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Hypoallergenic formulas: what, when and to whom.

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Time and place: Kaunas, Lithuania, year 2019.
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1. Summary

This is a literature review, “Hypoallergenic formulas: what, when and to whom”. The aim of this study: to explore what different types of infant hypoallergenic formulas exists, when to give them and to whom. The objectives of this research are:

1. What infant formulas are used for cow’s milk protein allergy prophylaxis?
2. What infant formulas are used for cow’s milk protein allergy treatment?
3. Are there other hypoallergenic non-dairy infant formulas and what are they used for?

The method of this study: This is a literature review. Studies and articles were collected in the data base of The National Center for Biotechnology Information (NCBI). Articles related to infant hypoallergenic formulas were identified and collected using search phrases: “Infant milk allergy”, “Milk allergy”, “Milk allergy prevention”, “Milk allergy treatment”, “Infant formula”, “Hydrolyzed formula”, “Amino acid infant formula”, “Partially hydrolyzed formula”, “and Infant rice formulas ”, “ Infant soy formulas”. The articles and studies were selected for inclusion in this thesis based on their relevance on the topic and the age and language of the article. The results of this study: Sixteen studies regarding infant formulas have been included in the results of this literature review. The overall conception regarding infant formula feeding in children with CMPA are as follows: pHF are superior to standard IF when it comes to prophylaxis in children at high risk of CMPA. The first choice treatment of CMPA is the use of eHF, but AAF is also a good choice, especially in highly sensitive infants. SBIF can also be used as treatment in CMPA, but is not recommended to the same extent. Rice based IF is well tolerated in children with CMPA and could be an interesting option as first line treatment in the future. However rice based IF are very low in protein, and put the CMPA child at risk for malnutrition. No other PBB meet nutritional standards and are not an option for infant feeding. Conclusions: IFs used for prophylaxis includes pHF. The pHF can’t be used as treatment in CMPA. The first choice treatment option for CMPA is extensively hydrolyzed IF. AAF can also be used as treatment, especially in highly sensitive children. SBIF is the most accepted of the plant based formulas, and can be used as a treatment option in children with CMPA, but can’t be given to children less than 6 months old. An option for the treatment of CMA could be rice based formulas, they are tolerated of > 90 % of infants with CMA, but they need to be supplemented with proteins if they are to meet adequate nutritional values, and today they are not recommended for treatment. Other PBB are being studied, but none of them are recommended for prophylaxis or treatment.
2. Acknowledgement

To my family, especially my father Lars Karlsson, for his technical support, and to my dear friend Elise Lööw for her support and guidance.

3. Conflict of interest

The author reports no conflicts of interest
4. Abbreviations list

CMPA – cow’s milk protein allergy
CMP – cow’s milk protein
CMA – Cow’s milk allergy
CM – cow’s milk
pHF – partially hydrolyzed formula
eHF – extensively hydrolyzed formula
OIT – oral immuno therapy
pHWF – partially hydrolyzed whey formula
OFC – oral food challenge
Ig-E – Immunoglobulin E
AAF – amino acid formula
SBF – soy based formula
SBIF – Soy based infant formula
AD – Atopic dermatitis
HRF – Hydrolyzed rice formula
HRPF – Hydrolyzed rice protein formulas
SPI - Soy protein isolate
FDA - American food and drug administration
eRHF - Extensively hydrolyzed rice protein infant formula
SBS - Symptom-based score
PBB – plant based beverages
rCMF - regular cow's milk protein-based formula
IF – infant formula
kDa – Kilo Daltons (molecular weight)
ESPGHAN - European Society for Paediatric Gastroenterology Hepatology and Nutrition
LPA – Luminex-based peptide assay
5. Introduction

Milk is the key component of every mammal's diet, however not all individuals can tolerate this kind of food [1]. There has been a clear increase in life-threatening food allergies in the Westernized societies for the past generations. The cause is not fully clear but one hypothesis to explain this rising prevalence is the life-style of the twenty-first century which include higher rates of caesarian sections, overuse and misuse of antibiotics, dietary changes and an increase in formula feeding which altogether has changed the intestinal bacterial flora [2]. Cow’s milk protein allergy (CMPA) in young infants is a relatively common phenomenon. Symptoms suggestive of CMPA may be encountered in 5-15% of infants. Cow’s milk protein allergy may be divided into IgE-mediated food allergy and non-IgE mediated food allergy. Allergy to cow’s milk protein (CMP) can give rise to skin symptoms, gastro intestinal symptoms and respiratory symptoms. This allergy and these symptoms can interfere with the infant ability to thrive and its quality of life. It can even be life threatening [3].

