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Milk hypersensitivities: where is the grey line regarding their dietary management?

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Summary
The proportion of people suffering or reporting to have a hypersensitivity caused by cow's milk consumption is increasing, and even health professionals often face difficulties into elaborating properly with a milk reaction due to misdiagnosis. The scope of this review is to present literature data that lead into putting the border line between cow's milk allergy and cow's milk intolerance, mainly focusing on how the different pathophysiology leads to their different dietary diagnosis and management.

Introduction

According to the European Academy of Allergy and Clinical Immunology (1) any adverse reaction to food is called food hypersensitivity. Non-toxic adverse reactions to foods are divided according to the implication or not of the immune system into food allergies and food intolerances. Apart from these, reactions to toxic substances and psychological reactions also belong into the adverse reactions to foods.

Despite the clear differentiation of their pathophysiological mechanisms, food allergies and intolerances very often confuse people thinking themselves as sufferers of food hypersensitivity, without being able to confirm this by proper diagnostic examination, food exclusion and food challenges or reintroduction of the offending food. Additionally, in the clinical practice often food allergy and intolerance are misdiagnosed, due to the time delay between ingestion and symptoms and insufficient diagnostic tools. On the other hand, food allergies and intolerances, when not diagnosed and managed properly, can affect growth or nutritional status significantly, in some cases can be life threatening, but also can reduce significantly the quality of life of the sufferers (2).

Overall, milk hypersensitivities are common, with milk being the major trigger of allergic reactions in childhood (2-3%) (3,4), but also lactose intolerance affecting a high proportion of adults, reaching the incredible number of 80-95% the UK and Germany (5).

This review aims to put the borderline of different types of milk hypersensitivities in order to ensure the appropriate dietary management further to proper medical diagnosis and treatment.

Materials and methods

A literature search was performed on PubMed, ScienceDirect, Springerlink, The Cochrane Library. Articles with evidence and recommendations regarding the phenotype (characteristics) and

dietary management of specific on cow's milk related hypersensitivities published up to December 2014 were collected.
Search terms included "cow's milk allergy", "lactose intolerance", "IgE-mediated", "non-IgE mediated", "Dietary management", "Growth", "Elimination diet", "Calcium", "Vitamin D".

Cow's milk allergy (CMA)

Following the general terminology of food allergy, CMA is any reaction caused after milk consumption that triggers the immune system. The main cow's allergens are casein (αs1-, αs2-, β-, and κ-casein) and whey homologs (α-lactalbumin, β-lactaglobulin). Three types of CMA present: IgE-mediated, non-IgE/cell-mediated and the mixed form (IgE and non-IgE) (3).

Epidemiology

Although reports for milk allergy are high, ranging from 1-17.5% among preschoolers (6), the actual diagnosed incidences are lower ranging to 2-4% in infancy (7-9). Symptoms develop usually during infancy, within the first month after cow's milk protein introduction in the diet, whereas remission of symptoms develops at 3 years of age in a rate of 85-90% of children (10). Data for milk allergy in adulthood indicate low prevalence ranging from 0.1-0.5% of the population (11).

Immediate reactions

Specific-IgE antibodies are produced against milk allergens after exposure to CM, at any age but mainly during infancy - even in breastfed infants- and early childhood (12). Symptoms occur from minutes up to 2 hours after ingestion and involve one or more systems, with symptoms from the skin (urticaria and angioedema), gastrointestinal (nausea, vomiting and diarrhea), nervous, cardiac (13) and respiratory system (rhinoconjunctivitis and asthma), delayed growth and failure to thrive, but also anaphylaxis (14-16).

Non-IgE mediated CMA

Apart from the cases of the IgE-mediated features of immediate hypersensitivity, there is an equal proportion of pediatric patients presenting symptoms mediated from non-IgE mechanisms with symptoms of atopic eczema, gastro-oesophageal reflux, persistent crying, diarrhea and sometimes constipation. Diagnosing non-IgE mediated CMA can be challenging as those symptoms are common in infancy, even in the absence of atopy. Removing milk from the diet, follow up of symptoms resolution and re-challenge can lead to a clear diagnosis.
Non-IgE mediated CMA describes unclear mechanisms of T-cells (probably Th2) responses, without the production of IgE antibodies, but mediated by proinflammatory cytokines (17), occurring usually in 1-3 hours up to 2-3 days after milk ingestion (18). Symptoms from the gastrointestinal (GI) tract and the skin are the most common manifestations. CM-protein induced enterocolitis syndrome (CMPIES) involves the whole GI (19,20) with severe symptoms of repetitive vomiting usually 2-4 hours after ingestion and/or diarrhea and lethargy 5-10 hours after consumption (21), lack of other symptoms related to the offending food, and a resolution of symptoms after its removal from the diet (22,23). In infants with FPIES caused by cow's milk, breastfeeding is recommended, although there are few reports of infants with chronic symptoms of regurgitation, colic, diarrhea and failure to thrive, caused from CM proteins passing through breast milk (24). Interestingly, it is also reported a newborn with CMPIES before first feeding, with persistent symptoms when fed with CM formula and symptoms resolved when the last was discontinued and initially with intravenous nutrition and then with a diet of extensively hydrolyzed formula with breast milk (25). Avoidance of milk and its products from the nursing mother and casein-hydrolyzed formulas or amino acid formulas led to FPIES symptoms resolution (19,26).
CM-induced enteropathy involves the small bowel and CM induced proctitis and proctocolitis of the rectum and colon, with remission of symptoms when milk is removed from the diet (3,18).

