Diagnostic Approach and Management of CMPA in Infants and Children

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Case 1

- A 6-mo-old breastfed male infant
- Eczematoid itchy rashes in the face, extremities and trunk since the first days of life
- Restlessness
- A history of wheezing

What should be done?

Case 2

- A 2-mo-old breast and formula fed female
- Intermittent watery stool, just once with blood streaks
- Restlessness and crying hours the day and night
- Being diagnosed with GERD under treatment

  with Nexium and Baclofen

What is the next step?

Introduction

- One form or another of **Cow's milk is ingested daily** by infants in greater amounts than any other individual food.
- **Broad and nonspecific** symptoms and signs of CMPA make diagnosis delayed
- It is important to describe the **age of onset**, **type and frequency of symptoms**, **time between ingestion and onset** of symptoms, **dietary details**, and any personal and/or family **history of atopy**.
- It is necessary to define whether a **mother** who is breast feeding a baby is **herself consuming dairy products** and their derivatives because cow's milk proteins may appear in breast milk and expose the baby to development of CMPA.

Introduction

- Similarly, it must be established whether a child who is exclusively breastfed was exposed to breast milk substitute **formulas during the 24 hours after birth** because of institutional care protocols for newborns or in cases of hypoglycemic prevention.
- It has been observed that children subjected to this practice have a risk of developing CMPA that is **seven times greater** than controls who were exclusively breast fed during the first 24 hours.

Diagnostic detection procedures

Specific IgE and skin prick tests	Positive result indicates **sensitization and an IgE-mediated** mechanism. They should be correlated with clinical history and elimination and oral challenge tests. The higher the specific IgE titers and the larger the skin prick test diameter, the greater the probability of CMPA and persistence of allergy. Specific IgE. Sensitivity:33.3- 87%; specificity: 97.6%
Patch test, total IgE and skin tests	The patch test may be used for patients with CMPA who test negative for specific IgE, but its results are **not standardized**. Interpretation is difficult and subjective, so routine use is discouraged. Determination of total IgE and the ratio of total/specific IgE are **not better than specific IgE**. Skin tests have a risk of causing **systemic reactions in highly sensitized children**. Patch test. Sensitivity: 25%; specificity: 99.9%
IgG	Determination of IgG and its subclasses has no diagnostic role.
Endoscopy and histology	Endoscopy and histology Endoscopy and histology are appropriate in children with **severe and unexplained symptoms such as failure to thrive and iron deficiency anemia.** They can be used for differential diagnoses beyond diagnostic confirmation of CMPA.

Diagnosis of CMPA

- In the colon, focal erythema, friable mucosa, lymphoid follicular hyperplasia (present in 75% of cases) and allergic vasculitis must be found **macroscopically**.
- **Microscopically,** it is necessary to find local eosinophil infiltrate in all compartments

Skin tests

Cow's milk-specific IgE and SPT

- Wheal size of ≥5 mm (≥2 mm in an infant <2 year) is associated with a higher specificity.
- Infants are generally less responsive to skin prick tests.
- A negative skin test rules out IgE-mediated reactions, with **negative predictive values of 95%.**
- The wheal size is significantly larger in children with persistent disease compared to those who outgrow CMPA and therefore is useful as a prognostic indicator.
- In general**, the higher the CM-IgE, the less likely** the child is to become tolerant over time.

Introduction

The diagnosis of a food allergy requires

- consideration of the details of an individual's **history**,
- knowledge about the **epidemiology** of different food allergies, and
- specific **test** results.
- clinician-supervised oral food challenge (**OFC**).
  - to confirm diagnosis of a specific food allergy and
  - to determine if an identified allergy persists or has resolved.
  - define other adverse reactions to foods, such as intolerance.

1. Up to date

Indications for OFC for diagnosis

- To **allow expansion of the diet** after resolution of symptoms by elimination of several foods based upon history, and specific IgE,
- A **highly suspected food with negative specific IgE**
- **No symptom resolution after food elimination** of a highly suspected allergen
- An illness **irrelevant or only partly relevant** to specific IgE (eg, food protein-induced enterocolitis syndrome) (eg, atopic dermatitis or eosinophilic esophagitis)

Procedure for oral food challenge

- formula or pasteurized milk (in <12 months age) or pasteurized milk (in >12 months age) is administered cautiously in the following manner:
- 1 mL, 3 mL, 10 mL, 30mL, 100 mL (given every 30 minutes), which can be done on an out-patient basis
- The child should be observed for two hours, and
- then sent home with an instruction to continue at least 200 mL of milk/day and to stop if there is recurrence of symptoms.
- The child should be reviewed after two weeks to decide whether to continue milk or to stop milk again depending on the clinical response to milk introduction.

Procedure for oral food challenge

- For those with severe reactions on initial presentation (IgE-type), the milk challenge is administered in an even more graded fashion (0.1 mL, 0.3 mL, 1 mL, 3 mL, 10 mL, 30 mL, 100 mL: given every 30 minutes) as an in-patient with all resuscitation facilities including injection adrenaline to manage anaphylaxis.
- A positive reaction to milk introduction confirms the diagnosis of CMPA. If no reactions occur, 200 mL/day of milk is continued for twoweeks to look for any delayed manifestations.