Breast feeding is recommended for at least 6 months and for as long as the mother and the infant wish to continue. There is not consistent evidence that breastfeeding is effective as a prevention of allergic diseases [4]. When breast feeding is not sufficient or not possible, it is of high importance that there are high quality infant formulas available. Situations including premature infants, or in those in which there is a rejection to breastfeeding, require the use of infant formulas for total or partial replacement of human milk [18]. As a substitute for breast milk there are infant formulas, traditionally infant formulas (IF) are based on CMP [5], but in addition to the cow’s milk based formulas there are also formulas marketed for signs and symptoms of intolerance. For children who cannot be breastfed, hydrolyzed CM formulas has been recommended for the prevention of allergic reactions, as well as for the prevention of allergic sensitization and allergy development in high-risk children. The cow’s milk formulas differ in regards to the degree of hydrolysis of the milk proteins, as well as in the regards to the hydrolysis procedure. The formulas range from partially to extensively hydrolyzed formulas. Amino acid substitutes are available for infants that are highly allergic to CM. The pHF are supposed to contain small and larger oligopeptides with a molecular weight of <5 kDa. eHF should only contain peptides with a molecular weight of <3 kDa, and the amino acid-based formulas are made of essential and non-essential amino acids [23]. Infants on specially modified formulas should be closely monitored by medical professionals [6].
So when an infant is suffering from CMPA it raises a problem when the infant has to be formula fed, because a lot of the formulas on the market today are based on cow’s milk. Because of the relevance of CMPA and due to a need and wish for formula feeding infants, the question of hypoallergenic formulas within pediatrics is a very up to date topic in modern medicine. It is of great importance that a pediatrician is able to identify and diagnose the CMPA and it is of great importance that the pediatrician knows what different types of infant formulas are out on the market and when to give which formula to which infant, since the ultimate treatment of CMPA is avoidance and total exclusion of CMP. To get a greater understanding about CMPA and the different hypoallergenic formulas, this literature review is conducted, in order to collect information and results from previously performed studies. This review contains information about hypoallergenic formulas: partially hydrolyzed, extensively hydrolyzed and amino acid formulas, soy based formulas, rice formulas as well as some other plant based formulas. In some parts of the world goat’s milk formulas are used, but information regarding them will not be covered in this literature review.

*The aim of this study:* to explore what different types of infant hypoallergenic formulas exists, when to give them and to whom. *The objectives of this research are:*

1. What infant formulas are used for cow’s milk protein allergy prophylaxis?
2. What infant formulas are used for cow’s milk protein allergy treatment?
3. Are there other hypoallergenic non-dairy infant formulas and what are they used for?
6. Aim and objectives

The aim of this literature review: To explore what different types of infant hypoallergenic formulas exists, when to give them and to whom.

The objectives of this literature review are:

1. What infant formulas are used for cow’s milk protein allergy prophylaxis?
2. What infant formulas are used for cow’s milk protein allergy treatment?
3. Are there other hypoallergenic non-dairy infant formulas and what are they used for?
7. Methodology

A literature review has been performed to explore what different types of infant hypoallergenic formulas exist, when to give them and to whom. Which infant formulas are used for prophylaxis, which ones are used for treatment and if there are other infant formulas on the market and what are their place.

7.1 Search strategy

A literature review has been conducted and studies and articles were recollected in the database of The National Center for Biotechnology Information (NCBI). The articles related to infant hypoallergenic formulas were identified and collected using search phrases.

Search phrases:

1. Infant milk allergy
2. Milk allergy
3. Milk allergy prevention
4. Milk allergy treatment
5. Infant formula
6. Hydrolyzed formula
7. Amino acid infant formula
8. Partially hydrolyzed formula
9. Infant rice formulas
10. Infant soy formulas
### 7.2 Article selection

The selection of articles was performed from October 2018 until January 2019. When the search for articles in the data base was performed, all articles older than 10 years were removed except for 2 articles that were kept despite being older than 10 years, and this because their information regarding SBIF and HRF was considered very important and relevant. All articles that were not in English language were removed, as well as the articles without open access, and this because the inclusion criteria's were: articles not more than 10 years old, articles in English language, articles with open access. When this was done there were 504 articles remaining. 2 articles were given additionally by the supervisor, these 2 articles are also more than 10 years old, but is being used in the introduction and in recommendations due to high interest and relevant information regarding these topics. A quick screening was then performed where the title and the abstracts were briefly read. This left a number of 103 articles. The articles removed in this step were removed due to duplication or irrelevance. Articles were considered irrelevant when they did not contain relevant and up to date information regarding cow’s milk protein allergy in infants or how to diagnose CMPA in infants, how to prevent CMPA in infants or how to treat CMPA in infants. Other articles removed did not contain information or results regarding infant formulas used for prophylaxis or treatment of CMPA.
Figure 1. Flow diagram of article selection.
8. Results

8.1 Partially hydrolyzed and extensively hydrolyzed infant formulas

In “meta-analysis of the evidence for partially hydrolyzed 100% whey formula for the prevention of allergic diseases” done by Hanja Szajewska and Andrea Horvarth we can see that the use of pHF is more effective in allergy prevention for children that are at high risk for allergy, compared to standard formulas. However it also showed that there is no significant difference in outcomes between the groups who received pHF and eHF [7].

In the study “partially hydrolyzed Whey formula intolerance in Cow’s milk allergic patients” performed by Maureen Egan et al. at the children’s hospital of Colorado, all patients aged 6 months to 18 years with CMA between March and December of 2015 was invited to participate. In the study the CMA was defined as allergic reaction to milk within 6 months before study entry,, and that a milk specific IgE-level or a skin prick test was highly predictive to give a clinical reactivity. For each patient that participated in the study immune-blotting against CM and pHWF was conducted, and all the patients who participated also underwent an OFC to pHWF. The result of this study was clear; the first 10 subjects that underwent the OFC all had unfavorable reactions to the pHWF which indicates a lack of tolerance. The unfavorable reactions presented in the subjects are listed in figure 2.

![Reactions to pHWF](image)

<table>
<thead>
<tr>
<th>Reactions to pHWF:</th>
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<tbody>
<tr>
<td>Throat tightness</td>
</tr>
<tr>
<td>Itchy mouth</td>
</tr>
<tr>
<td>Hives</td>
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<tr>
<td>Cough</td>
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<td>Rhinorrhea</td>
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**Figure 2.** Allergic reactions presented in patients undergoing OFC to pHWF.