Diagnosis of CMA

Following the general diagnostic approach of food allergy, for diagnosing CMA detailed medical and dietary history should be taken, followed by physical examination, SPTs, sIgE measurements, elimination diet for milk and milk products and oral food challenges (27)

Dietary management

Elimination diet has still the key role into managing CMA (28,29). Heat or enzymatic treatment results to formulas at a variable range of hydrolysis of cow's milk proteins, and together with elemental (amino acid) formulas are the forefront alternative choices to CM (30,31). Soy milk after the 6th month of age is an option (32), but hydrolyzed rice-based formula is under consideration as its nutrient adequacy still needs to be further studied as up to date results are controversial (33,34). Probiotics role is investigated in various aspects: in prevention (35-37) or reduction of atopy (38,39), controlling eczema (37,40,41) increasing the proportion of acquired tolerance in milk allergic children (28), but evidence is still being sought (42-44). Notwithstanding some hypoallergenic, hydrolyzed or amino-acid infant formulas are supplemented with probiotics, although scientific research is not yet clear regarding their effectiveness. **Table 1** is a comparative presentation of milk formulas with different grade of hydrolyzation (partially, extensively, elemental), or derived from different sources (cow's milk, soya, rice) regard-

ing their macronutrient and selected important micronutrient composition (calcium, iron, zinc).
Donkey's, mare's, camel's and even pig's milk (45-49) have also been proposed as safe alternatives for some CMA patients, but need to be further evaluated in terms of nutrients adequacy and cross reactivity to CM proteins (15). Contradictory, goat's and sheep's milk frequently cause reactions due to the high sequence homology between these related species (50-52).

The selection of the correct formula is based on the patient's history and clinical evaluation after introduction of the new CM substitute. Allergic symptoms, stool patterns, regurgitation, or even frequency of crying are some of the indicators of acceptability (34,35). Educating patients and guardians into avoiding all possible sources of milk is essential in order to ensure accidental reactions. Although according to EU Regulation 1169/2011 (53) milk labeling on commercial products is mandatory, still dif-

Table 1 *- Comparison of milk formulas with different grade of hydrolyzation (partially, extensively, elemental), lactose content or derived from different sources (cow, soya, rice).*

Category	Product Name	Brand Name	Energy	Carbohydrates	Fat	Protein	Calcium	Iron	Zinc
Infant Formula	S-26 Original Newborn	Pfizer	67.1	7.2	3.6	1.5	46	0.8	0.6
Infant Formula	Enfalac A+	Mead Johnson	66	6.9	3.5	1.65	44	0.79	1
PARTIALLY HYDROLYZED FORMULAS: the high content of high Molecular Weight Peptides (MW > 4.000 Dalton and 5% peptides with MW > 15.000) and unaffected protein molecules explains their intact allergenic activity Indications: allergy prevention when positive history of atopy.									
HA	NAN HA Gold	Nestle	67	7.8	3.4	1.3	49	0.7	0.7
	Similac Advance HA	Abbot	64.3	6.92	3.62	1.33	52.7	1.22	0.51
	Aptamil Gold HA	Danone Nutricia	65	7.2	3.4	1.5	46	0.53	0.5
EXTENSIVELLY HYDROLYSED FORMULAS (EHF): extensive hydrolysis results high quantity of small peptides (di- and tripeptides. MW < 1200 Dalton) and smaller quantities of large peptides and free amino acids. This change of the protein structure. reduces the antigenicity and allergenicity of 10 to 100 times compared with conventional milk. The possibility of raising a reaction even in milks with extensive hydrolysis is due to the fact that the remaining epitopes can be recognized by the immune system of very sensitive infants Indications: Milk and soy allergy. Eosinophilic Enterocolitis. Eosinophilic Oesophagitis. Eosinophilic Gastroenteritis.									
	Nutramigen with Enflora	Enfamil	70.4	7.25	3.73	1.97	66.2	1.27	0.7
	Alfare	Nestle	70	7.7	3.6	2.1	54	0.7	0.7
	Pregomin Pepti	Danone	66	6.8	3.5	1.6	50	0.8	n/a
ELEMENTAL (AMINO ACID) FORMULAS: manufactured from free amino acids Indications: CMA when EHF cannot be tolerated.									
Amino Acid	Elecare	Abbot	70.4	7.54	3.38	2.18	81.7	1.27	0.81
	Neocate	Nutricia	67	7.84	3.02	2.08	83.1	1.24	1.11
	Nutramigen AA	Mead Johnson		7	3.6	1.86	64	1.22	0.68
LACTOSE FREE FORMULAS Indications: Lactose intolerance.									
Lactose-free	S-26 Lactose Free	Pfizer	67.1	7.2	3.6	1.5	55mg	0.8	0.6
	Lactose Free	SMA	67	7.2	3.6	1.5			
Alternative products									
Soy milk	Prosobee	Enfamil	70	10.6	5.3	2.5	73.9 mg	1.27	0.85
Partially hydrolyzed rice milk	Novarice	Novalac	67.9	7.4	1.8	3.4	60.8	0.9	0.7

Table 2 *- Terminology used for labeling CM on commercial food products.*

Terms used for milk labeling: Whey, Rennet, Casein, Cheese, Lactalbumin, Curd, Quark, Yogurt
Terms that might imply the presence of milk protein: Butter, Milk fat, Praline, Sherbet, Ghee

ferent terms can be found on food labels of products produces and marketed. **Table 2** presents some common terms used for labeling milk or implying the possible presence of milk.

Processed products, baked/ cooked products

Although the effect of industrial processing (pasteurization, ultra-high-temperature heating, or dry blending for cow's milk formula) remains controversial to whether it can affect the antigenic / allergenic properties of cow's milk proteins (54-57), 70% of the children with diagnosed CMA can tolerate baked products, probably due to the change of the isoforms resulting from the prolonged heating in higher temperatures (58-61). This also applies to some patients with CM eosinophil esophagitis (62). Accordingly, baked milk is used for oral immunotherapy protocols (63,64) successfully, as it probably accelerates tolerance (65). In a big rate of patients, being able to introduce baked milk gradually into their diet is extremely significant as it improves tolerance and improves significantly quality of life (66).

