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The Rational Alternative for Feeding Children with Cow's Milk Allergy: State of the Art

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Abstract

Background

Normal newborns have a limited immunocompetence therefore they need breast milk (BM), which represent an excellent immune protection for the neonate during the critical period of intestinal vulnerability, owing to a great variety of functionally interactive immunological, antibacterial, antiviral, anti-inflammatory and immuno-modulating factors. Evidence suggests that the protection afforded by BM to the recipient infant is greatest when breast-feeding is exclusive and of substantial duration. BM is not always available, but it is not surprising that cow's milk (CM) can induce a whole spectrum of allergic manifestations, even life-threatening or fatal, especially a minute CM amount, in addition to sensitize genetically atopy-prone infants.

Considerations

For both pediatricians and allergists the management of infants with CM allergy (CMA) is a challenge. In the first years of life of many children CM represents the primary source of nutrients with high biological value insuring almost the whole dietary supply of proteins, carbohydrates, and fat: its high nutritional value and low cost should be noted. Children with CMA older than two years can avoid CM without nutritional loss if the nutrients necessary to cover daily requirements are provided by other foods. In the first years of life, dietary treatment of CMA is necessary for evident reasons. Accordingly, the choice of an adequate CM substitute among several hypoallergenic formulas is mandatory for infants with CMA.

Conclusion

In this paper we will discuss the nutritional adequacy, the immunogenicity and the allergenicity of the available CM substitutes, including soy-protein, home-made, meat-based, hydrolysate, goat and mare, and amino acid-derived formulas, as well as the challenges posed by both genetically modified foods (GMFs), and bovine spongiform encephalopathy (BSE). According to recent data, the above formulas can be also useful for feeding "high risk" babies, when BM is unavailable for the prevention of atopic diseases, and the stopping of the atopic march.

Keywords

Atopy prevention; Atopic march; Breast milk; Cow's milk allergy; Soy-protein formulas; American Academy of Pediatrics; Home-made; Meat-based formulas (Rezza's diet); Hydrolysate formulas; Goat and mare formulas; Amino acid-derived formulas; Genetically modified foods; Bovine spongiform encephalopathy

Introduction

For a long time has been known that every food contain potential allergens, and can thereby trigger allergic reactions in sensitized children. The first step in the management of food allergy (FA) is the identification and elimination of the triggering food. The subsequent step is the replacement with CM substitutes which should not induce the relapse of symptoms. When a food is not a necessary nutrient, it can be easily eliminated from the diet provided that the child will not be exposed to nutritional derangements. Thus, treatment of FA is necessary only when children younger than two years are affected by CMA [1].

Mother nature has provided BM as the only way of feeding human newborns, therefore in the past CMA was virtually unknown in infants. Since the turn of the century a variety of CM formulas became an always more common BM substitute when mother's milk was unavailable and other formulas have been developed in order to reduce the antigen load and the ensuing risk of sensitization. Pediatricians and pediatric allergists are bombarded with a large spectrum of information of new formulas and challenged with the flexibility necessary to choose among the armamentarium of "hypoallergenic" (HA) formulas to confront any given clinical situation [2].

The properties of an ideal substitute formula for feeding children with CMA are outlined in (Table 1). The peptides of this formula should not cross-react with CM proteins and no native protein from of the original formula should be present in the substitute formula, furthermore in making a choice for use in CMA the formula should be nutritionally adequate according to the infant's age, also taking into account the availability, the cost, and taste in order to obtain a good compliance (Table 1). CM alternatives currently available are soy proteins formulas (SPFs), Rezza's diet, CM protein hydrolysate formulas (HFs), goat and mare milks, and elementary diets [3].