These findings support those at the time current recommendations that pHWF should not be recommended to those patients with CMA. This study also shows that the intolerance to pHWF in CMA patients is much higher than previously thought, since in this study 100% of the participants had adverse reactions to pHWF and other studies, according to the authors of the study, had shown that 40-60% of CMA patients in Europe had tolerated pHWF. The immunoblotting and the LPA that was performed in association to the study suggested that the residual casein in pHWF were the cause of the allergic reactions in the subjects [8].

In the original article “Infant milk formulas differ regarding their allergenic activity and induction of T-cell and cytokine responses” by Hochwallner et al., a blinded analysis of a total of 10 different CM formulas was performed, in regards to evaluate their biochemical and immunological characteristics. These formulas included non-hydrolyzed, partially hydrolyzed formulas, extensively hydrolyzed formulas and amino acid formula. Sera from 26 CMA patients were taken and IgE-reactivity and allergenic activity of the different formulas were tested. Assessment of induction of T-cell proliferation and secretion of cytokines in peripheral blood mononuclear cell culture from both CMA and non-allergic patients was performed. The study showed that milk formulas show major differences regarding Ig-E reactivity and allergenic activity. Almost all of the 21 subjects with CMA participating in the study showed Ig-E reactivity to the formulas that were non-hydrolyzed, and to the formulas containing whole milk whey protein and casein proteins. The study also showed that the milk formulas have different capacities to induce lymphocyte proliferation. The whole milk preparation together with the non-hydrolyzed and the pHF showed the highest lymphocyte proliferation. The pHF induced T-cell proliferation almost to the same extent as formulas containing complete allergen. The Lymphocyte proliferation was the lowest with eHF and AAF. The eHF and the AAF were the ones who also induced the least amount of allergenic/proinflammatory cytokines [9].

In the randomized controlled trial “Oral immunotherapy using partially hydrolyzed formula for cow’s milk protein allergy: a randomized controlled trial” by Dr. Chisato Inuo et al., 3 formulas were used; a pHF, an eHF and a rCMF. The participants who all had a known
history of systemic symptoms induced by ingestion of small amounts of milk allergens or with high values of cow’s milk-specific IgE were divided into 2 double-blind groups. A pHF-pHF group and an eHF-pHF group. Participants in both groups underwent food challenges 3 times using pHF, eHF or rCMF. This was taken place in a hospital ward, on 3 separate days with a 1-week interval between the challenges. A total volume of 20 ml of pHF, eHF or rCMF was administered every 30 min in 5-7 installments. Participants who were unable to consume 20 ml of rCMF received OIT. The participants who were able to tolerate 20 ml of rCMF without presenting symptoms were excluded. Blood samples were collected from the participants <2 weeks before the food challenge at baseline and < 1 week after each phase. The participants serum cow’s milk-specific or casein-specific IgE and IgG antibody levels were determined, and the participants basophil activation test was also performed. 20 participants completed the treatment in this study (10 in the pHF-pHF group and 10 in the eHF-pHF group). The median casein-specific IgE into body level at the end of the trial was lower than at the baseline in the eHF-pHF group ($p = 0.014$), but not in the pHF-pHF group ($p > 0.05$). In both groups, milk-specific IgE and IgG, casein-specific IgG, and casein-specific basophil activation levels in participants did not change between phases. The result of the study suggests that OIT associated with the intake of pHF in a safe manner can improve the tolerance to CM in children with CMPA, relative to that with eHF intake. The findings indicate that OIT increased the amount of milk that could be tolerated without systemic allergic symptoms. OIT with pHF is thus a potential option for therapeutic use in children with CMPA [10].

8.2 Amino acid based formulas

According to Burs AW et al. in “Synbiotics-supplemented amino acid-based formula supports adequate growth in cow’s milk allergic infants”, children suffering from CMA run a risk of inadequate growth and nutritional intake, thus a suitable formula for the allergic infant should not only be hypoallergenic, but also need to ensure adequate growth. In a randomized, double blind controlled study infants diagnosed with CMPA were given AAF with or without probiotics. And it showed that both groups of infants demonstrated adequate growth according to weight and length as shown in figure 3, where we can see weight-for-age and length-for-age z-score over time, calculated by using WHO 2006 growth standards. The study also showed that AAF (either with or without probiotics) is safe and suitable for the dietary management of CMA. [11]
**Figure 3.** Weight-for-age (a) and length-for-age (b) Z-scores over time. Z-scores were calculated by using the WHO 2006 growth standards. Values are given as mean ± SEM.


In the 12-months long multicenter randomized control trial “Amino Acid-based Formula in Cow’s Milk Allergy: Long Term Effects on Body Growth and Protein Metabolism” performed by Roberto Berni Canani et al. children with CMA were treated with either AAF or eHWF. The growth and protein metabolism of the children included in the study were comparatively evaluated and it showed that the long term use of AAF in children with CMA is able to stimulate a growth pattern similar to the growth pattern in children with CMA that are given eHWF. It shows that long term treatment with AAF is safe and allows adequate growth in children with CMA. The study shows that both eHWF and AAF is suitable for the treatment of CMA and the choice between the two should rely mainly on clinical consideration [12].

In “Evaluation of an Amino Acid-Based Formula in Infants Not Responding to Extensively Hydrolyzed Protein Formula” by Jon Vanderhoof et al., one can read that most infants with CMA responds well and demonstrates clinically improvement when given an eHF, however highly sensitive infants may require and AAF. In the observational prospective study, 30 infants with CMA with continuing persistent allergic manifestations and weight loss despite treatment with eHF where given an AAF instead, this for a period of 12 weeks. After the 12 week period
mean weight gain improved, as well as improvement in many allergic symptoms, including a significant decrease in atopic dermatitis (AD) severity. 8 of the infants who demonstrated watery stools on visit one during the study had recovered after the 12 weeks of AAF feeding. The results of the study thus indicate that new AAF supports healthy weight gain and improvement of the allergic manifestations in infants with CMA and not responding to treatment with eHF [13].