Growth and nutritional assessment

Food allergies result in malnourished children, according to several studies (67-69), making normal growth one of the major concerns also to CMA allergic children (4) (70). Recently, Harvey et al. presented that an amino acid based formula containing synbiotics could ensure normal growth in healthy, non-allergic children exclusively fed with this formula (71). Similarly, earlier publications for various extensively hydrolyzed and elemental formulas with docosahexaenoic acid (DHA) and arachidonic acid (ARA) have shown that these products sustain growth in healthy or CM-allergic infants and are well tolerated from the last (72). Contradictorily, many publications emphasize the link between milk allergy and decreased growth in children (71,72) when they do not consume another appropriate substitute, as they are found shorter and to weigh less when compared with their matched counterparts (72).
Therefore, appropriate nutritional assessment, analysis and management are essential to avoid growth impairment in this population. A nutrition-focused medical history and nutrition-focused physical examination can place the link between nutrient adequacy as denoted from the diet history and growth (75,76). These will evaluate anthropometrics (weight, height, BMI, head circumference) measurements compared with appropriate local growth charts, biochemical evaluation also taking into account amylase, iron, calcium, vitamin D levels, as well as medical history, diet history including dietary intake and evaluation of children's and family's eating practices and environmental factors such as activity level of the patient and ability to socialize due to the CM.
Based on the above, nutritional diagnosis will lead to the appropriate dietary guidelines, that will ensure nutrient adequacy especially for protein, calcium and vitamin D (77,78), but also facilitate and protect quality of life. Evidenced-based alternatives should be provided to the family, together with detailed explanation on the reasons for introducing to the child's diet the "new" foods. **Table 3** and **table 4** present good sources of Calcium and vitamin D respectively, in comparison to CM and various CM-products.

CM allergy in older children and adults

Although CM allergy is more common during infancy and early childhood, when this does not resolve or when it occurs in adulthood, then symptoms are severe and often anaphylactic, affecting enormously the patients' quality of life (79,81).

Lactose intolerance

Lactase is responsible for hydrolyzing lactose into its components: monosaccharides, glucose and galactose. Lactose intolerance (LI) is caused due to a downregulation of lactase expression in the small intestine and can explain symptoms of bloating, flatulence, diarrhea (81).
Congenital lactase deficiency, also called congenital alactasia, occurs in infancy due to mutations in the LCT gene, which is responsible for the lactase synthesis. Unbroken lactose from breast milk or formula causes severe diarrhea leading to dehydration and weight loss, if milk is not substituted with a lactose-free formula.
In adulthood, lactose intolerance is caused by gradually decreasing activity (expression) of the LCT gene after infancy. LCT gene expression is controlled by regulatory element of the DNA located within a nearby gene (MCM6). Some individuals have inherited changes in this element that lead to sustained lactase production in the small intestine and the ability to digest lactose throughout life. People without these changes have a reduced ability to digest lactose as they get older, resulting in the signs and symptoms of lactose intolerance.
The severity of the symptoms depends on the amount of the lactase produced, but also the amount of lactose consumed from the diet, and the type of meal, the colonic macrobiota and individual sensitivity and perceptions. The last lays to over-self-diagnosis as lactose intolerant, when this is not confirmed with genetic analysis, H2-breath test or duodenal biopsies for measuring lactase expression. Blinded lactose challenges are also under investigation as a diagnostic tool for LI (81). Although the prevalence of LI is difficult

Table 3 *- Dairy (shaded) and Non-dairy Calcium-rich foods (non-shaded).*

Food, Standard Amount	Calcium (mg)
Plain yogurt, non-fat (13 g protein / 8 oz), 8-oz container	452
Romano cheese, 1.5 oz	452
Pasteurized process Swiss cheese, 2 oz	438
Plain yogurt, low-fat (12 g protein / 8 oz), 8-oz container	415
Fruit yogurt, low-fat (10 g protein / 8 oz), 8-oz container	345
Swiss cheese, 1.5 oz	336
Ricotta cheese, part skim, ½ cup	335
Pasteurized process American cheese food, 2 oz	323
Provolone cheese, 1.5 oz	321
Mozzarella cheese, part-skim, 1.5 oz	311
Cheddar cheese, 1.5 oz	307
Fat-free (skim) milk, 1 cup	306
Muenster cheese, 1.5 oz	305
1% low-fat milk, 1 cup	290
Low-fat chocolate milk (1%), 1 cup	288
2% reduced fat milk, 1 cup	285
Reduced fat chocolate milk (2%), 1 cup	285
Buttermilk, low-fat, 1 cup	284
Chocolate milk, 1 cup	280
Whole milk, 1 cup	276
Yogurt, plain, whole milk (8 g protein / 8 oz), 8-oz container	275
Ricotta cheese, whole milk, ½ cup	255
Blue cheese, 1.5 oz	225
Mozzarella cheese, whole milk, 1.5 oz	215
Feta cheese, 1.5 oz	210
Fortified ready-to-eat cereals (various), 1 oz	236-1043
Soy beverage, calcium fortified, 1 cup	368
Sardines, Atlantic, in oil, drained, 3 oz	325
Tofu, firm, ½ cup	253
Pink salmon, canned, with bone, 3 oz	181
Collards, cooked from frozen, ½ cup	178
Molasses, blackstrap, 1 Tbsp	172
Spinach, cooked from frozen, ½ cup	146
Soybeans, green, cooked, ½ cup	130
Turnip greens, cooked from frozen, ½ cup	124
Ocean perch, Atlantic, cooked, 3 oz	116
Oatmeal, plain and flavored, instant, fortified, 1 packet prepared	99-110
Cowpeas, cooked, ½ cup	106
White beans, canned, ½ cup	96
Kale, cooked from frozen, ½ cup	90
Okra, cooked from frozen, ½ cup	88
Soybeans, mature, cooked, ½ cup	88
Blue crab, canned, 3 oz	86
Beet greens, cooked from fresh, ½ cup	82
Pak-choi, Chinese cabbage, cooked from fresh, ½ cup	79
Clams, canned, 3 oz	78
Dandelion greens, cooked from fresh, ½ cup	74
Rainbow trout, farmed, cooked, 3 oz	73