Table 1: Main properties of an alternative formula

Main properties of an alternative formula	No immunogenicity (sensitizing property) between CM proteins and peptides of the alternative formula
	No allergenicity (trigger symptoms)
	Normal antigenicity
	No native proteins from which the formula derives
	Not crossreacting with CM proteins and peptides of the alternative formula
	Nutritionally adequate
	Normal availability
	Pleasant taste
	Low cost

CM = cow milk
Adapted from reference [5]

First of all we shall analyze some basic facts on the composition of infant formulas, which is a prerequisite for understanding how special formulas for feeding babies with CMA should be formulated, in addition to the nutritional adequacy, the allergenicity and the efficacy of the proposed CM substitutes. These formulas should be completely free of immunogenic and allergenic CM epitopes for feeding babies with CMA and according to recent data, also "high risk" babies, when BM is not available, for the prevention of atopic diseases and the stop of the atopic march.

Soy-protein Formulas

Since SPFs have been available for over 70 years, several long-term studies of their use for feeding babies with CMA have demonstrated normal growth and development, and a nutritional adequacy comparable to that of CM formulas, in addition SPFs are well accepted by most infants. SPFs contain purified soy proteins, the fat is a mixture of vegetable oils, and carbohydrates are represented by maltodextrins, corn, starch, or saccharose, and vitamins and minerals [4].

Recent studies done by us in babies solely SPF-fed during the first six months of life have not proved immunologic abnormality or increase in infection morbidity as formerly referred. The antibody responses to poliovirus immunization in babies fed BM, SPFs, or BM and SPFs were within normal limits. No differences in the percentage of infants who seroconverted where found by type of feeding [5] and bone mineral content is similar in infants fed SPFs and BM, thus insuring a normal bone mineralization in SPF-fed babies [6]. The daily recommended vitamin doses are added to SPFs, including vitamin D, hence problems similar to those found in preterm infants have never been found in full-term infants, and carnitine has been added to some SPFs in the same amount as that present in BM since SPFs in contrast to BM and CM, contain no intrinsic L-carnitine [5].

SPFs are used for a variety of conditions other than CMA, to prevent the atopic march in babies with atopic parents or siblings, to treat infants with CM protein, lactose and galactose intolerance, and with severe gastroenteritis. In infants suffering from atopic dermatitis (AD) with CM hypersensitivity, SPF induced a substantial amelioration also allowing a normal growth [4]. Soy allergenicity is also far from being as common as once reported [5].

Soy proteins may cause intolerance and allergy as other proteins. However, most of evidence for soy allergenicity is derived from a study supposedly demonstrating an increased antibody response to soy proteins in SPF-fed babies similar to that found to CM proteins in CM-fed babies, concluding that "soy protein is as antigenic as CM protein" [7]. We stress that only soy antigenicity was studied in this work, because not IgE but hemagglutinins to soy and to CM were measured. It is generally agreed that IgG antibodies to foods are also produced by healthy subjects, and the rate of IgG production is enhanced during infancy by an amplified uptake of macromolecules via the intestinal mucosa. These antibodies are related to the antigenicity, and not to the allergenicity of a given protein, in addition to being probably involved in inducing tolerance to oral food antigens. As a consequence, IgG antibodies to foods should not be considered harmful, but perhaps protective even more frequently than expected [4]. We deem that the allegation that soy protein is as allergenic as CM proteins are scientifically incorrect.

Regarding the true incidence of soy allergy, Sampson [8] has found that only 5% of 204 children with AD showed soy sensitivity, as demonstrated by double-blind-placebo controlled challenge (DBPCFC). In addition, 75% of the soy sensitive patients lost soy sensitivity two years later. We have found that SPFs were very effective in infants with AD due to CMA; soy sensitivity was found in about 2.5% of these patients [9]. In all studies appeared in the literature but seven [8-14] which used the challenge test, the diagnosis of soy allergy was based on clinical history and/or evaluation, SPTs, or parental reports [15-19], even by telephone [17] without confirming the diagnosis with challenge tests. The studies employing challenge tests for the diagnosis of soy allergy include 2594 subjects [8-14], and the mean reaction rate to soy in these studies is 4%. SPFs are often scarcely tolerated by infants affected with chronic diarrhea and intolerance to CM proteins. Thereby, intolerance to soy proteins may be a cause of chronic diarrhea often concurrent with CM intolerance. In 8 pertinent studies the mean prevalence was equal to 20.08 [5] but in the only study using DBPCFC the prevalence was 0 [20]. Some authors consider soy intolerance to be caused by sensitivity to soy protein. However, neither a demonstration of soy protein sensitivity nor the mechanisms of this intolerance have been demonstrated. It was documented that a SPF with lactose was useful for feeding infants with chronic diarrhoea and secondary multiple protein intolerance, including CM and soy proteins [21].

