

Soy formulas and nonbovine milk

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Background: Cow's milk allergy is frequently observed during the first year of life when nutritional requirements are critical. In those cases where breast-feeding is not available, a safe and adequate substitute to cow's milk should be offered.

Objective: The primary aim of this review is to evaluate the clinical use of milk derived from vegetable proteins, such as soy, or from animals such as goat, mare, or donkey, or elemental diet in children with cow's milk allergy.

Methods: MEDLINE searches were conducted with key words such as *soy*, *goat's milk*, *donkey's milk*, *mare's milk*, and *elemental diet*. Additional articles were identified from references in books or articles. Original research papers and review articles from peer-reviewed journals were chosen.

Results: Soy formulas are nutritionally adequate and can be used in children with immunoglobulin E-mediated nongastrointestinal manifestations of cow's milk allergy. Goat's milk is as allergenic as cow's milk. Mare's milk and donkey's milk may be used in selected cases of cow's milk allergy after appropriate modification to make them suitable for human infants. Elemental diets are usually restricted to the most severe cases of cow's milk allergy (ie, sensitivity to extensively hydrolyzed protein formulas).

Conclusions: Vegetable formulas obtained from soy and milk derived from other mammals, such as mare or donkey, homemade preparations, and elemental diet may represent valid alternatives for children with cow's milk allergy. Extensive clinical trials are needed on the safety profile of any alternative mammal-derived milk. The choice of alternative milk should take into account the clinical profile of the child allergic to cow's milk, particularly as concerns age, severity of symptoms, degree of sensitivity to cow's milk proteins, and any multiple food allergies.

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INTRODUCTION

Cow's milk allergy affects 2.2 to 2.8% of children in their first year of life.^{1,2} Although most children will recover by the age of 3, it is reported that up to 30% of children are still symptomatic after 4 years of age.³ As milk represents the principal nutritional source for infants, the search for a valid alternative is mandatory for the child's proper growth and well-being. Any substitute should have the key nutritional characteristics of breast milk, eg, it must be nourishing, hypoallergenic, and hypoimmunogenic. In addition, a valid substitute should also be palatable and available at low cost. Milk substitutes for infants allergic to cow's milk should meet the criteria for hypoallergenic formulas established by the American Academy of Pediatrics⁴: they should be tolerated by 90% of infants allergic to cow's milk, with a 95% confidence interval. At present, the hypoallergenic casein or whey protein formulas derived from extensive cow's milk hydrolysis are preferred. However, these formulas have several drawbacks, such as high cost, bitter taste, and the risk of cross-reactions in highly sensitive patients.⁵⁻⁷ As an alternative to such hypoallergenic formulas, in clinical practice the use of vegetable proteins such as soy, animal proteins (goat's milk, mare's-donkey's milk, lamb/chicken meat-based formulas), and elemental diet is now widespread.

SOY FORMULAS

Soy formulas currently represent a valid nutritional alternative in patients with cow's milk allergy.⁸ Several clinical studies have extensively documented normal growth, adequate protein nutritional status, and normal bone mineralization in full-term infants.⁹⁻¹¹ Some concern has been associated with the use of such preparations, however. First, these formulas contain high levels of aluminum. Although the high aluminum content has not been associated with any documented toxic effects in full-term infants, it prevents their use in preterm infants and children with renal failure.^{12,13} Second, these formulas contain two to six times the concentration of manganese with respect to cow's milk; several authors have voiced their concern about the potential long-term effects of such manganese levels on the central nervous system.⁸ Third, the presence of physiologically active substances, eg, phytoestrogens, has been demonstrated in such preparations, and their long-term effects on children are still not clear.¹⁴ Fourth, although the preparations manufactured by the specialist industry meet the children's nutritional requirements, in the absence of clearly defined regulations there are soy-based milk products readily available in "health food" stores that are often unsuitable because their calcium, vitamin, and calorie values are inadequate. There is also the problem that soy formulas may not be entirely safe from an allergologic standpoint. Some studies have documented that soy formulas contain two major allergenic peptides.^{15,16} These are contained in the conglycinin 7S and glycinin 11S fractions and are represented respectively by Gly m 1 30 kDa (a major soybean allergen in soy-sensitive patients) and 22-kDa G₂ glycinin (a major allergen). In addition, a third potentially allergenic

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peptide, the trypsin inhibitor, 80 to 90% of which is removed by the heat applied to prepare the formulas, is considered a minor allergen.