Table 4 *- Vitamin D Food sources (82, 97).*

Food	IUs per serving*	Percent DV**
Cod liver oil, 1 tablespoon	1,360	340
Swordfish, cooked, 3 ounces	566	142
Salmon (sockeye), cooked, 3 ounces	447	112
Tuna fish, canned in water, drained, 3 ounces	154	39
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	137	34
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115-124	29-31
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	80	20
Margarine, fortified, 1 tablespoon	60	15
Sardines, canned in oil, drained, 2 sardines	46	12
Liver, beef, cooked, 3 ounces	42	11
Egg, 1 large (vitamin D is found in yolk)	41	10
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Cheese, Swiss, 1 ounce	6	2

*IUs = International Units. ** DV = Daily Value.

to discern and varies among different populations, it is considered to affect 30% of the population, but its frequency varies considerably between different ethnic groups and population. The lowest rates are seen in white North Europeans, North Americans and Australasians from 4.7% in British populations to 17% in Finland and Northern France. The highest rates tend to be found in South America, Africa and Asia with approximately 50% of the population affected and almost 100% in some Asian countries. Ethnic groups also tend to lose lactase activity differently, with Chinese and Japanese lacking 80-90% of lactase activity within 3-4 years after weaning, Jews and Asians losing 60-70% over several years post weaning and white Northern Europeans may take up to 18-20 years for lactase activity to reach its minimal expression (5).

Diagnosis of LI

Several methods have been proposed for LI diagnosis, such as genotype determination, Lactose Tolerance Test, Quick Lactose Test. Nevertheless, the most reliable, inexpensive and non-invasive test is Lactose Breath Test, which has shown excellent specificity and good sensitivity (82).

Dietary management of LI

Calcium inadequacy is the main nutritional risk for lactose-intolerant patients. Interestingly, most lactose intolerant patients can tolerate without a problem up to 12 grams of lactose, equal to 1 cup of milk, with minor symptoms, especially if these are consumed with other foods or spread over the day. Some studies have examined whether it is possible to induce adaptation by consuming incremental lactose loads over a period of time, but the evidence in support of this strategy is inconsistent (83). Alternatively, low-lactose dairy products, including yogurt, aged cheeses (such as Cheddar and Swiss) or lactose-reduced or lactose-free milk are good sources of calcium without provoking symptoms. Additionally, nondairy food sources high in calcium should be included in the diet of all milk allergic and intolerant individuals, such as teleost fish such as anchovy, small sardines and mola (84) that can be consumed with the bone, chicken bone cartilage, kale, bok choy, Chinese cabbage, broccoli, collards, but also fortified with calcium foods such as juices and cereals (85,86). Calcium bioavailability should be considered when selecting plant sources as this might vary significantly, and from some is not that well absorbed as from others (87) (**table 3**).

Calcium supplementation in milk hypersensitivities

Milk is the first food for neonates and infants ensuring proper development, by providing the necessary nutrients and energy. Furthermore, it has a crucial role in the formation of the bone mass. Especially children with CMA, but also patients with lac-

tose intolerance are under a high risk of inadequate quantities of calcium in the diet resulting in reduced bone mass density and early osteoporosis, due to disturbances in bone mineralization and metabolism (79). A milk-free diet is also related to fractures during growth (88-90). Nevertheless, symptoms resolve in the incidence of milk desensitization or with appropriate supplementation or substitution of essential minerals (90-94).

Adequate calcium intake is only ensured when these patients, while being on a nondairy diet, have the appropriate nutritional supervision and guidance (79).

Supplementation with calcium and vitamin D can be used in order to prevent nutritional rickets. But recommended dietary allowance and tolerable upper intake levels should be considered in order to provide adequate amounts and avoid adverse / toxic reaction (**tables 5** and **6**).

There are several available forms of calcium in supplements, with two most extensively used: carbonate and citrate. Calcium citrate was at first suggested to be easier absorbed, even in empty stomach and also useful for people suffering from achlorydria, inflammatory bowel disease or absorption disorders (97), but these results were not later confirmed by other studies (98). The amount of calcium absorbed depends on the total amount of elemental calcium consumed at one time, with the bioavailability and solubilization playing an important role under conditions of low calcium intake (≤ 500 mg), but with this becoming insignificant in high calcium doses (> 800 mg) (99-101).

Table 5 *- Calcium and vitamin D recommended dietary allowance according the age group (98)*

Age	Calcium Recommended Dietary Allowance (mg/day)	Vitamin D Recommended Dietary Allowance (IU/day)
Infants 0 to 6 months	*	**
Infants 6 to 12 months	*	**
1 - 3 years old	700	**
4 - 8 years old	1,000	600
9 - 13 years old	1,300	600
14 - 18 years old	1,300	600
19 - 30 years old	1,000	600
31 - 50 years old	1,000	600
51 - 70 years old	1,000	600
51 - 70 year old females	1,200	600
71+ years old	1,200	800
14 - 18 years old, pregnant/lactating	1,300	600
19 - 50 years old, pregnant/lactating	1,000	600

*For infants, adequate intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age.
**For infants, adequate intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age

Table 6 *- Tolerable Upper Intake Levels (ULs) a. for Calcium (average nutrient intake unlike to pose adverse reactions) b. for Vitamin D.*

	Calcium			
Age	**Male**	**Female**	**Pregnant**	**Lactating**
0-6 months	1,000 mg	1,000 mg		
7-12 months	1,500 mg	1,500 mg		
1-8 years	2,500 mg	2,500 mg		
9-18 years	3,000 mg	3,000 mg	3,000 mg	3,000 mg
19-50 years	2,500 mg	2,500 mg	2,500 mg	2,500 mg
51+ years	2,000 mg	2,000 mg		
Vitamin D				
0-6 months	1,000 IU (25 mcg)	1,000 IU (25 mcg)		
7-12 months	1,500 IU (38 mcg)	1,500 IU (38 mcg)		
1-3 years	2,500 IU (63 mcg)	2,500 IU (63 mcg)		
4-8 years	3,000 IU (75 mcg)	3,000 IU (75 mcg)		
≥ 9 years	4,000 IU (100 mcg)	4,000 IU (100 mcg)	4,000 IU (100 mcg)	4,000 IU (100 mcg)