Recently the Committee on Nutrition of the American Academy of Pediatrics (AAP) has affirmed that "recognizing that soy protein is antigenic does not mean that soy protein is highly allergenic", thus "most infants with documented IgE-mediated allergy to cow milk protein will do well on isolated soy protein-based formulas" [22].

A new concern has arisen about the potential hormonal effects from exposure of SPF-fed babies to levels of phytoestrogens or isoflavones, notably in Asian countries where SPFs are largely employed since the first months of life, even in breast-fed infants [23]. Seven out of 24 male infants aged 1-4 months were SPF-fed, however the total isoflavone exposure for each infant was 6-9mg/kg body weight (b/w) per day, and phytoestrogens were found to circulate in the 7 infants at concentrations 13,000 to 22,000 higher than plasma estradiol levels found in early life [24]: the small group of infants automatically introduces the chance of a type II error in the data. In principle, even if the levels of isoflavones in CM and BM are minimal [23], it is clear that phytoestrogen concentrations are present also in individuals not consuming soy meals. Therefore such biological activity should also depend on the form in which isoflavones are present in plasma, their concentration in target cells, and the hormonal status of the organism as well [25]. In a previous study the authors have found by urinary analyses that isoflavones were regularly absorbed and metabolized by SPF-fed infants [26]. The data have been confirmed by a subsequent study, also in a small cohort, showing that neither plasma sample contained detectable free isoflavones, even after ongoing SPF feeding for more than 4 weeks [25].

In conclusion Fomon [27] summing up his 30-year studies on the use of SPFs for infant nutrition, has emphasized that less than 1% of the SPF-fed babies show adverse reactions to soy-protein, thus indicating that, atleast in children with CMA and without serious gastrointestinal symptoms, SPFs are safe. According to recent studies the natural history of soy allergy seems to be quite good [28,29]. SPFs are nutritionally adequate and well accepted and tolerated by many infants with CMA, they do not cross-react with CM proteins, do not have minute amounts of CM proteins, in addition SPFs have a lower allergenicity than CM proteins [30]. It should be taken into consideration that SPFs are less expensive and have a more pleasant taste than other CM substitutes. When soy hypersensitivity occurs, the affected infants should be offered a Rezza's diet [31,32].

Hydrolysate Formulas

CM proteins HFs have been formulated with the aim of lessening or eliminating the allergenicity of CM proteins. The use of these formulas is based on the postulate that predigested protein, when fed as amino acids (AAs) and peptides, provides nutrients in a non antigenic form. Thus, protein HFs has been classified as "HA". Since there are a variety of methods for HF preparation (e.g: enzyme hydrolysis followed by heat treatment), the MW (molecular weight) of the peptides in the final product may range from 100 to 6,000D. Progressive hydrolysis affects sequential determinants, while heat treatment eliminates conformational epitopes. These different technical procedures are necessary to obtain an acceptable palatability. The reduction of the antigenicity (peptides with very low MW) is also associated with a reduction of the palatability. The allergenicity of these formulas is dependent on several factors including the degree of digestion, post-hydrolysis processing, elimination of the enzymes used for the hydrolysis and protein source [33].

Depending on the protein source, there are four types of HFs (Table 2): bovine casein, bovine whey, soy and bovine collagen, and a whey 50% and casein 50% partly HF (Aptamil HA). HFs can be partially (pHF) or extensively (eHF) hydrolyzed. These formulas are integrated with vegetable lipids, and Alfarè, Alimentum and Pregestimil contain in addition medium chain triglycerides (MCT). All HFs contain small amount of carnitine, and are lactose free, except some formulas with lactose, e.g. a bovine whey pHF (Nidina HA in Italy, Beba HA in different European countries, and Good Start HA in USA). They are rather unpalatable (excepted the pHFs) and compliance is therefore poor.