Several clinical signs have been associated with soy allergy. In the case of immunoglobulin (Ig)E-mediated symptoms, these are primarily represented by atopic dermatitis, gastrointestinal and respiratory symptoms, or anaphylaxis, although the latter has very rarely been reported.¹⁷ In contrast, in the case of non-IgE-mediated allergy, enteropathy with villus atrophy represents the most frequently observed untoward effect.¹⁸ Soy allergy has a reported prevalence varying from 3 to 40%.^{18,19} Several reasons may account for such a variability in its prevalence, including patient selection, observation period, type of study (prospective vs retrospective), diagnostic criteria, particularly the absence of double-blind, placebo-controlled food challenge (DBPCFC). The accuracy of soy allergy diagnosis is particularly intriguing, as both skin prick tests and in vitro soy-specific IgE radioallergosorbent test CAP fluorescence enzyme immunoassay (Pharmacia, Uppsala, Sweden) are of limited value.²⁰ In the case of skin prick tests, it has been reported that the positive predictive accuracy is 40.9%, whereas the negative predictive accuracy is 94.2%. Similarly, in the case of in vitro soy-specific IgE radioallergosorbent test CAP fluorescence enzyme immunoassay, the specificity is very low and the positive predictive value is 50% at 65 KU_A/L. When the prevalence of soy allergy was estimated on the basis of DBPCFC studies, it was found to be as low as 0.3% in the general population²¹ and 1.1% in a population of atopic children.²² In the case of children with food allergy, soy allergy was documented in 4 to 5% of patients with atopic dermatitis^{23,24} and 7 to 14% with cow's milk allergy.²⁰ The highest prevalence (30 to 50%) was reported in cases with non-IgE-mediated enterocolitis or enteropathies. Taken together, these data indicate that the prevalence of soy milk allergy is not as high as originally reported.

From an in vivo animal trial, soy proteins were reported to be less sensitizing than cow's milk in the passive cutaneous anaphylaxis model,^{25,26} and no fatal anaphylactic reactions were triggered in animals sensitized to soy proteins.²⁷ This situation is further confirmed by the natural history of soy allergy, where tolerance, documented by DBPCFC, is usually achieved in the majority of patients at 3 years of age, usually 2 years after a positive challenge.^{24,28,29} Finally, the recently reported cases of peanut co-allergy triggering anaphylactic reactions should be considered with caution, and further confirmation is required.³⁰ Despite the homology of the protein sequences in peanuts and soybeans, clinical studies conducted so far have shown that patients allergic to peanuts could safely eat other legumes, and that very few patients highly sensitive to peanuts had any reaction to soy. If they did, it was usually extremely mild.³¹ In a recent position paper, the American Academy of Pediatrics Committee on Nutrition³² concluded that, although they are not hypoallergenic, soy formulas can be well tolerated and safe in patients with IgE-mediated cow's milk allergy beyond 6 months of life.

However, they are not recommended in infants with cow's milk enterocolitis or non-IgE-mediated enteropathies.^{32,33}

ALTERNATIVES TO SOY FORMULAS

Several types of milk have been proposed as an alternative to cow's milk and soy formulas in daily clinical practice. They offer the advantage of a low cost and a better taste than soy or hydrolysates.