"In cow's milk protein allergy – suspected infants not responding to extensively hydrolyzed formulas, the initiation of amino acid-based formula improved growth following a 12-week feeding period. Atopic dermatitis and gastrointestinal complications were also significantly reduced after amino acid-based infant formula feeding." [13]

8.3 Soy and rice based formulas

As one can read in “Soy- and Rice-Based Formula and Infant Allergic to Cow’s Milk” by Flora Tzifi et al. today eHF is the first choice recommendation for the treatment of CMA in infants and children that are not breastfeeding. But taking in to account the cost of eHF the grain-based formulas could possibly be an option. Rice and soy-based formulas are the only grain-based formulas that have been extensively studied. The use of soy milk formula has limited medical indications when it comes to infant feeding. However before the introduction of the eHF the soy-based formula was the main alternative for feeding a child with CMA, unless the child was breastfeeding. The use of soy-based formula has been restricted in the treatment of CMA due to the fact that children can have a soy allergy or a concomitant soy allergy together with the CMA. Hydrolyzed rice formulas (HRF) is an interesting alternative option for the treatment of CMA in infants in regards that HRF meets the current guidelines that a therapeutic formula has to be tolerated by at least 90% of infants with CMA, however there is a big concern regarding the nutritional value of HRF due to the low levels of protein concentration. This concern rise from the fact that rice milk is extremely poor in its protein content and that in a case study involving 4 infants the use of rice milk formula for a duration of 5-13 months resulted in severe malnutrition that exposed itself as hypoalbuminemia and poor weight gain in 3 of the 4 infants, and multiple secondary infections in the 4th one. This malnutrition was a result of a daily protein intake of just 25% of the daily dietary allowance [14].
Also in “The effect of a partially hydrolyzed formula on rice protein in the treatment of infants with cow’s milk protein allergy” by Reche M et al. we can learn that hydrolyzed rice protein infant formulas (HRPF) have become available as a treatment option for children with CMA, they have also been shown to be well tolerated. In a prospective open randomized clinical study the clinical tolerance of a new experimental HRPF was compared to the clinical tolerance of an eHF. In the study the HRPF was well tolerated by infants with moderate to severe symptoms of IgE-mediated CMPA. In figure 4 we can see the number of infants allergic to CMP over time after being fed HRPF compared to infants being fed eHF, and in figure 5 we can see CMP-specific IgE in infants being fed HRPF compared to infants fed with eHF, in both cases p is not significant. The ones who did receive the new experimental HRPF also showed similar growth and development compared to those who received an eHF as shown in figure 6, 7 and 8. Here weight for age-, height for age-, and weight for height z-scores in infants being fed HRPF are compared to those infants being fed eHF, and in all 3 p is not significant. But to be noticed is that the HRPF was supplemented with lysine and threonine to improve the nutritional value of the similar to that of normal breast milk. According to the results of that study the HRPF could provide an adequate and safe treatment alternative to eHF in infants with CMPA [15].

Figure 4. Number of infants allergic to CMP over time. p = not significant.

**Figure 5.** CMP-specific IgE (who did not become tolerant to CMP). *p* = not significant.


**Figure 6.** Weight for age *z*-scores. *p* = not significant.

Figure 7. Height for age z-scores. $p = \text{not significant.}$


Figure 8. Weight for height z-scores. $p = \text{not significant.}$


In “Safety of Soy-Based Infant Formulas Containing Isoflavones: The clinical Evidence” by Russell J. et al. one can see that soy based infant formulas have a long history of safe use in the United States and around the rest of the world. The first soy milk based formula contained soy flour and was introduced over 100 years ago, however soy protein isolate (SPI) replaced soy flour almost 45 years ago. This makes SPI the primary source of soy-protein in soy based infant formulas (SBIF) worldwide. The safety and efficacy of SBIF has been
questioned. But SBIF are well-recognized as a healthy alternative to human breast milk and cow’s milk. It has a long history of safe use. SBIF is a high quality, plant-based protein alternative for infant formula. Recent in depth reviews of the safety of dietary isoflavones in soy have found that there is no conclusive evidence from animal or human adult of infant populations that indicates that dietary isoflavones may adversely affect human health development or reproduction. Comprehensive literature reviews and clinical studies of infants fed SBIF have resolved questions or raised any clinical concerns with respect to nutritional adequacy, sexual development, neurobehavioral development, immune development, or thyroid disease. SBIF provides complete nutrition that adequately supports normal infant growth and development. American food and drug administration (FDA) has accepted SBIFs as safe for use as the sole source of nutrition. Although large prospective or retrospective long-term studies involving more than a few hundred infants fed SBIF are lacking, the available evidence indicates that SBIF is safe [16].

In the article “An extensively hydrolyzed rice protein-based formula in the management of infants with cow’s milk protein allergy: preliminary results after 1 month” by Yvan Vandenplans et al. we can also learn that eHF are the first choice in the treatment of CMPA, but these formulas are not available everywhere, they are expensive, have a bad palatability and some infants are even still allergic to the CM peptides present in the hydrolysate. SBIF has been proposed as a second option, but the negative perception of the high levels of phytoestrogens and the fact that ESPGHAN recommend that soy-based formulas should not be given to infants <6 months of age hampers their use, and in addition to this, 10-15 % of infants that are allergic to CM also don’t tolerate soy. And in these cases an extensive rice protein based formula is shown to be effective in the treatment of CMPA. If future studies will confirm the efficacy and acceptability of rice based infant formulas, it may even become a first choice option for treatment of CMPA since rice is much cheaper and has a better palatability than cow’s milk based extensive hydrolates, and since it does not contain estrophytogens [17].