HFs is nutritionally adequate and infants generally gain weight until they refuse the formula because of its bad taste. However, caution should be taken when these formulas are given for prolonged periods of time; no data is available on long-term nutritional assessment of infants exclusively fed with such formulas for many months [34]. Studies in animal models it have shown that HFs do not induce an IgG response nor a cutaneous passive anaphylaxis. Additionally infants fed casein eHFs during the first three months of life do not show IgG antibodies to HFs. This data strongly suggested that such formulas were not antigenic. However they do contain peptides of MW even of 6000 D, which may elicit IgE responses in predisposed infants. eHFs are considered more hypoallergenic, and pHFs less hypoallergenic and even dangerous in children with CMA [35,36]. The assay of the components of different HFs is very surprising, since whey has been found in commercial casein preparations [37,38] but not in two casein HFs (Alimentum and Nutramigen) [34], while residual casein IgE epitopes were present in all the HFs tested, Alfa-Rè, and Pregomin [39], and in a larger amount in a whey HF (Good Start HA).

Table 2: Protein hydrolysate formulas

Type	Brand Name®
Highly hydrolyzed :	Alimentum
Casein:	Nutramigen
	Pregestimil
	AlfaRé
	Prophylac/Hypolac * (ultrafiltrate)
Whey:	Pepti-Junior
	Nutrilon Pepti
	Nutrilon Pepti Plus
Soy + pig collagen:	Pregomin
Partially hydrolyzed:	Beba HA **
Whey:	Good Start **
	Nan HA **
	Nidina HA **
Casein and whey:	Aptamil HA

HA = Hypoallergenic
*, ** similar products marketed in different countries under two different brand names

MW profiles of protein HFs are an index of the extent of hydrolysis. As regards the MW distribution of some protein HFs, the Alimentum and Nutramigen products are very similar and both are very different from Good Start HA products. This one contains a considerably greater amount of peptides, greater >5,000 MW [34]. In addition it was shown that seven different HFs contain a large amount of ß-lactoglobulin (ßLG) and that the ßLG amount was 40,000 fold higher in pHFs versus eHFs [40].

Although all HFs are in a wide clinical usage for the treatment of CMA, they are also capable of inducing allergic reactions to a varying degree. For example, we first reported anaphylactic reactions in infants with IgE-mediated CMA fed HFs [41] which was subsequently confirmed by other studies [42]. Five 3 to 8 month-old infants (median 5 months) with IgE-mediated CMA experienced anaphylactic reactions when first fed a small dose of a whey HF (Alfarè). All the infants had positive skin tests (SPTs) and RAST to CM proteins and to Alfarè. Moreover, total IgE levels were (GM) 199.5+ 575.4 U/ml. then they were successfully fed with a SPF (Isomil). This data shows that whey HFs can trigger severe anaphylactic reactions in children with IgE-mediated CMA [41]. The above data agrees with the evidence that antibodies raised against a CM formula recognized epitopes displayed by peptides of some HFs, including Pregomin, Alfarè, Nutramigen, Pregestimil. The same authors showed that HFs in experimental animals in-duce cell mediated immunity, and that cross-reactivity exists also between IgE antibodies to CM and peptides of HFs in this limb of the immune response [35]. Bauer confirmed that HFs contain protein fractions which resulted in a specific IgE binding after incubation with serum samples from patients with CMA. In conclusion, albeit the proteins of HFs have been processed by heat and enzymatic hydrolysis and therefore contain peptides of lower MW than the native protein source, the peptides still have allergenic potency and can be recognized by the cell-bound IgE of a child with CMA [42]. In an elegant study, 9 out of 15 children sensitive to CM and with a positive histamine release from mixed leukocytes had a positive histamine release to atleast one of five tested HFs. The histamine release by basophils incubated with HFs in patients with IgE-mediated CMA [43] stresses that HFs still have epitopes recognized by IgE bound to basophils.