Diagnosis

- **None** of the diagnostic tests available in routine clinical situations **fully demonstrate or exclude** CMPA.
- Skin prick test, specific IgE determination, and/or patch tests **only indicate sensitization** to the substrate which does not necessarily constitute confirmation of an allergic reaction.
- Response to CMP withdrawal is noticed within 3-5 days for those with immediate manifestations, 1-2 weeks for those with delayed clinical manifestations, and 2-4 weeks for those with chronic diarrhea/ failure to thrive

Non-IgE mediated tests

- There are also other tests such as cellular function, precipitins, intestinal permeability, eosinophils and TNFα.
- Invasive gastrointestinal **endoscopy for biopsies** requires histological study and is not usually recommended.
- Histological diagnosis of samples from the small intestine requires a pathologist's report of
  - **more than 60 eosinophils in six high-power fields**, or
  - **more than 15 to 20 eosinophils** per field with **more than 25% inflammatory infiltrate**,
  - **intraepithelial eosinophils plus eosinophilic abscesses in the crypts**.

Diagnostic tools

- The Cow's Milk-related Symptom Score (CoMiSS) facilitates the diagnosis.
- It includes gastrointestinal, skin, respiratory, and general symptoms.
- The CoMiSS varies from 0 to 33 points.
- A cut-off point of 12 was proposed by the expert panel.
- CoMiSS was validated, its sensitivity to be 87.5% and its specificity to be 78.6%.

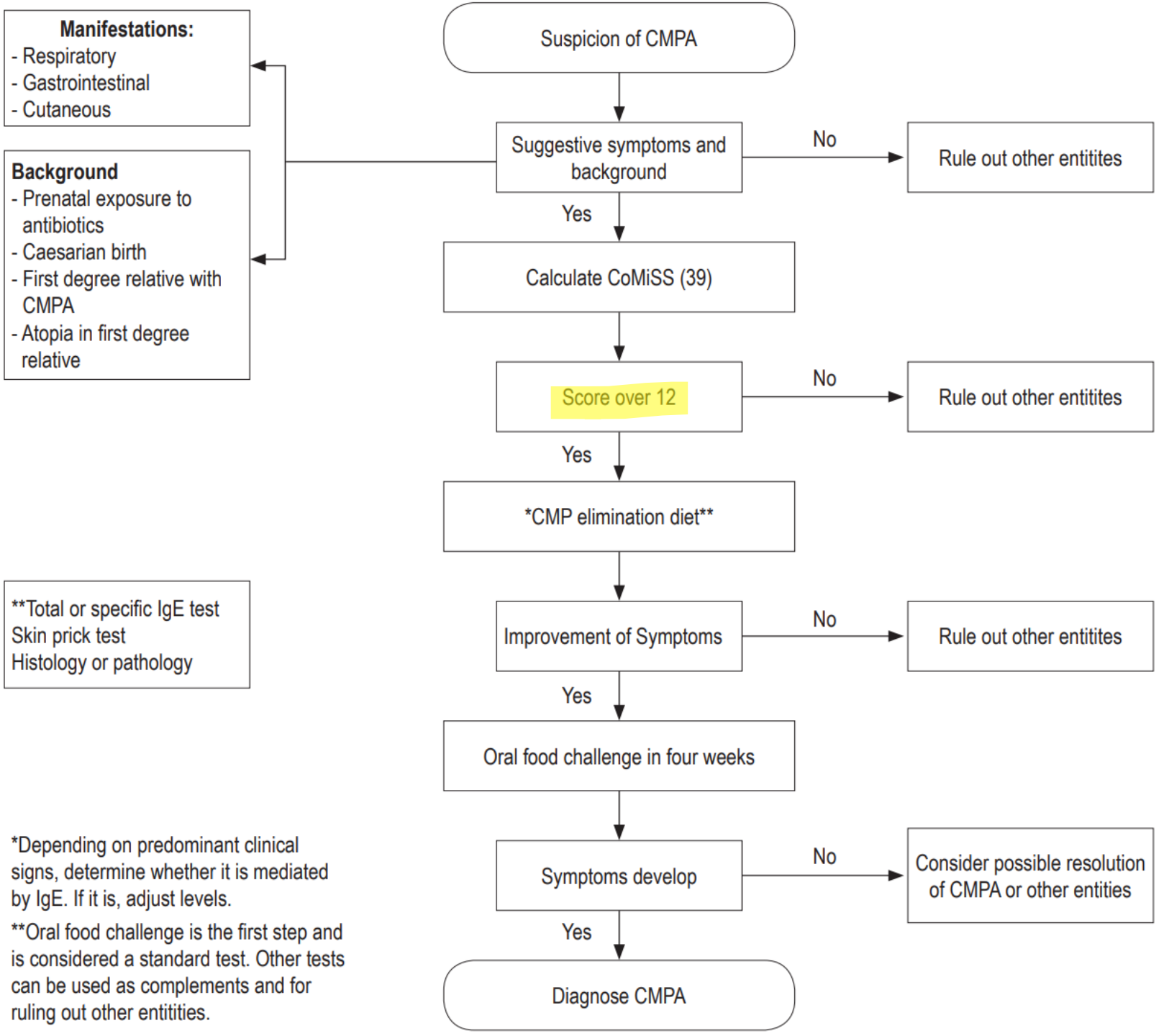
1. Ángela Mayerly Cubides-Munévar et al. , Diagnostic and therapeutic approach to cow's milk protein allergy, Rev Col Gastroenterol vol.35 no.1 Bogotá Jan./Mar. 2020