Conclusion

Cow's milk allergy is less common than lactose intolerance, affecting 0.6% to 0.9% of the population. Nevertheless, cow's milk allergic individuals require strict avoidance of cow's milk proteins containing products, as severe life threatening reactions may be elicited and are therefore at higher risk of obtaining insufficient protein and calcium intake. Avoidance of cross-reactive food products should be considered when providing guidance regarding their dietary management. In lactose intolerance, which is much more frequent especially in late puberty and adulthood, symptoms are mild and lactose free products together with alternative non-dairy products can reduce the risk of calcium inadequacies. For all cow's milk hypersensitive patients,

calcium and vitamin D supplementation should be considered at individual's basis when diet is not considered adequate in order to protect bones mass density.

Overall a nutrition focused medical and physical examination should be obtained by experienced dietitians and appropriate counseling should be provided in order to reduce the risk of growth or nutrients impairments.

References

1. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. Revised nomenclature for allergy for global use: Report of the nomenclature review committee of the world allergy organization, October 2003. J Allergy Clin Immunol. 2004;113(5):832-6.
2. Montalto M, Santoro L, D'Onofrio F, Curigliano V, Gallo A, Visca D, Cammarota G, Gasbarrini A, Gasbarrini G. Adverse reactions to food: Allergies and intolerances. Dig Dis. 2008;26(2):96-103.
3. Lifschitz C, Szajewska H. Cow's milk allergy: Evidence-based diagnosis and management for the practitioner. Eur J Pediatr. 2014Sep26.
4. Robbins KA, Wood RA, Keet CA. Milk allergy is associated with decreased growth in US children. J Allergy Clin Immunol. 2014;134(6):1466,1468.e6.
5. Misselwitz B, Pohl D, Frühauf H, Fried M, Vavricka SR, Fox M. Lactose malabsorption and intolerance: Pathogenesis, diagnosis and treatment. United European Gastroenterology Journal. 2013March28.
6. Jarvinen KM, Chatchatee P. Mammalian milk allergy: Clinical suspicion, cross-reactivities and diagnosis. Curr Opin Allergy Clin Immunol. 2009;9(3):251-8.
7. Luyt D, Ball H, Makwana N, Green MR, Bravin K, Nasser SM, Clark AT, Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI). BSACI guideline for the diagnosis and management of cow's milk allergy. Clin Exp Allergy. 2014;44(5):642-72.
8. Vandenplas Y, De Greef E, Devreker T. Treatment of cow's milk protein allergy. Pediatr Gastroenterol Hepatol Nutr. 2014;17(1):1-5.
9. Host A. Frequency of cow's milk allergy in childhood. Ann Allergy Asthma Immunol. 2002;89(6 Suppl 1):33-7.
10. Vandenplas Y, Bhatia J, Shamir R, Agostoni C, Turck D, Staiano A, Szajewska H. Hydrolyzed formulas for allergy prevention. J Pediatr Gastroenterol Nutr. 2014;58(5):549-52.
11. Odedra KM. Milk allergy in adults and children. Nurs Stand. 2015;29(44):43-8.
12. Wyness L. Nutrition in early life and the risk of asthma and allergic disease. Br J Community Nurs. 2014;Suppl:S28-32.
13. Ece I, Demiroren K, Demir N, Uner A, Balli S. Assessment of cardiac functions in infants with cow's milk allergy. Med Sci Monit. 2014;20:1383-8.
14. Falsaperla R, Pavone P, Miceli Sopo S, Mahmood F, Scalia F, Corsello G, Lubrano R, Vitaliti G. Epileptic seizures as a manifestation of cow's milk allergy: A studied relationship and description of our pediatric experience. Expert Rev Clin Immunol. 2014;10(12):1597-609.