According to “Safety and tolerance of a new hydrolyzed rice protein-based formula in the management of infants with cow’s milk protein allergy” by Yvan Vandenplans et al. extensively hydrolyzed rice protein infant formula (eRHF) has recently become available and could offer a valid alternative to eHF in the treatment of CMPA infants. A prospective study was performed to evaluate the hypo-allergenicity and safety of a new eRHF in infants with a confirmed CMPA. The infants were fed the study formula for 6 months and the clinical tolerance to the eRHF was evaluated with a symptom-based score (SBS) and growth (weight
and length) was monitored. 40 infants with a mean age of 3.4 months, (range 1-6 months) with confirmed CMPA according to an OFCT were enrolled. The symptoms included in the SBS were crying, regurgitation, stools, dermatological symptoms and respiratory symptoms. All the infants tolerated the eRHF and the SBS significantly decreased as of the first month of intervention. Moreover the study showed that eRHF allowed a catch up to normal weight gain as of first month as well as a normalization of the weight for age, weight for length, and BMI z-scores within the study period of 6 months. So in conclusion the study showed that in accordance with current guidelines, the new eRHF was tolerated by > 90 % of children with proven CMPA with a 95 % confidence interval which means that the new eRHF used in the study is a safe and adequate alternative to the cow’s milk based eHF [19].

"In occurrence with current guidelines, this eRHF is tolerated by more than 90 % of children with proven CMPA with a 95 % CI, and is an adequate alternative to cow’s milk –based eHF” [20].

A prospective, randomized, single center (San Paolo Hospital, Milan, Italy) clinical trial was designed and performed by E D’auria et al. to assess if a rice hydrolysate formula allows normal growth and adequate metabolic balance in infants with CMPA. The result was presented in the article “Nutritional Value of a Rice-Hydrolysate Formula in Infants with Cow’s Milk Protein Allergy: a Randomized Pilot Study”. Infants (7 females, 9 males; age 6-14 months) were randomly assigned to receive a rice hydrolysate formula (n = 8) or a soy formula (control group, n = 8). During a treatment period of 6 months standardized growth indices (z-scores) and biochemical parameters were evaluated. During the 6 months, infants of both groups showed normal growth patterns and no adverse reactions. Mean plasma biochemical markers were within normal ranges and they did not differ between the groups. In conclusion the study showed that rice hydrolysate formula can be a nutritionally suitable alternative for infants with CMPA [20].

8.4 Plant based beverages

In the article “The nutritional limitations of plant – based beverages in infancy and childhood” by I. Vitoria the composition of 164 brands of plant based beverages (PBB) marketed in Spain was reviewed (54 soy beverages, 24 rice beverages, 22 almond beverages,
31 oat beverages, 6 coconut beverages, 12 beverages from other miscellaneous plants [barely, canary grass, hazelnut, hemp, macadamia nut, sesame or spelt] and 15 mixed PBBs [rice and almond, coconut, hazelnut or quinoa, and oat with coconut or almond]). The composition of PBBs was compared to the recommended composition of infant formula and soy infant formula and to the composition of cow’s milk. The results of the study showed that in 43 of the 54 brands of soy beverage the calorie provision was less than 60 kcal/100 ml. Protein content was 2.1-3.8 g/100 ml. 43 brands were supplemented with calcium and 23 of those was also supplemented with vitamin D. 25 of the soy beverages was also supplemented with other vitamins, especially with B₂, B₁₂ and A. Only 2 of the soy beverages were supplemented with minerals such as iron. The composition of 24 brands of rice beverages had a mean calorie content of 56.8 ± 6.3 kcal/100 ml, with a range from 47 – 68 kcal/100 ml, a low mean protein content of 0.3 ± 0.2 g/100 ml and low fat levels (0.8-2 g/100 ml). Of the 24 brans of rice beverages, only 8 of them specified added amounts of vitamin D. The percentage of energy provided by proteins was less than 3% in most cases. The composition of 22 almond based beverages showed to be hypo caloric and hypo proetic compared to infant formula and cow’s milk. Mean calorie provision was 40.2 ± 14.3 kcal/100 ml, and equal or less than 60 kcal/100 ml in 19 of the 22 brands studied. Protein content was 0.3 – 1.6 g/100 ml. Carbohydrate content was intermediate between soy and rice beverages. Of 22 brands, only 5 were supplemented with calcium and vitamin D. The group of oat, coconut and miscellaneous consisted of 49 brands. Mean calorie content was 44.9 ± 10.7 kcal/100 ml (range 15 – 65), mostly at the expense of carbohydrates (mean value 6.9 ± 2.5 g/100 ml, range 2 – 11) and to a lesser extent of fats (mean value 1.4 ± 0.8 g/100 ml, range 0.1 – 3.6). Mean protein content was low but not as low as for rice beverages (mean value 0.7 ± 0.2 g/100 ml, range 0.1 – 1.4). Only 13 of these 49 beverages were supplemented with calcium and vitamin D. As shown in figure 9, the group of 6 coconut beverages had the lowest calorie content of the PBBs (mean value 33.8 ± 15.1 kcal/100 ml) and a protein content similar to rice beverages (0.2 ± 0.2 g/100 ml). The mixed group of beverages included 15 brands. The composition of the 12 beverages that contained rice had higher calorie content at the expense of carbohydrates and to a lesser extent of proteins than mixed oat beverages. In figure 10 we can see the nutritional composition of cow’s milk and the recommended composition of soy formula and infant formula.
Figure 9. Nutritional composition of plant-based beverages. * = Miscellaneous beverages are from other miscellaneous plants (barley, canary grass, hazelnut, hemp, macadamia nut, sesame or spelt. ** = Mixed beverages are rice and almond, coconut, hazelnut or quinoa, and oat with coconut or almond.