Symptom-based clinical score

Symptom	Score	
Crying (°)	0	< 1 hour/day
	1	1 - 1.5 hours/day
	2	1.5 - 2 hours/day
	3	2 to 3 hours/day
	4	3 to 4 hours/day
	5	4 to 5 hours/day
	6	> 5 hours/day
Regurgitation (23)*	0	0-2 episodes/day
	1	> 3 - < 5 of small volume
	2	> 5 episodes of > 1 coffee spoon
	3	> 5 episodes of + half of the feed in < half of the feeds
	4	continuous regurgitations of small volumes > 30 min after each feed
	5	regurgitation of half to complete volume of a feed in at least half of the feeds
	6	regurgitation of the complete feed after each feeding

Symptom-based clinical score

Stools (Bristol scale) (25)*	4 0 2 4 6	type 1 and 2 (hard stools) type 3 and 4 (normal stools) type 5 (soft stool) type 6 (liquid stool, if unrelated to infection) type 7 (watery stools)
Skin symptoms	0 to 6 0 or 6	Atopic eczema Head neck trunk / Arms hands legs feet Absent 0 / 0 Mild 1 / 1 Moderate 2 / 2 Severe 3 / 3 Urticaria (no 0 / yes 6)
Respiratory symptoms	0 1 2 3	no respiratory symptoms slight symptoms mild symptoms severe symptoms


Manifestations:
- Respiratory
- Gastrointestinal
- Cutaneous
Background
- Prenatal exposure to antibiotics
- Caesarian birth
- First degree relative with CMPA
- Atopia in first degree relative
Suspicion of CMPA
Suggestive symptoms and background
No
Rule out other entitites
Yes
Calculate CoMiSS (39)
Score over 12
No
Rule out other entitites
Yes
*CMP elimination diet**
**Total or specific IgE test
Skin prick test
Histology or pathology
Improvement of Symptoms
No
Rule out other entitites
Yes
Oral food challenge in four weeks
Symptoms develop
No
Consider possible resolution of CMPA or other entities
Yes
Diagnose CMPA
*Depending on predominant clinical signs, determine whether it is mediated by IgE. If it is, adjust levels.
**Oral food challenge is the first step and is considered a standard test. Other tests can be used as complements and for ruling out other entitities.

Differential diagnosis of CMPA

- CMPA has also been associated with about **10% of infant colic cases**.
- Reactions to other foods (especially egg and soy, wheat, and fish) frequently occur in combination with CMPA.
- Therefore, these foods should be avoided during diagnostic exclusion testing

Diagnosis of CMPA

- When CMPA is confirmed, the elimination diet should be continued until the patient is between 9 and 12 months of age, or at least 6 months.
- After that, a new challenge can be performed.
- Children who do not develop allergy-related manifestations within a week can resume their normal diets.

Treatment of CMPA

- The safest strategy for treating CMPA **is strict avoidance of cow's milk protein.**
- The **decision to use a substitute formula** and the option chosen to meet the nutritional needs of children with CMPA should be made primarily on the basis of the patient's **age and any history of other food allergies.**
- For infants who are **exclusively breastfed,** elimination implies exclusion of milk derivatives from the maternal diet.
- Mothers need to receive **calcium supplements** and dietary advice to avoid nutritional deficiencies.
- **All formulas** based on cow's milk and all complementary **food containing cow's milk** derivatives should be avoided in exclusively breastfed infants.

Treatment of CMPA

- When allergy symptoms occur in infants who are **fed formula**, either exclusively or as a supplement to breastfeeding, they should be given a **therapeutic formula** that has been clinically proven to reduce allergenicity and has high tolerability.
- Extensively hydrolyzed formula (**EHFs**) and amino acid-based formulas (**AAFs**) are the two alternatives recommended for formula fed infants with CMPA.
- EHFs are indicated for **treatment and prevention** of CMPA and are tolerated by most infants and children with this condition.

Box II Factors to Consider When Deciding Alternatives to Bovine Milk

Age: Whether older than or younger than 6 months

Feeding pattern: Exclusive breastfeeding, mixed feeds (breastfeed and formula) or exclusive formula feeds.

Type of allergy: IgE-mediated or non-IgE mediated.

Severity of reaction: Severe or mild to moderate

Clinical manifestations: Gastrointestinal, respiratory or skin.