A recent study has shown that children with CMA have IgE antibodies to CM proteins and to numerous HFs [44]. In addition children with IgE-mediated CMA had positive SPT responses to both whey and casein HFs, however the wheal diameter to the whey HF was significantly larger [45]. A more recent study [46] showed that DBPCFCs with two casein eHFs (Alimentum and Nutramigen) were negative in children with documented IgE mediated CMA. However acute IgE-mediated allergic reactions to Nutramigen, Alimentum, Good Start, Ultrafiltered Good Start, and Alfaré were later reported in a 7-year-old child [47].

The only issue of the AAP Committee on Nutrition states that no published, DBPCFC study exists to support the use of whey HFs either for prophylaxis or treatment of infants with CM hypersensitivity [48]. This as yet limited clinical experience suggests that a whey HF may be a useful alternative to CM and SPFs for infants intolerant, but not allergic, to CM: however, considering the cases referred to in the literature, the use of HFs has provoked a 200 reactions, many of which IgE-mediated, 120 to casein HFs (1 case of shock, 3 of anaphylaxis, 5 of generalized urticaria, 1 apparent life-threatening event) (+ 2 localized) and 82 to whey HFs (either eHFs or pHFs) (1 case of shock, 3 of anaphylaxis, 13 systemic reactions, 2 apparent life-threatening events) [42].

(Table 3) outlines the properties of CM protein HFs: the antigenicity is lower than that of CM proteins, the allergenicity is possible and the crossreactivity with CM proteins is more common with whey HFs. Both types of HFs contain minute amounts of native CM proteins, and variable amounts of ßLG [40]. It is well known that ßLG is considered the most important allergen of CM proteins. Soy is antigenic, can be allergenic, but does not cross-react with IgE antibodies to CM. HFs are also antigenic, and more allergenic, however they do cross-react with IgE antibodies to CM. Hence SPFs should be used in babies with IgE-mediated CMA and HFs in babies with CM intolerance. All special formulas available for feeding babies with CMA are lactose-free, but this makes little sense, lactose being the major carbohydrate of BM, like in all mammalian milk.

Table 3: Properties of CM-Protein-Hydrolysate Formulas

Properties of CM-Protein-Hydrolysate Formulas	Possible cross-reactivity with CM proteins (more common with whey HFs)
	Minute amounts of native CM proteins (casein in whey HFs and vice versa)
	Possible immunogenicity (partly or whey HFs)
	Allergenicity (equal number of reactions to casein and whey HFs)
	Presence of reactive epitopes (more in whey, less in casein HFs)
	Presence of native CM proteins (more in whey, less in casein HFs)
	Nutritional adequacy not known in long term studies
	Unpleasant taste (except partly HFs)
	Cost 80% more than a CM formula (except partly HFs)

A number of studies done in genetically prone neonates have suggested using HFs for the prevention of the atopic march in the first months of life [42]. We propose two studies to decide to use or not HFs [49,50]. To investigate the immunogenicity in the IgE system of a pHF, 39 mothers of HR babies, and 39 control mothers of HR babies received daily 400ml of this product or of CM during the lactation period. At one year of age, the number of babies with IgE antibodies to CM and with total IgE levels more than 2SD for normal values for age were significantly higher in the group of babies breast-fed by mothers receiving the HF ($p= 0.02$). Thus we speculate that if a mother drinks this pHF, a large amount of immunogenic peptides are easily absorbed through the gut mucosa, thus rapidly reaching the breast and then presented to the T and B cells of her baby. This data suggests that such pHF seems to be more immunogenic in the IgE system than CM [49].

Nine exclusively breast-fed babies experienced anaphylaxis when fed a pHF. The sensitization seems to have occurred in the very first days of life as a consequence of some feeds in the Maternity Hospital with the pHF, which was given again at 6 months of life for CMA prophylaxis. While we could not prove that the infants were the targets of pirate bottles, nor we analyzed BM samples for the presence of CM proteins, we emphasize that the mothers totally avoided CM and dairy products during lactation, thus ruling out a sensitization via BM, and that although the babies were healthy during breast feeding and did not show any symptom or sign suggestive of CMA, they presented with high levels of IgE antibodies and strongly positive SPTs to the HF [50].