Goat's Milk

Goat's milk is usually sold in health food stores and considered by the layman as a safe cow's milk substitute. It is characterized by a protein, calcium, and energy content similar to that of cow's milk with an essential amino acid profile resembling human milk. Goat's milk lacks vitamins B12 and B9 and must be enriched with these vitamins.³⁴ Both animal and in vitro studies have documented a high cross-reactivity among goat, cow, and sheep α -caseins.³⁵ One hundred percent of weaning rats sensitized to cow's milk also reacted to goat's milk, and 50% of children allergic to cow's milk have circulating IgE antibody capable of recognizing goat proteins.³⁶⁻³⁸ Analyzing the sera of affected children by immunoblotting, no children allergic to cow's milk showed a negative pattern to goat's milk.³⁸ Using in vivo parameters of allergenic potential in 26 children highly sensitive to cow's milk, the skin prick test was found to be positive in all cases and the DBPCFC in 24 of 26 children.³⁹ However, the amount of goat's milk eliciting a reaction after challenge was significantly greater than for cow's milk, a finding consistent with the lower concentration of cross-reacting allergens in goat's milk as determined by cross-inhibition immunoblotting. Collectively, these studies suggest that in most children allergic to cow's milk, goat's milk was just as allergenic as cow's milk. A better understanding of the content of α -s-1-casein in milk from different breeds of goat showed a high genetic polymorphism of goat milk proteins; this might explain the controversial clinical results reported in the literature.⁴⁰

Mare's Milk—Donkey's Milk

Mare's milk has a composition much more similar to human milk than can be said of cow's milk.^{41,42} The protein content is low (1.3 to 2.8 g/100 mL) and it does not produce an excessive renal load of solute; the protein fraction is particularly rich in whey proteins (35 to 50%). Further, the high lactose content (5.8 to 7.0 g/100 mL) makes it pleasant to taste. As lactose is known to stimulate the intestinal absorption of calcium, this can have a favorable effect on bone mineralization in the first few months after birth. The Ca/P ratio is 1.7, which is very close to the optimal value for calcium absorption and metabolism.^{42,43} Although the distribution of di- and triglycerides in mare's milk is very similar to that of human milk, it differs from the distribution of glycerides in cow's milk. The ratio between unsaturated and saturated fatty acids is 1.32 (0.45 for cow's milk), and the ratio between polyunsaturated and monounsaturated fatty acids is 0.83 (0.08 for cow's milk).⁴³

Mare's milk also contains large amounts of linoleic and linolenic acids.⁴⁴ Several studies report that the addition of γ -linolenic acid in the human diet improves the degree of eczematous involvement of the skin in some atopic dermatitis patients.⁴⁵⁻⁴⁷ A recent study⁴⁴ evaluated the variability of fatty acid composition of and nutritional content of mare's milk obtained from a variety of breeds with a view to its potential use as a good linoleic and linolenic acid source. By capillary gas chromatographic analysis of fatty acid methyl esters, four different mare's milk pools from Trotter, Thoroughbred, Noriker, and Haflinger between 2 and 3 months of lactation, were analyzed. The linoleic and linolenic acid composition is shown in Table 1. In contrast to cow's milk content, the concentrations of linoleic and linolenic acids were found to be very high in mare's milk. These data suggest that mare's milk can also be considered a potential nutritional source in the future for children suffering from atopic dermatitis.

Businco et al⁴⁸ demonstrated the low allergenic potential of mare's milk in a population of 25 selected children with severe IgE-mediated cow's milk allergy. All the children had strong positive skin test responses to cow's milk; two children had positive skin test reactions to mare's milk, too. All children were positive to oral DBPCFC for cow's milk, but only one was positive for mare's milk. The primary structures of equine α -lactalbumin have been determined. The phylogenetic difference between equine α -lactalbumin and bovine α -lactalbumin has been shown to be related to 39- and 40-amino acid substitutions, respectively.⁴¹ These differences in the amino acid sequences of bovine and equine proteins could account for the different levels of inhibition obtained with the two types of milk tested against cow's milk as the antigen using immunoblotting techniques.⁴⁸ In fact, the epitopes relevant for IgE binding to cow's milk could be different, or even completely lacking, in mare's milk. Because the donkey has the same phylogenetic origin as the mare (Equidae), but different from that of the cow (Bovidae), donkey's milk was successfully used in nine children with multiple food allergy, including cow's milk allergy and severe symptoms (vomiting, diarrhea, shock). The results of this study suggested that the children could tolerate donkey's milk without difficulty up to an age ranging from 15 to 20 months, at which time cow's milk could be reintroduced in some patients without pathogenic sequelae.⁴⁹