Financial considerations: Affordability

Treatment of CMPA

- AAFs were developed to overcome hypersensitivity to residual proteins in EHF, particularly in patients with **severe enteropathy or with multiple food allergies**.
- For this reason, AAFs can be considered only for infants with **severe reactions such as anaphylaxis, enteropathy, eosinophilic esophagitis, protein-induced enterocolitis** and for patients who have compromises of multiple systems, **several food allergies, and intolerance to EHF.**
- While **soy formulas** are associated with lower allergenicity than those based on cow's milk, concerns have been raised about their **high isoflavone (phytoestrogen) content**.
- The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the American Academy of Pediatrics (AAP) consider the use of **EHF and AAF to be the first treatment option for infants with CMPA**.

Treatment of CMPA

- Similarly, they **do not recommend** the use of **partially hydrolyzed formulas** (PHF) based on **cow's milk or other mammals' milk.**
- Despite this, the Middle Eastern consensus has included the use of **PHF as a bridge therapy between EHF and AAF** in their management algorithm for selected cases.
- For infants with documented CMPA who are fed exclusively with breast milk and formula, **transitional foods should be free of cow's milk protein** until the development of tolerance is confirmed by oral exposure tests.
- **Dietary supervision** by a health professional who specializes in, or is trained in, pediatric nutrition is recommended for children with **CMPA who are over 12 months** of age who are on an exclusion diet.

Treatment of CMPA

- This supervision is important for making decisions about sufficient amounts of nutrients, **proteins, calcium, vitamin D and vitamin A** in the child's diet.
- This is also essential for choosing any nutritional formula or supplements needed for achievement of **normal growth** according to the child's age.
- Similarly, it is essential to **determine a child's tolerance** to cow's milk protein in order to **avoid prolonging restrictive** diets that affect a child's growth and development of the child and that may also compromise the nutritional status of a breastfeeding mother.

Exclusively breastfed children

- During exclusive breastfeeding, any food containing milk protein must be removed from the mother’s diet.
- The physician must tell the woman that **foods whose labels** indicate that they contain **milk, whey, milk solids, casein and caseinate** are prohibited.
- At the end of six months, **complementary feeding** should begin but the consumption of food containing cow’s milk protein should be delayed.
- During the **mother**’s elimination diet, she should receive nutritional counseling and **supplements of 1000 mg of calcium per day and 800 IU of vitamin D per day**.

Maternal dietary avoidance for infants with proven CMPA

- Options regarding the **maternal diet** include strict avoidance, reduced ingestion, no avoidance, or, for milk and egg, ingestion of only extensively heated forms (eg, bakery goods) that appear to have reduced allergenicity.
- An alternative option is the **cessation of breastfeeding**.
- In one study of infants with cow's milk allergy, the **median dose of milk** ingested by the mother that elicited symptoms, primarily flaring of eczema, in the breastfed infant was **700 mL**

Children fed with formula or formula plus breast milk

- These patients should receive a diet that excludes dairy products with a therapeutic formula for CMPA.
- Since AAF are synthetic formulas are lactose free, they are the **first line option** for treatment of CMPA.
- **EHF** are formulas produced by enzymatic hydrolysis, heat treatment and ultrafiltration processes which are adapted for use in infants.
- These processes break cow’s milk protein into **shorter peptide** chains.

EHF vs AAF

- An **EHF** is recommended over an AAF or soy formula for **the majority** of patients with CMA since **more than 90 percent** of infants with CMA tolerate extensively hydrolyzed milk protein-based infant formulas.
- An AAF is recommended over an EHF in certain circumstances:
  - Infants with immunoglobulin E (IgE)-mediated CMA at high risk of anaphylaxis who are not already on and tolerating an eHF.
  - Any patient with eosinophilic esophagitis (EoE).
  - Infants who continue to exhibit symptoms on eHFs.
  - Infants with poor growth who have not improved on an eHF.

Children fed with formula or formula plus breast milk

- Amino acid formulas with **oligosaccharide** supplementation of breast milk are now being developed.
- They are proposed as supplements for EHF with 2'fucosyllactose (2'FL) and lacto-N-neotetraose (LNnT).
- These two supplements are based on the use of oligosaccharides found in breast milk whose addition they could **reduce the risk of enteric infections.**
- Furthermore, they may provide a substrate for colonization of the child's intestine with **beneficial bifidobacteria** thereby reducing colonization by pathogens.
- These supplements could positively affect intestinal epithelial integrity, apoptosis, and intestinal permeability.