It follows that sensitization can be triggered by a small amount of HF when given HR babies in the very first days of life for prophylaxis of IgE-mediated CMA [49,50]. We conclude that whey HFs should not be used in infants with IgE-mediated CMA, nor casein eHFs appear to be safer than whey HFs [42]. HFs, either for the treatment or prevention of CMA should be tested in vivo and only products well tolerated by at least 90% of CMA children, using DBPCFCs, should be labelled as hypoallergenic [51]. Further trials are needed to study the nutritional adequacy of HFs in babies exclusively given such formulas for many months [52-55]. Rigo et al. [52] showed that a whey pHF induced in full-term newborns fed this product for 6 days a significant increase in plasma concentration of several essential AAs, which were greater in the babies fed the whey pHF than in those fed BM or a HF. Subsequently [53] the authors noted that at age 33 days the plasma threonine concentration remained twice as high and the plasma tyrosine, phenylalanine and proline levels were significantly lower in the whey pHF group than in the BM-fed infants. Recently the AA level alterations were confirmed, and a drastic reduction in fat Ca and P absorption with the use of a whey-casein HF was observed. In preterm infants, compared with the standard preterm formulas, HFs led to a significant increase in plasma threonine, and a decrease in several AAs [54].

Home-Made, Meat-based Formulas

CM can be substituted with commercial and home-made, meat-based formulas composed of lamb, rabbit, or chicken, and rice, vegetables, and olive oil, with varying degrees of success. In 1973 Professor Rezza of the Pediatric Department at the University of Rome, prepared a very effective lamb-based formula [31]. The composition per liter of the Rezza's diet is shown in (Table 4) [32]. The formula is prepared as follows: fresh or frozen lean lamb's meat (free of fat and tendons) is cut into small pieces, boiled and minced, then mixed with the other components of the diet. Once clinical improvement is accomplished, wheat and saccharose are first reintroduced into the diet, then various foods in sequence, with the obvious exception of CM. This diet provides 740 calories per liter and is widely recommended to infants with CMA. As a rule it is well tolerated even by toddlers with diarrhea caused by CM intolerance, is very palatable and consequently meets a good compliance. Instead of lamb's meat, chicken, or rabbit meat may be employed. Chicken and related meats should not given egg-allergic children. Bovine meat should be avoided because it may have proteins cross-reacting with CM proteins and bovine serum albumin is present both in CM and in bovine meat [31], in addition due to challenges posed by BSE.

Table 4: Composition of Rezza's Diet (HMMBF) (per liter)

Lamb Meat	100g
Olive Oil	40g
Rice Flour	70g
Table salt	2g
Water until to	1 liter
Calcium	500mg
Vitamins	As needed

Adapted from reference [32]

We have used Rezza's diet with success for the management of children with different manifestations of CMA (chronic diarrhea, AD, asthma etc). In a prospective study on 41 critically ill infants with chronic diarrhea due to CMA, 21 males and 30 females, aged one month to two years (median age three months) were fed with the Rezza's diet. Once clinical improvement was obtained, saccharose, and wheat were gradually reintroduced into the diet; then various foods in sequence. Subsequently, CM reintroduction was tested at given intervals (three to six months after diarrhea subsided) under appropriate supervision. When an infant did not tolerate CM, the diet was continued for an additional period of six to twelve months. In all children diarrhea subsided within a median time of seven days and they resumed weight within 15 days (Table 5). At the first control of a ten-year follow-up of the children, 15/40 children (one case lost to follow-up) did not tolerate CM. At a median age of 7 years, 12/37 children (four children lost to follow-up) did not yet tolerate CM. In 25/37 children, tolerance to CM was achieved by a median age of 24 months [56].