<table>
<thead>
<tr>
<th>Plant-based</th>
<th>Number of brands</th>
<th>Kcal/100 ml (range)</th>
<th>Carbohydrates g/100 ml (range)</th>
<th>Fats g/100 ml (range)</th>
<th>Proteins g/100 ml (range)</th>
<th>Protein energy/Total energy (%)</th>
<th>Calcium</th>
<th>Vitamin D</th>
<th>Other minerals</th>
<th>Other vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy</td>
<td>54</td>
<td>46.7 ± 13.1 (27-60.7)</td>
<td>4.3 ± 2.9 (0.1-11.8)</td>
<td>1.8 ± 0.4 (0.9-2.8)</td>
<td>3.1 ± 0.4 (2.1-3.6)</td>
<td>28.0 ± 6.9 (20.0-42.0)</td>
<td>42</td>
<td>23</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Rice</td>
<td>24</td>
<td>50.8 ± 6.3 (47-69)</td>
<td>11.5 ± 1.5 (9.6-14.2)</td>
<td>0.9 ± 0.1 (0.6-2)</td>
<td>0.3 ± 0.2 (0.1-0.8)</td>
<td>2.4 ± 1.4 (0.8-6.4)</td>
<td>9</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Almond</td>
<td>22</td>
<td>40.7 ± 14.3 (25-74)</td>
<td>4.4 ± 2.5 (0.1-10.5)</td>
<td>2.0 ± 0.8 (1.1-2.8)</td>
<td>0.8 ± 0.5 (0.3-1.6)</td>
<td>8.0 ± 2.5 (4.3-12.0)</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Cat</td>
<td>31</td>
<td>45.3 ± 8.3 (30-66)</td>
<td>7.5 ± 1.7 (4.4-11)</td>
<td>1.1 ± 0.4 (0.6-1.8)</td>
<td>0.9 ± 0.3 (0.3-1.4)</td>
<td>8.3 ± 3.1 (5.3-13.7)</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Coconut</td>
<td>6</td>
<td>30.8 ± 10.1 (15-50)</td>
<td>4.3 ± 2.5 (2.0-9.1)</td>
<td>1.8 ± 1.1 (0.1-3.2)</td>
<td>0.7 ± 0.2 (0.1-0.5)</td>
<td>3.0 ± 1.9 (1.2-6.3)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous *</td>
<td>12</td>
<td>48.1 ± 10.2 (29-69)</td>
<td>6.0 ± 3.0 (2.2-10.5)</td>
<td>2.2 ± 0.8 (1-3.0)</td>
<td>0.7 ± 0.3 (0.4-1.1)</td>
<td>6.4 ± 2.6 (5.5-7.1)</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mixed **</td>
<td>15</td>
<td>61.3 ± 13.0 (36-86)</td>
<td>10.7 ± 2.7 (5.2-14.5)</td>
<td>1.6 ± 0.7 (0.8-3.1)</td>
<td>0.6 ± 0.4 (0.3-1.8)</td>
<td>8.5 ± 3.3 (2.5-10.4)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 10. Nutritional composition of cow’s milk and recommended composition of soy formula and infant formula.


In this study by I. Vitoria a review of nutritional diseases associated with primary intake of PBBs was also performed. She found 30 clinical cases associated with consumption of soy, rice or almond beverages. A characteristic association between soy beverages and rickets, rice beverage and kwashiorkor and almond-based beverage and metabolic alkalosis was found. In summary the study showed that PBBs are inappropriate alternatives to breast milk, infant formula or cow’s milk in the 1st year of life as they are low in calories, proteins, fat, lactose and vitamins. In the case of older children with nonexclusive feeding with PBBs, the pediatrician should be aware of the nutritional risks and the limitations of these beverages in order to complement the deficiencies with other foods. Nearly exclusive consumption of any PBB is associated with a specific type of disease. Therefore, soy beverage not supplemented with vitamins or minerals primarily cause rickets and failure to thrive. Rice beverages
primarily cause kwashiorkor, associated with failure to thrive and anemia. Almond beverages can cause severe metabolic alkalosis, though cases of rickets, hyperoxaluria or scurvy have also been reported [21].