15. Fiocchi A, Schunemann HJ, Brozek J, Restani P, Beyer K, Troncone R, Martelli A, Terracciano L, Bahna SL, Rance F, Ebisawa M, Heine RG, Assa'ad A, Sampson H, Verduci E, Bouygue GR, Baena-Cagnani C, Canonica W, Lockey RF. Diagnosis and rationale for action against cow's milk allergy (DRACMA): A summary report. J Allergy Clin Immunol. 2010;126(6):1119,28.e12.
16. Teymourpour P, Pourpak Z, Fazlollahi MR, Barzegar S, Shokouhi R, Akramian R, Movahedi M, Mansouri M, Mirsaeedghazi B, Moin M. Cow's milk anaphylaxis in children first report of iranian food allergy registry. Iran J Allergy Asthma Immunol. 2012;11(1):29-36.
17. Hojsak I, Kljaic-Turkalj M, Misak Z, Kolacek S. Rice protein-induced enterocolitis syndrome. Clin Nutr. 2006;25(3):533-6.
18. Chadha SN, Wang L, Correa H, Moulton D, Hummell DS. Pediatric eosinophilic esophagitis: The vanderbilt experience. Ann Allergy Asthma Immunol. 2014;113(4):445-51.
19. Caubet JC, Ford LS, Sickles L, Jarvinen KM, Sicherer SH, Sampson HA, Nowak-Wegrzyn A. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol. 2014;134(2):382-9.
20. Fiocchi A, Claps A, Dahdah L, Brindisi G, Dionisi-Vici C, Martelli A. Differential diagnosis of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol. 2014;14(3):246-54.
21. Jarvinen KM, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome (FPIES): Current management strategies and review of the literature. J Allergy Clin Immunol Pract. 2013;1(4):317-22.
22. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: A large-scale, prospective population-based study. J Allergy Clin Immunol. 2011;127(3):647,53.e1-3.
23. Hwang JB. Is this symptom even a food allergy?: Clinical types of food protein-induced enterocolitis syndrome. Pediatr Gastroenterol Hepatol Nutr. 2014;17(2):74-9.
24. Miceli Sopo S, Monaco S, Greco M, Scala G. Chronic food protein-induced enterocolitis syndrome caused by cow's milk proteins passed through breast milk. Int Arch Allergy Immunol. 2014;164(3):207-9.
25. Mizuno M, Masaki H, Yoshinare R, Ito Y, Morita H, Yoshio H. Hematochezia before the first feeding in a newborn with food protein-induced enterocolitis syndrome. AJP Rep. 2011;1(1):53-8.
26. Kabuki T, Joh K. Extensively hydrolyzed formula (MA-mi) induced exacerbation of food protein-induced enterocolitis syndrome (FPIES) in a male infant. Allergol Int. 2007;56(4):473-6.
27. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014;133(2):291,307; quiz 308.
28. Berni Canani R, Nocerino R, Terrin G, Frediani T, Lucarelli S, Cosenza L, Passariello A, Leone L, Granata V, Di Costanzo M, Pezzella V, Troncone R. Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: A prospective multicenter study. J Pediatr. 2013;163(3):771,7.e1.
29. Jung-Wu S. Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: A prospective multicenter study. Pediatrics. 2014;134 Suppl 3:S154-5.
30. Petrus NC, Schoemaker AF, van Hoek MW, Jansen L, Jansen-van der Weide MC, van Aalderen WM, Sprikkelman AB. Remaining symptoms in half the children treated for milk allergy. Eur J Pediatr. 2014Nov22.
31. Vandenplas Y, Abuabat A, Al-Hammadi S, Aly GS, Miqdady MS, Shaaban SY, Torbey PH. Middle east consensus statement on the prevention, diagnosis, and management of cow's milk protein allergy. Pediatr Gastroenterol Hepatol Nutr. 2014;17(2):61-73.
32. Vandenplas Y, Castrellon PG, Rivas R, Gutierrez CJ, Garcia LD, Jimenez JE, Anzo A, Hegar B, Alarcon P. Safety of soya-based infant formulas in children. Br J Nutr. 2014;111(8):1340-60.