Table 5: Follow-up (to 10 years) of 41 infants with chronic diarrhea due to CMA

Clinical data	Time	No. of Cases (median)
Diarrhea subsided	7 days	41/41
Growth resumption	15 days	41/41
Tolerance to CM	24 months	25/37
Intolerance to CM	6 yrs	12/37
Other sensitivities	6 yrs	27/37

p = 0.0001

Adapted from reference [1];

We have calculated the nutritional value of Rezza's diet [31], confronting it with ESPGAN Guidelines [32] (Table 6). Rezza's diet is nutritionally adequate, has a low cost, good taste, and the added advantage of no cross reactivity with CM proteins and of no minute amount of CM proteins (Table 7) [32]. In summary, home-made meat-based formulas are very well accepted by infants and children [57-59], and are also a useful oligoantigenic diet for the diagnosis of FA [32].

Table 6: Nutritional Value of HMMBF (1973) and Comparison with ESPGAN Guidelines on Infant Nutrition (1987)

	ESPGAN (g/dl)	HMMBF
Energy (KJ)	268 - 301	310
Protein	1.2 - 1.9	2
Fat	2.7 - 4.1	4.5
Carbohydrate	5.4 - 8.2	5.9
Sodium (mEq/l)	< 12	4.3
Calcium	40	31
Vitamin B1	0.4	0.12
Vitamin B2	0.6	0.2
Vitamin PP	3	4.9

g/dl when not otherwise stated

Table 7: Properties of Rezza's diet

Properties of Rezza's diet	No cross-reactivity with CM proteins
	No minute amount of CM proteins
	Allergenicity much lower than CM proteins
	Normal antigenicity
	Nutritional adequacy not known
	Excellent palatability
	Cost 20% more than a CM formula
	Useful oligo-antigenic diet for the diagnosis of FA

Adapted from reference [32]

Goat and Mare Milk

Goat's milk is not a suitable CM substitute, even if it is now-a-days commonly sold even in supermarkets, because it contains a high percentage of proteins cross-reacting with CM proteins, in up to 100% of CMA children [60]. Generally, mare milk proteins have not epitopes in common with CM proteins, hence it could be evaluated with prudence in CMA children.

Elementary Formulas

Good results have been reported in children with CMA fed formulas composed of AAs, carbohydrates, minerals, and vitamins [57,58]; however one AA-derived formula was found to contain ß-LG in the same order of magnitude as in the HF also used, presumably owing to contamination during the manufacturing or packaging procedures [57].

Additional Risks for Children

Recently, several alimentary problems have been posed by the introduction of GMFs and the explosion of the so called mad cow (MC) danger. As regards GMFs, it is significant the consumer attitude to call them "Frankenstein food". MC has provoked much confusion, since European governments have retarded in taking significant and early steps to banish the so-called animal foods which have largely substituted the cattle vegetal forages, perhaps responsible of BSE, through the well known dioxin. Both challenges can be bypassed using the Rezza diet [32] and related meats.

Conclusion

In conclusion, primary or secondary prevention must be antigen specific that is foods for feeding babies for atopy prevention should be absolutely free of immunogenic and allergenic epitopes stemming from CM proteins. Institutions devoted to the control of foods for babies at risk of atopy should ensure careful control of these formulas in order to avoid non-appropriate food products [2]. (Table 8) [32] Resumes the pros and contras of the formulas so far analyzed. We repeat that breast is best: Firer et al. have demonstrated that low doses of CM trigger an IgE-mediated response in the recipient newborn or young infant [61-63].

Table 8: Prerequisites of an ideal CM substitute

	Soy proteins	Hydrolysates		Elementary diet	Rezza's diet	Goat's milk
		H	P			
Immunogenicity	±	+	+	no	no	+
Allergenicity	±	+	+++	±	±	++
CM proteins (ßLG)	no	+	++	no	no	++*
Nutritional adequacy	yes	?	?	?	yes	?
Pleasant taste	±	no	±	no	yes	yes
Low cost	yes	no	±	no	yes	no
Easy availability	yes	yes	yes	?	yes	±

H = highly, P = partially, ßLG = ß-lactoglobulin, * = high cross-reactivity

Adapted from reference [32]

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