The use of donkey's milk was confirmed as a safe and valid treatment in 21 children with multiple food allergies

who were sensitive to extensively hydrolyzed protein formulas.⁵⁰ In conclusion, mare's milk, and probably donkey's milk (with appropriate modifications), can be considered possible substitutes for cow's milk in children with severe IgE-mediated cow's milk allergy.

Lamb- or Chicken-Based Formulas

Lamb- or chicken-based formulas are well tolerated, home-made, sweet-tasting preparations, commonly used in children sensitive to hydrolysates or to soy, or who refuse to drink the hydrolysates. These recipes must be adjusted to meet the infant's dietary requirements (in terms of energy, fat, calcium, and vitamins), because, in the absence of regular monitoring, they could expose the patient to nutritional deficiencies.⁵¹

Elemental Diet

In some cases of severe IgE-mediated cow's milk allergy, enterocolitis syndrome, or multiple food allergies, children react even to the extensively hydrolyzed protein formulas. In such cases an elemental diet is recommended. Amino acid mixtures currently on the European market consist of nutritionally complete formulas, with carbohydrates (maltodextrins), fat (hybrid sunflower oil, soy oil, and refined coconut oil) vitamins, minerals, and trace elements. No proteins were detected in studies on an elemental formula using sensitive *in vitro* methods (enzyme-linked immunoadsorbent assay-immunoblotting). Hypoallergenicity was confirmed by *in vivo* studies with DBPCFC, and the formula was proposed as a placebo in oral challenge.⁵² Breast-fed children with multiple food allergies have developed normally on elemental formula, after the cessation of breast-feeding.⁵³ As the elemental formulas currently available are costly (two to three times the price of an extensively hydrolyzed protein formula) and unpalatable, their use should be considered only for children highly sensitive to cow's milk proteins who are also allergic to hydrolysates, ie, patients with multiple food allergies or food-protein-induced enterocolitis syndrome.

CONCLUSION

The selection of an alternative milk should take into account the clinical profile of the child allergic to cow's milk, with particular attention to age, severity of symptoms, degree of sensitivity to cow's milk proteins, and presence of multiple food allergies. Soy formulas may be considered a valid alternative to cow's milk provided their use is restricted to patients with IgE-mediated cow's milk allergy after 6 months of life in the absence of gastrointestinal symptoms.^{32,33} Milk from other species phylogenetically different from the cow could represent a suitable substitute for cow's milk. However, such milk may require appropriate nutritional modification before administration to human infants, and its safety profile should be fully carefully validated by extensive clinical trials before its use. In addition, a thorough analysis of possible homologous epitopic sequences between proteins from different types of milk is needed to determine the allergenic profile of the preparations and avoid the unnecessary expo-

Table 1. Mare's Milk Linoleic and Linolenic Composition as % of Total Fatty Acids in Different Horse Breeds at Different Feeding Levels

EFA	T	TH	N	aH	bH
C18:2n-6 (LA)	14.9	16.7	8.4	6,2	8,1
C18:3n-3 (ALA)	6.5	6.9	24.3	14,6	3,6

T, Trotter; TH, Thoroughbred; N, Noriker; aH and bH, Haflinger.

sure to inappropriate and potentially harmful milk components. Finally, the production costs of these milk substitutes should be carefully evaluated. Further studies to elucidate and characterize soy allergens are awaited with some expectation. This might lead to the genetic engineering of plants lacking specific allergenic proteins and to the production of recombinant nonallergenic proteins for use in immunotherapy or of formulas from which single allergens have been removed.⁵⁴

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