice formula is unknown. Most outcomes of interest were not measured and the estimates of the outcomes that were measured are very imprecise. The guideline panel felt that any

recommendation is not warranted until further research is done comparing the effects of using a soy formula versus a hydrolyzed rice formula.

Summary for Research

There is a need for rigorously designed and executed randomized trials comparing different types of formula used long-term (as opposed to single-dose challenge) in patients with cow's milk allergy that would measure and properly report (17, 18) patient-important outcomes and adverse effects.

Clinical Recommendations, Question 7

Recommendation 7.1

In children with IgE-mediated CMA at high risk of anaphylactic reactions (prior history of anaphylaxis and currently not using extensively hydrolyzed milk formula), we suggest amino acid formula rather than extensively hydrolyzed milk formula (conditional recommendation/very low quality evidence).

Underlying Values and Preferences. This recommendation places a relatively high value on avoiding possible anaphylactic reactions and a lower value on avoiding the direct cost of amino acid formula in settings where the cost of amino acid formulas is high.

Remarks. In controlled settings a trial feeding with an extensively hydrolyzed milk formula may be appropriate.

Recommendation 7.2

In children with IgE-mediated CMA at low risk of anaphylactic reactions (no prior history of anaphylaxis or currently on extensively hydrolyzed milk formula), we suggest extensively hydrolyzed milk formula over amino acid formula (conditional recommendation/very low quality evidence).

Underlying Values and Preferences. This recommendation places a relatively high value on avoiding the direct cost of amino acid formula in settings where the cost of amino acid formula is high. In settings where the cost of amino acid formula is lower the use of amino acid formula may be equally reasonable.

Remarks. Extensively hydrolyzed milk formula should be tested in clinical studies before being used (19). If a new formula is introduced, one should carefully monitor if any adverse reactions develop after first administration.

Recommendation 7.3

In children with IgE-mediated CMA, we suggest extensively hydrolyzed milk formula rather than soy formula (conditional recommendation/very low quality evidence).

Underlying Values and Preferences. This recommendation places a relatively high value on avoiding adverse reactions to soy formula, and a relatively low value on an inferior acceptance of the extensively hydrolyzed formula and resource utilization. In settings where relative importance of resource expenditure is lower an alternative choice may be equally reasonable.

Remarks. Soy should not be used in first 6 months of life, because of nutritional risks.

Recommendation 7.4

In children with IgE-mediated CMA, we suggest extensively hydrolyzed milk formula rather than extensively hydrolyzed rice formula (conditional recommendation/very low quality evidence).

Underlying Values and Preferences. This recommendation places a relatively high value on wide availability of extensively hydrolyzed milk formula relative to hydrolyzed rice formula.

Recommendation 7.5

We suggest that more well designed and executed randomized trials comparing soy formula to extensively hydrolyzed rice formula are performed in patients suspected of IgE-mediated CMA.

Remarks. There is very sparse evidence suggesting possible benefit from using extensively hydrolyzed formula compared with soy formula, but more research is needed to confirm these observations.

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