A chart review on three patients treated for protein malnutrition in association with multiple diagnosed food allergies that result in refractory eczema revealed adverse outcomes that resulted from elimination diets, performed by Michael D. Keller et al. is presented in the article “Severe malnutrition resulting from use of rice milk in food elimination diets for atopic dermatitis”. It shows that other milk products such as rice and almond milk are insufficient protein sources for children less than 2 years of age. The use of rice milk resulted in hypoalbuminemia and poor weight gain in all cases, and multiple secondary infections in one patient.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at onset of hypoproteinemia (mos)</th>
<th>Length of elimination diet (mos)</th>
<th>Albumin at presentation (g/dl)</th>
<th>Absolute eosinophil count</th>
<th>Infectious complications</th>
<th>Other complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>6</td>
<td>1.6</td>
<td>420–539</td>
<td>Bacteremia: Pseudomonas aeruginosa</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>4</td>
<td>1.2</td>
<td>265–1065</td>
<td>Herpes: Herpes simplex virus</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>5</td>
<td>2.0</td>
<td>104–102</td>
<td>Fungemia: Candida albicans</td>
<td>Left tibial fracture</td>
</tr>
</tbody>
</table>

**Figure 11.** Patient characteristics and complications of elimination diets.

*Michael D. Keller et al. Severe malnutrition resulting from use of rice milk in food elimination diets for atopic dermatitis. Division of Allergy & Immunology, The Children’s Hospital of Philadelphia, 2012.*

As demonstrated by these cases shown in figure 11, elimination diets in the absence of nutritional counseling can lead to severe malnutrition and associated complications. In all three cases the malnutrition resolved on elemental formula, and their eczema was managed via topical treatments. In case of eczema worsened by food allergy, careful dietary management is essential for preventing malnutrition. Alternatives to cow’s milk such as rice or almond milk, in spite of fortification, are not a sufficient protein source. The recommended protein intake for children aged 0-6 months is 1.5 g/kg, 1.2 g/kg for children aged 7-12 months, and 1.1 g/kg/day for children aged 1-3 years. Hydrolyzed or elemental formulas provide a safe alternative for children allergic to cow’s milk or soy [22].
9. Discussion of the results

Studies show that pHF are more effective in allergy prevention for children that are at a high risk for CMPA when compared to standard IF, and thus they can be used as a prophylaxis. However studies have also shown that there is no significant difference between pHF and eHF in the area of CMPA prophylaxis [7]. In a randomized control trial where a pHF, an eHF and a rCMP were used on participants who all had a known history of systemic symptoms when ingesting small amounts of CM and/or had values of CM-specific IgE, the results suggest that OIT associated with the intake of pHF in a safe manner can improve the tolerance to CM in children with CMPA [10] thus this is also a suggestion that pHF can be used as a prophylaxis in children at high risk of CMPA, it might even suggest that pHF can be used as a treatment, however other studies suggest different. Since the studies show that children who are being formula fed and are exposed to pHF can develop an improved tolerance to cow’s milk protein, these should be the formulas used for the prophylaxis of CMPA.

Studies has also shown that infants who are diagnosed with CMPA by showing adverse reaction when ingesting CM and also having specific IgE-levels to suggest CMPA all had unfavorable reactions to pHWF, these unfavorable reactions included throat tightness, itchy mouth, hives, cough, rhinorrhea which indicates a lack of tolerance. These findings support the current guidelines of today that pHWF should not be recommended to infants with CMPA and therefore can’t be used as a treatment. It also shows that intolerance to pHWF in CMPA infants is much higher than previously thought, since 100 % of participants had adverse reactions to pHWF. Other studies had shown a tolerance in about 40-60% of CMPA patients in Europe when exposed to pHWF. In conclusion we can say that since the children with a diagnosed CMPA all had symptoms of various degrees when ingesting pHWF a treatment of CMPA must exclude CMP and a pHWF can’t be used for treatment, but only the eHF. The study showed that participants reacted to the residual casein in pWHF and this was the reason of the allergic reactions [8]. In another study the biochemical and the immunological characteristics of 10 different IFs was performed and the result showed that the formulas shows major differences regarding IgE reactivity and allergic reactivity. It showed that partially hydrolyzed formula induced T-cell proliferation to almost the same extent as formulas containing the whole allergen, and this shows partially hydrolyzed formulas cannot be used as a treatment in infants with CMPA. Lymphocyte proliferation was
the lowest with extensively hydrolyzed formulas and amino acid formulas, and they also produced the least amount of allergenic/proinflammatory cytokines of the formulas compared, thus they can be used as treatment of CMPA [9]. Also this study shows that we can draw the conclusion that pHF can’t be used as treatment option for children with CMPA, since they reacted as strongly to the pHF as to formulas containing the whole allergen.

According to most studies eHF should be the first line treatment in infants with CMPA [13] [14][17][20], and although most infants with CMPA responds well and demonstrates clinical improvement when given an eHF, there are some highly sensitive infants who still exhibit adverse reaction even when fed eHF, for those children AAF is an option [13]. Children suffering from CMPA run a risk of inadequate growth and inadequate nutritional intake, and therefore an IF doesn’t only have to be hypoallergenic, it also need to ensure adequate growth and nutritional value [11]. Studies has shown that infants with CMPA who are being fed an AAF have shown adequate growth according to weight, length, and head circumference, it has also shown that AAF is safe and suitable for the dietary management of CMPA. It has been shown that CMPA infants fed with AAF long term have showed growth patterns and protein metabolism similar to that of infants who has been fed eHF [11] [12]. Infants who could not tolerate even eHF who were given an AAF instead all showed an improvement in mean weight gain as well as improvement in many allergic symptoms, including a significant decrease in AD severity, this after only 12 weeks [13]. Thus both eHF and AAF are suitable for the treatment of CMPA and the choice between them should rely mainly on clinical consideration [11] [12] [13].