Formula-fed infants

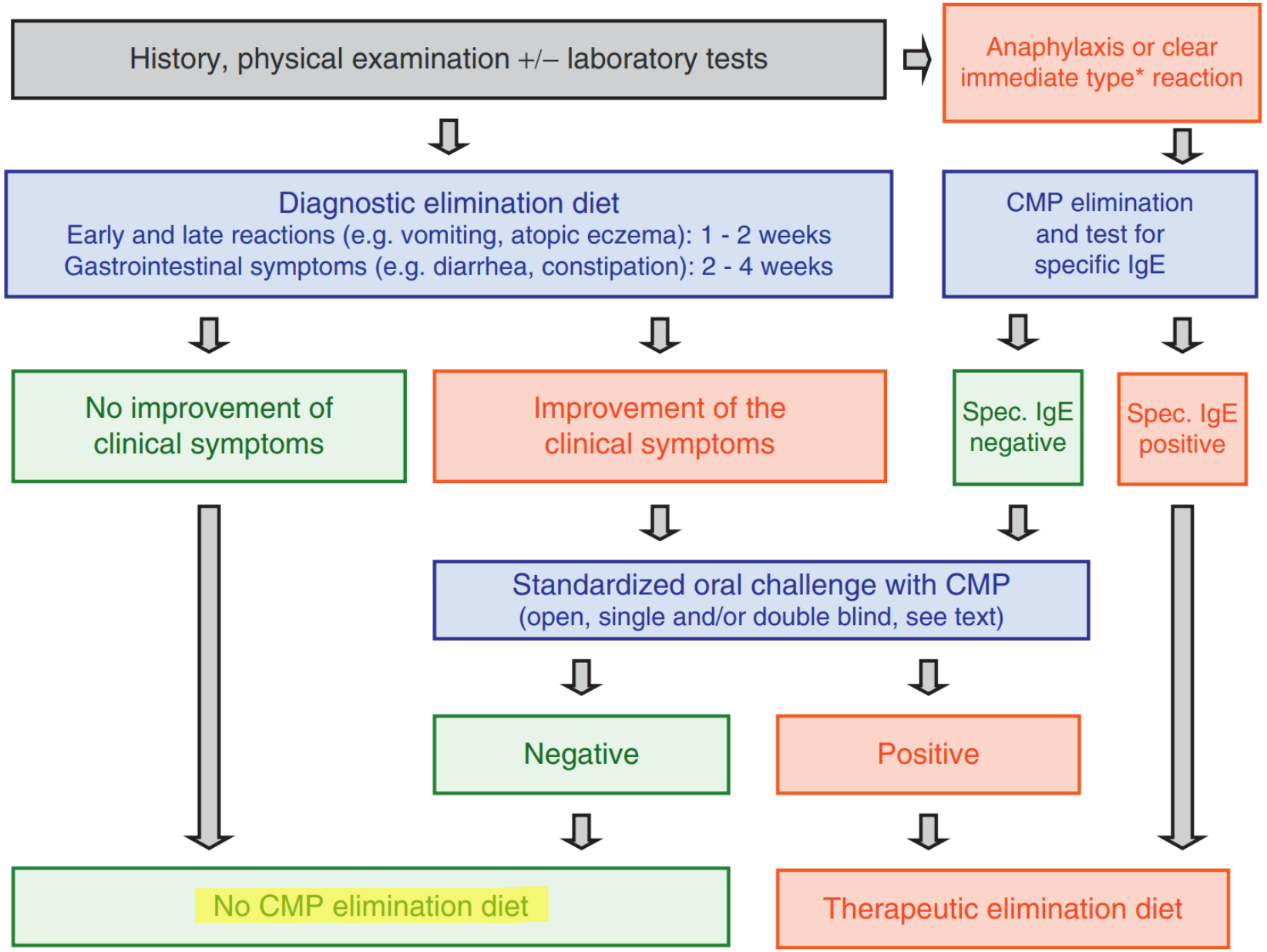
- Another option that is available in Europe is **extensively hydrolyzed rice protein-based formula** (eRHF).
- Partially hydrolyzed cow's milk formulas (**PHF)** are formulas in which peptide epitopes capable of producing allergic reactions are conserved.
- pHFs are not considered hypoallergenic in the United States and are not suitable options for infants with CMA.
- Formulas from Europe labeled hypoallergenic (HA) are typically partially hydrolyzed and not suitable for management of CMA.