33. Fiocchi A, Restani P, Bernardini R, Lucarelli S, Lombardi G, Magazzu G, Marseglia GL, Pittschieler K, Tripodi S, Troncone R, Ranzini C. A hydrolysed rice-based formula is tolerated by children with cow's milk allergy: A multi-centre study. Clin Exp Allergy. 2006;36(3):311-6.
34. Vandenplas Y, De Greef E, Hauser B, Paradice Study Group, Paradice Study Group. An extensively hydrolysed rice protein-based formula in the management of infants with cow's milk protein allergy: Preliminary results after 1 month. Arch Dis Child. 2014;99(10):933-6.
35. Nowak-Wegrzyn A, Czerkies LA, Collins B, Saavedra JM. Evaluation of hypoallergenicity of a new, amino acid-based formula. Clin Pediatr (Phila). 2014Nov12.
36. Marchand V. Using probiotics in the paediatric population. Paediatr Child Health. 2012;17(10):575-6.
37. Ta V, Laubach S. Probiotic administration in early life, atopy, and asthma: A meta-analysis of clinical trials. Pediatrics. 2014;134 Suppl 3:S141-1817O.
38. Madonini ER. Probiotics and allergies: Myth or reality? Eur Ann Allergy Clin Immunol. 2014;46(6):196-200.
39. Vitaliti G, Pavone P, Guglielmo F, Spataro G, Falsaperla R. The immunomodulatory effect of probiotics beyond atopy: An update. J Asthma. 2014;51(3):320-32.
40. Loo EX, Llanora GV, Lu Q, Aw MM, Lee BW, Shek LP. Supplementation with probiotics in the first 6 months of life did not protect against eczema and allergy in at-risk asian infants: A 5-year follow-up. Int Arch Allergy Immunol. 2014;163(1):25-8.
41. Morgan AR, Han DY, Wickens K, Barthow C, Mitchell EA, Stanley TV, Dekker J, Crane J, Ferguson LR. Differential modification of genetic susceptibility to childhood eczema by two probiotics. Clin Exp Allergy. 2014;44(10):1255-65.
42. Nermes M, Salminen S, Isolauri E. Is there a role for probiotics in the prevention or treatment of food allergy? Curr Allergy Asthma Rep. 2013;13(6):622-30.
43. Nieto A, Wahn U, Bufe A, Eigenmann P, Halken S, Hedlin G, Host A, Hourihane J, Just J, Lack G, Lau S, Matricardi PM, Muraro A, Papadopoulos N, Roberts G, Simpson A, Valovirta E, Weidinger S, Wickman M, Mazon A. Allergy and asthma prevention 2014. Pediatr Allergy Immunol. 2014;25(6):516-33.
44. Castellazzi AM, Valsecchi C, Caimmi S, Licari A, Marseglia A, Leoni MC, Caimmi D, Miraglia del Giudice M, Leonardi S, La Rosa M, Marseglia GL. Probiotics and food allergy. Ital J Pediatr. 2013;39:47,7288-39-47.
45. Jirillo F, Jirillo E, Magrone T. Donkey's and goat's milk consumption and benefits to human health with special reference to the inflammatory status. Curr Pharm Des. 2010;16(7):859-63.
46. Ehlayel M, Bener A, Abu Hazeima K, Al-Mesaifri F. Camel milk is a safer choice than goat milk for feeding children with cow milk allergy. ISRN Allergy. 2011;2011:391641.
47. Katz Y, Goldberg MR, Zadik-Mnuhin G, Leshno M, Heyman E. Cross-sensitization between milk proteins: Reactivity to a "kosher" epitope? Isr Med Assoc J. 2008;10(1):85-8.
48. Host A, Halken S. Cow's milk allergy: Where have we come from and where are we going? Endocr Metab Immune Disord Drug Targets. 2014;14(1):2-8.
49. Pizzano R, Salimei E. Isoelectric focusing and ELISA for detecting adulteration of donkey milk with cow milk. J Agric Food Chem. 2014;62(25):5853-8.
50. Martorell Aragones A, Martorell Calatayud C, Pineda F, Felix Toledo R, Cerda Mir JC, de las Marinas MD. Persistence of allergy to goat's milk after specific induction of tolerance to cow's milk. J Investig Allergol Clin Immunol. 2012;22(4):301-2.
51. de Boissieu D, Dupont C. Allergy to goat and sheep milk without allergy to cow's milk. Arch Pediatr. 2008;15(3):349-51.
52. Vinas M, Carnes J, Lopez-Matas MA, Hernandez N, Castillo MJ, Ibero M. Allergy to goat and sheep cheese with tolerance to cow's milk and its derivatives. Allergol Immunopathol (Madr). 2014;42(3):186-90.
53. European Commission Eu Regulation 1169/2011 [Internet].
54. Shandilya UK, Kapila R, Haq RM, Kapila S, Kansal VK. Effect of thermal processing of cow and buffalo milk on the allergenic response to caseins and whey proteins in mice. J Sci Food Agric. 2013;93(9):2287-92.
55. Macdonald LE, Brett J, Kelton D, Majowicz SE, Snedeker K, Sargeant JM. A systematic review and meta-analysis of the effects of pasteurization on milk vitamins, and evidence for raw milk consumption and other health-related outcomes. J Food Prot. 2011;74(11):1814-32.
56. Roth-Walter F, Berin MC, Arnaboldi P, Escalante CR, Dahan S, Rauch J, Jensen-Jarolim E, Mayer L. Pasteurization of milk proteins promotes allergic sensitization by enhancing uptake through peyer's patches. Allergy. 2008;63(7):882-90.
57. von Mutius E. Maternal farm exposure/ingestion of unpasteurized cow's milk and allergic disease. Curr Opin Gastroenterol. 2012;28(6):570-6.
58. Bloom KA, Huang FR, Bencharitiwong R, Bardina L, Ross A, Sampson HA, Nowak-Wegrzyn A. Effect of heat treatment on milk and egg proteins allergenicity. Pediatr Allergy Immunol. 2014Sep24.
59. Nowak-Wegrzyn A, Fiocchi A. Rare, medium, or well done? the effect of heating and food matrix on food protein allergenicity. Curr Opin Allergy Clin Immunol. 2009;9(3):234-7.
60. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, Sampson HA. Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol. 2008;122(2):342,7, 347.e1-2.
61. Netting M, Makrides M, Gold M, Quinn P, Penttila I. Heated allergens and induction of tolerance in food allergic children. Nutrients. 2013;5(6):2028-46.
62. Leung J, Hundal NV, Katz AJ, Shreffler WG, Yuan Q, Butterworth CA, Hesterberg PE. Tolerance of baked milk in patients with cow's milk-mediated eosinophilic esophagitis. J Allergy Clin Immunol. 2013;132(5):1215,1216.e1.
63. Huang F, Nowak-Wegrzyn A. Extensively heated milk and egg as oral immunotherapy. Curr Opin Allergy Clin Immunol. 2012;12(3):283-92.
64. Nowak-Wegrzyn A. Future therapies for food allergy. Przegl Lek. 2013;70(12):1065-70.
65. Kim JS, Nowak-Wegrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. J Allergy Clin Immunol. 2011;128(1):125,131.e2.
66. Mehr S, Turner PJ, Joshi P, Wong M, Campbell DE. Safety and clinical predictors of reacting to extensively heated cow's milk challenge in cow's milk-allergic children. Ann Allergy Asthma Immunol. 2014;113(4):425-9.
67. Sova C, Feuling MB, Baumler M, Gleason L, Tam JS, Zafra H, Goday PS. Systematic review of nutrient intake and growth in children with multiple IgE-mediated food allergies. Nutr Clin Pract. 2013;28(6):669-75.