SBIF have a long history of safe use and the first soy milk based formula contained soy flour and was introduced over 100 years ago, however soy protein isolate replaced soy flour almost 45 years ago and is now the primary source of soy protein in soy based infant formulas [16]. Before the introduction of eHF, soy based infant formulas was the main alternative for children with CMPA who were not breastfeeding [14]. Comprehensive literature reviews and clinical studies have shown that SBIF is a high quality, plant-based protein alternative for infant formulas. They support normal infant growth and development [16]. However the use of SBIF has been restricted in the treatment of CMPA due to the fact that children with CMPA can also have a soy-allergy or a concomitant soy-allergy together with the CMPA [14]. Another reason to why SBIF are being questioned as a second option to eHF other than the fact that 10-15% of children with CMPA also have a soy-allergy is the fact that they can contain high levels of phytoestrogens and that according to ESPGHAN SBIF should not be given to children <6 months of age [17].
These facts give rise to the interest to find other options to the eHF, and this is where the question about the efficacy, tolerance and safety of RBIF comes to mind. RBIF has recently become available and could be a good alternative to eHF [19], since they are cheaper and have a better palatability compared to eHF [17], but studies shows different result regarding the safety of RBIF. The hydrolyzed rice formulas meet the current guidelines that a therapeutic formula has to be tolerated by at least 90 % of infants with CMA, however there is a big concern in regards to their nutritional value [14] [15]. One study showed that 3 out of 3 infants fed rice formula as an elimination diet all suffered from malnutrition that took expression in hypoalbuminemia, poor weight gain and multiple secondary infections [22], as where other studies showed that all of the participants included in the study met growth criteria and nutritional criteria [19] [20]. But studies has also shown that if the hydrolyzed rice formula is supplemented with lysine and threonine, it increases its nutritional value to be similar to that of normal breast milk, and in those cases hydrolyzed rice formula could be a very good treatment alternative to eHF [15], if future studies will confirm the efficacy and acceptability of rice based infant formulas, it may even become a first choice option for the treatment of CMPA [17]. One study that explored the nutritional limitations of PBB, 164 different PBB were evaluated and the results showed that the 3 formulas that meet the nutritional criteria and can be used for infants are traditional infant formulas, cow’s milk formulas (extensively hydrolyzed and partially hydrolyzed) and soy infant formulas. This study also found that certain nutritional diseases are associated with different types of PBB. Soy beverages that are not supplemented with vitamins or minerals are primarily associated with rickets and failure to thrive. Rice beverages primarily cause Kwashiorkor, failure to thrive and anemia and almond beverages can cause severe metabolic alkalosis [21]. Based on these facts, in the market of PBB the most accepted one is SBIF, but upcoming is also RBIF although RBIF is not meeting the nutritional criteria due to the low amount of protein content, and should therefore be supplemented with proteins.

One can say that partially hydrolyzed infant formulas are well suited for prophylaxis of CMPA and that extensively hydrolyzed formulas and amino acid formulas are well suited for the treatment of CMPA. The most accepted plant based infant formula is the soy-based formula, although it has its limitations and cannot be given to children <6 months of age. As of today rice-based formulas or other plant based formulas are not recommended for either treatment or prophylaxis of CMPA.
10. Conclusions

1. - Infant formulas used as prophylaxis of CMPA include pHF and in some cases eHF.

2. - The first choice treatment option for CMPA today is eHF.
   - AAF can also be used as treatment of CMPA, especially in highly sensitive children that still exhibit symptoms of allergy despite being fed with eHF.

3. - SBIF is the most accepted one of the plant based formulas, and can be used as a treatment option in children with CMPA, however children with CMPA can also be allergic to soy and therefore AAF is the better choice, it is also more nutritionally suitable compared to SBIF.
   - An upcoming option for the treatment of CMA is the rice based formulas, they are tolerated of > 90% of infants with CMA, however they need to be supplemented with proteins if they are to meet adequate nutritional values, and the rice based formulas are not yet fully accepted as a treatment option.
   - Other PBB (almond beverages, oat beverages, coconut beverages and beverages from other miscellaneous plants, as well as mixes of them) are being studied, but so far none has been found to be adequate to meet nutritional criteria, and further investigations and studies needs to be performed in that area.
11. Practical recommendations

If an infant is suspected to suffer from CMPA, which is based on history and examination, then strict allergen avoidance is initiated. In some circumstances such as a clear history of immediate symptoms, a life-threatening reaction together with a positive test for CMP-specific IgE, the diagnosis of CMPA can be made without an OFC. But in all other circumstances than the mentioned, a controlled OFC that is either open or blind must be performed. This OFC must be performed under medical supervision, and it’s done to either confirm or exclude CMPA.

If the infant with confirmed CMPA is breast-fed, the mother should start a strict CMP-free diet. If the infant is not breastfed and is confirmed suffering from CMPA, he should receive an extensively hydrolyzed protein-based formula. Amino acid based formulas are reserved for certain situations, and can be given to infants who still suffer from adverse reaction even under the treatment with an eHF. Soy protein formula, if tolerated, is an option, but only beyond 6 months of age. Nutritional counseling and regular monitoring of growth are mandatory in all age groups requiring CMP exclusion. In figure 12 we can see the algorithm for infants and children with symptoms suggestive of CMPA.

Infants that are confirmed having a CMPA and are being treated with an exclusion diet should be reevaluated every 6 to 12 months. This is to assess if they have developed a tolerance to CMP. This is achieved in >75% by 3 years of age and >90% by 6 years of age. Inappropriate or overly long dietary eliminations should be avoided because such restrictions can impair the quality of life of the child and its family. Unnecessary elimination diet can also interfere with the child’s ability to thrive and also be a reason of unnecessary health care costs [24].
Figure 12. Algorithm for infants and children with suspected CMPA.

Literature list


4. Australasian society of clinical immunology and allergy, ASCIA guidelines – infant feeding and allergy prevention 2016. Website: www.allergy.org.au Email: info@allergy.org.au Postal address: PO Box 450 Balgowlah NSW Australia 2093.