Inappropriate Formulas for CMPA

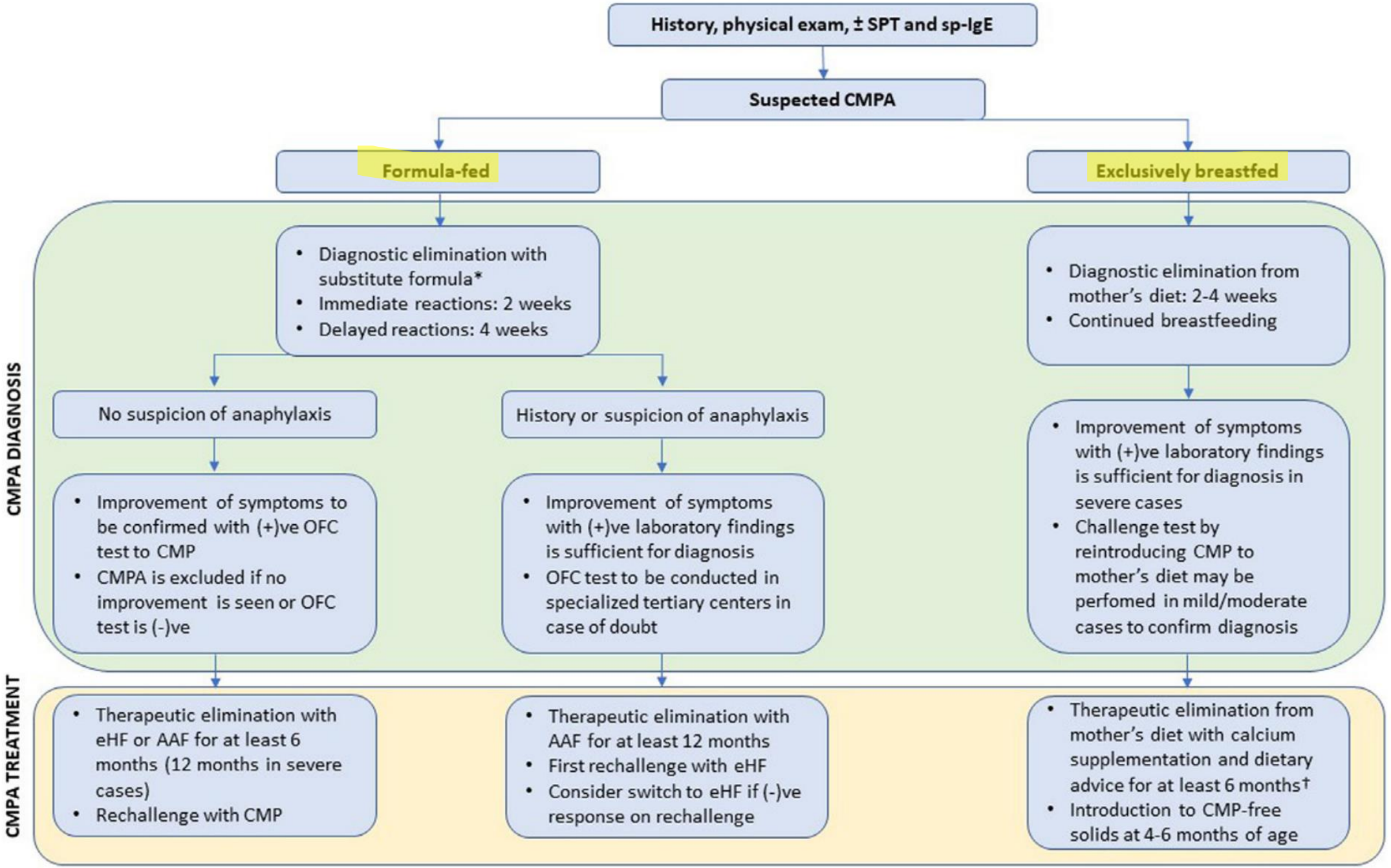
- **Milk from other mammals** is not nutritionally appropriate for use in infants.
- Milk made from almonds, hazelnuts, rice, soy, coconut and other vegetables is **not nutritionally adequate.**
- In fact, they are juices that are inappropriately called milk since they do not come from the any mammary glands.
- They provide low caloric intake and low bioavailability.

Inappropriate Formulas for CMPA

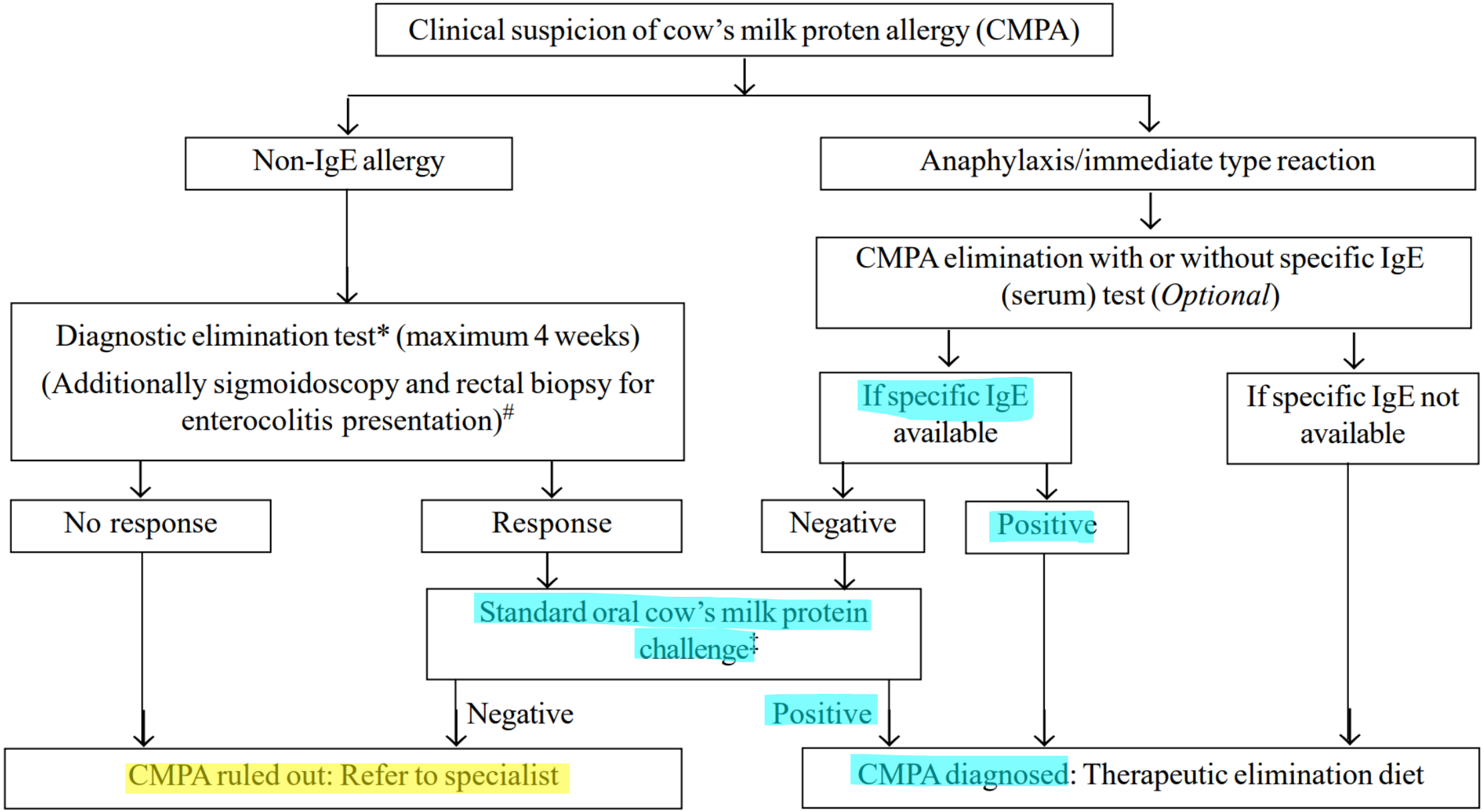
- **Soy formulas**, unlike the so-called milks of other vegetables, are adapted for use by infants.
- Nevertheless, the availability of **minerals such as zinc, iron, magnesium and phosphorus may be low due to their phytate content.**
- In addition, **cross-reactions** have been reported in 10% to 30% of cases with CMPA, regardless of whether they were positive or negative in tests for cow's milk protein specific IgE.
- In particular, infants with **multiple food allergies and eosinophilic enterocolitis react to soy protein.**
- Not surprisingly, specialist groups have different positions on the use of soy formula for CMPA, but they **generally agree that they should not be used before 6 months of age.**