68. Meyer R, De Koker C, Dziubak R, Venter C, Dominguez-Ortega G, Cutts R, Yerlett N, Skrapak AK, Fox AT, Shah N. Malnutrition in children with food allergies in the UK. J Hum Nutr Diet. 2014;27(3):227-35.
69. Mehta H, Groetch M, Wang J. Growth and nutritional concerns in children with food allergy. Curr Opin Allergy Clin Immunol. 2013;13(3):275-9.
70. O'Donovan SM, Murray DM, Hourihane JO, Kenny LC, Irvine AD, Kiely M. Cohort profile: The cork BASELINE birth cohort study: Babies after SCOPE: Evaluating the longitudinal impact on neurological and nutritional endpoints. Int J Epidemiol. 2014Aug7.
71. Harvey BM, Langford JE, Harthoorn LF, Gillman SA, Green TD, Schwartz RH, Burks AW. Effects on growth and tolerance and hypoallergenicity of an amino acid-based formula with synbiotics. Pediatr Res. 2014;75(2):343-51.
72. Vanderhoof JA. Hypoallergenicity and effects on growth and tolerance of a new amino acid-based formula with DHA and ARA. J Pediatr Gastroenterol Nutr. 2008;47Suppl2:S60-1.
73. Simons FE, Sampson HA. Anaphylaxis: Unique aspects of clinical diagnosis and management in infants (birth to age 2 years). J Allergy Clin Immunol. 2014Oct30.
74. Mehta H, Ramesh M, Feuille E, Groetch M, Wang J. Growth comparison in children with and without food allergies in 2 different demographic populations. J Pediatr. 2014;165(4):842-8.
75. Secker DJ, Jeejeebhoy KN. How to perform subjective global nutritional assessment in children. J Acad Nutr Diet. 2012;112(3):424,431.e6.
76. Secker DJ, Jeejeebhoy KN. Subjective global nutritional assessment for children. Am J Clin Nutr. 2007;85(4):1083-9.
77. Agostoni C, Turck D. Is cow's milk harmful to a child's health? J Pediatr Gastroenterol Nutr. 2011;53(6):594-600.
78. Paganus A, Juntunen-Backman K, Savilahti E. Follow-up of nutritional status and dietary survey in children with cow's milk allergy. Acta Paediatr. 1992;81(6-7):518-21.
79. Nachshon L, Goldberg MR, Schwartz N, Sinai T, Amitzur-Levy R, Elizur A, Eisenberg E, Katz Y. Decreased bone mineral density in young adult IgE-mediated cow's milk-allergic patients. J Allergy Clin Immunol. 2014;134(5):1108,1113.e3.
80. Jansson SA, Heibert-Arnlind M, Middelveld RJ, Bengtsson UJ, Sundqvist AC, Kallstrom-Bengtsson I, Marklund B, Rentzos G, Akerstrom J, Ostblom E, Dahlen SE, Ahlstedt S. Health-related quality of life, assessed with a disease-specific questionnaire, in Swedish adults suffering from well-diagnosed food allergy to staple foods. Clin Transl Allergy. 2013;3:21,7022-3-21. eCollection 2013.
81. Misselwitz B. Lactose intolerance: New insights due to blinded testing? Digestion. 2014;90(1):72-3.
82. Shaukat A, Levitt MD, Taylor BC, MacDonald R, Shamliyan TA, Kane RL, Wilt TJ. Systematic review: Effective management strategies for lactose intolerance. Ann Intern Med. 2010;152(12):797-803.
83. Kim SK, Jung WK. Beneficial effect of teleost fish bone peptide as calcium supplements for bone mineralization. Adv Food Nutr Res. 2012;65:287-95.
84. Di Rienzo T, D'Angelo G, D'Aversa F, Campanale MC, Cesario V, Montalto M, Gasbarrini A, Ojetti V. Lactose intolerance: From diagnosis to correct management. Eur Rev Med Pharmacol Sci. 2013;17Suppl2:18-25.
85. Cribb VL, Northstone K, Hopkins D, Emmett PM. Sources of vitamin D and calcium in the diets of preschool children in the UK and the theoretical effect of food fortification. J Hum Nutr Diet. 2014Oct3.
86. U.S.D.A. Dietary Guidelines Advisory Committee [Internet]. Available from: http://www.health.gov/dietaryguidelines/dga2005/document/html/appendixb.htm
87. Lanou AJ. Should dairy be recommended as part of a healthy vegetarian diet? counterpoint. Am J Clin Nutr. 2009;89(5):1638S-42S.
88. Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-Jastrzebska J, Seeman E. Fractures during growth: Potential role of a milk-free diet. Osteoporos Int. 2007;18(12):1601-7.
89. Monti G, Libanore V, Marinaro L, Lala R, Miniero R, Savino F. Multiple bone fractures in an 8-year-old child with cow's milk allergy and inappropriate calcium supplementation. Ann Nutr Metab. 2007;51(3):228-31.
90. Davidovits M, Levy Y, Avramovitz T, Eisenstein B. Calcium-deficiency rickets in a four-year-old boy with milk allergy. J Pediatr. 1993;122(2):249-51.
91. Hidvegi E, Arato A, Cserhati E, Horvath C, Szabo A, Szabo A. Slight decrease in bone mineralization in cow milk-sensitive children. J Pediatr Gastroenterol Nutr. 2003;36(1):44-9.
92. Jakusova L, Jesenak M, Schudichova J, Banovcin P. Bone metabolism in cow milk allergic children. Indian Pediatr. 2013;50(7):706.
93. Yu JW, Pekeles G, Legault L, McCusker CT. Milk allergy and vitamin D deficiency rickets: A common disorder associated with an uncommon disease. Ann Allergy Asthma Immunol. 2006;96(4):615-9.
94. Gupta R, Makharia G, Khadgawat R, Yadav RK. Evaluation of lactose and milk intolerance, and bone mineral density in indian patients with inflammatory bowel disease. Natl Med J India. 2012;25(6):327-31.
95. Pettifor JM. Nutritional rickets: Deficiency of vitamin D, calcium, or both? Am J Clin Nutr. 2004;80(6 Suppl):1725S-9S.
96. Winzenberg TM, Powell S, Shaw KA, Jones G. Vitamin D supplementation for improving bone mineral density in children. Cochrane Database Syst Rev. 2010;(10):CD006944. doi(10):CD006944.
97. Sakhaee K, Bhuket T, Adams-Huet B, Rao DS. Meta-analysis of calcium bioavailability: A comparison of calcium citrate with calcium carbonate. Am J Ther. 1999;6(6):313-21.
98. Wang H, Bua P, Capodice J. A comparative study of calcium absorption following a single serving administration of calcium carbonate powder versus calcium citrate tablets in healthy premenopausal women. Food Nutr Res. 2014 Apr 22;58:10.3402/fnr.v58.23229. eCollection 2014.
99. Bronner F, Pansu D. Nutritional aspects of calcium absorption. J Nutr. 1999;129(1):9-12.
100. National Institutes of Health. Vitamin D: Health Professional Fact Sheet [Internet]. USA.gov 2014November10. Available from: http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/
101. Ross, C.A., Abrams, S.A, Aloia, J.F., Brannon, P.M., Clinton, S.K., Durazo-Arvizu, R.A., Gallagher, J.C., Gallo, R.L., Jones, G., Kovacs, C.S., Manson, J.E., Mayne, S.T., Rosen, C.J., Shapses, S.A. Dietary Reference Intake for Calcium and vitamin D: Report Brief [Internet]. Washington: Institute of Medicine of the National Academies 2011March; [3]