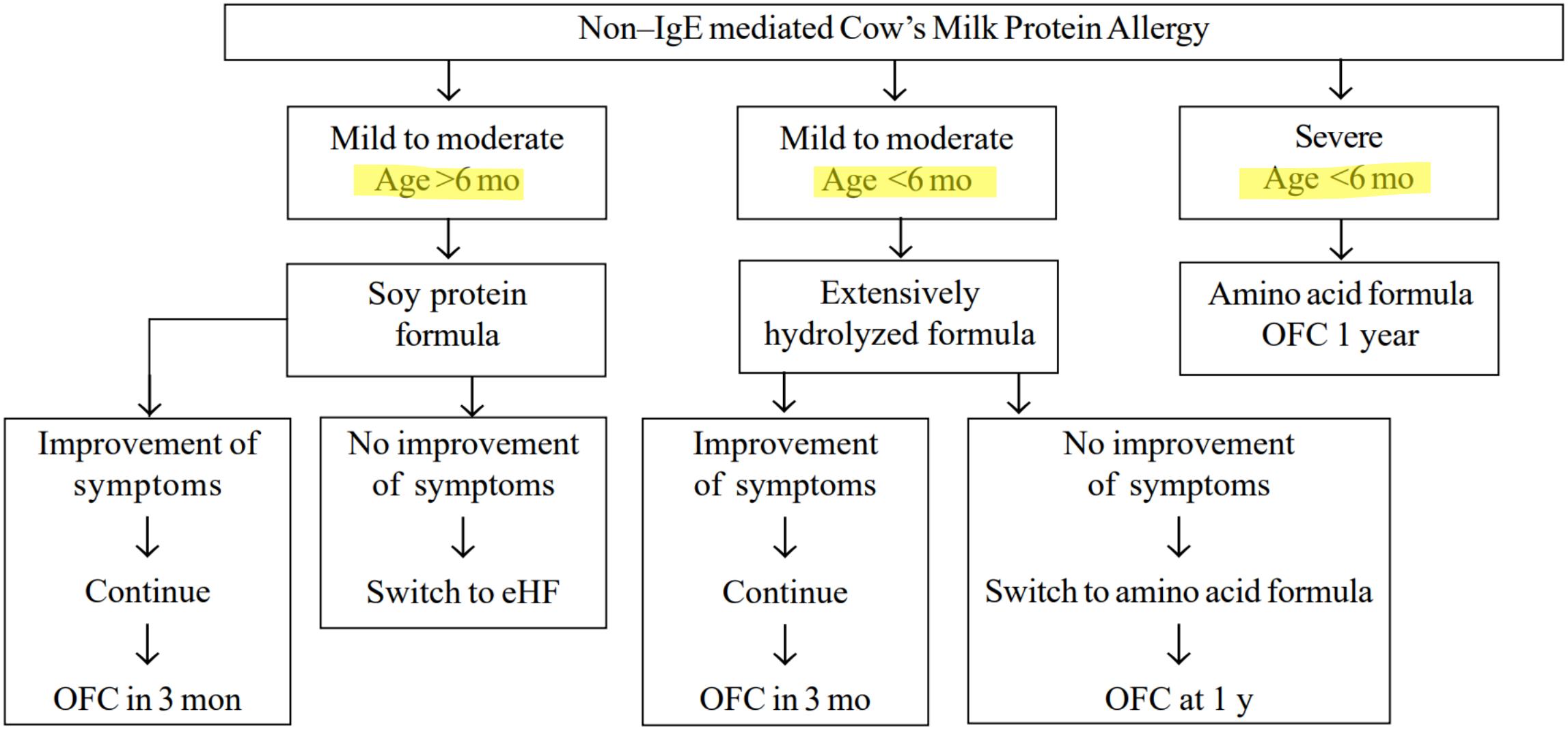


Cow's milk allergy: evidence-based diagnosis and management for the practitioner, Carlos Lifschitz [1], Hania Szajewska, Eur J Pediatr. 2015 Feb;174(2):141-50



Allergol Immunopathol (Madr), .Diagnosis and management of cow's milk protein allergy in Turkey: Region-specific recommendations by an **expert-panel,** N Guler· et al. Mar-Apr 2020;48(2):202-210. a


Clinical suspicion of cow's milk proten allergy (CMPA)
Non-IgE allergy
Anaphylaxis/immediate type reaction
CMPA elimination with or without specific IgE (serum) test (Optional)
Diagnostic elimination test* (maximum 4 weeks)
(Additionally sigmoidoscopy and rectal biopsy for enterocolitis presentation)#
If specific IgE available
If specific IgE not available
No response
Response
Negative
Positive
Standard oral cow's milk protein challenge‡
Negative
Positive
CMPA ruled out: Refer to specialist
CMPA diagnosed: Therapeutic elimination diet



Guidelines on Diagnosis and Management of Cow's Milk Protein Allergy, John Matthai et al., Indian Pediatr. 2020 Aug 15;57(8):723-729.

Resolution of CMPA

- The resolution of CMA is variable, depending upon the type of allergy (IgE mediated or non-IgE mediated) and the population examined (general public or referral populations).
- **Non-IgE-mediated CMA tends to resolve more quickly**.
- The common milk protein-induced proctocolitis typically resolves by one year of age, and, for this condition, milk can be introduced at home.
- For food protein-induced enterocolitis syndrome (FPIES), a careful OFC supervised by an allergy specialist in a setting appropriate for a high-risk procedure is warranted by the **age of two to three years** if there have been no recent reactions from accidental exposures.

Resolution of CMPA

- **Concomitant allergic rhinitis and asthma and onset of the allergy at less than one month** of age are risk factors for persistent IgE-mediated food allergies.
- Rates of resolution in children with **IgE-mediated CMA followed in allergy** practices are lower than those of children in the general population, probably because these children are more severely allergic.
- Subjects who were initially **tolerant to baked milk** were 28 times more likely to become tolerant to liquid milk over a median of 37 months than those who were initially baked milk reactive,

CMPA Prevention

- The risk of developing allergies has a genetic component that can be determined by a **family factor**.
- Historical data shows that the incidence of atopic disease is around 15% but that it is higher in children with a family history of atopic disease.
- If a family member has an allergy, the **risk** of it also occurring in **siblings is 10 times greater** than in the general population.
- **Breast milk** is universally recognized as the **ideal food for infants**, and breastfeeding as the ideal way to provide that milk for healthy growth and development of infants.

CMPA Prevention

- The World Health Organization recommends that infants be **exclusively breastfed for the first six months** of life to achieve healthy growth and development.
- After this period, **breastfeeding should continue** together with nutritionally adequate and safe complementary foods until the child is **two years or older.**
- **Exclusive breastfeeding has proven to be the best method for preventing allergies**
- CMPA is **less severe** for breastfed children than for formulas fed or both
- Because **breast milk has 100,000 times less protein than cow's milk**, and breast milk also contains immunomodulators.

CMPA Prevention

- There is conflicting evidence about whether **delaying the introduction of solid foods** into an infant's diet helps prevent the incidence of allergies.
- **Some suggest** that restriction and delay in the introduction of food can prevent allergies, but **others argue** that early introduction may even be protective against allergies.
- **restricting solid foods after six months** can lead to inadequate nutrient intake, feeding problems, and growth deficits.
- evidence suggests that there is **no benefit** in delaying introduction or imposing a specific restriction on potentially allergenic foods **beyond four to six months**.

CMPA Prevention

- Meanwhile, **prebiotics and probiotics** are often marketed with the promise that they may help prevent allergies.
- In fact, some studies suggest that mothers who take probiotic supplements during pregnancy and lactation may help prevent early atopic disease in infants.
- A systematic review has found that children who had received probiotics acquired greater tolerance of cow's milk protein at the end of three years than did children who received placebos.
- However, the level of evidence is low given the quality of the studies included.
- There is also evidence to suggest that **supplementing EHF with prebiotics** may decrease the incidence of allergic manifestations such as atopic dermatitis, recurrent wheezing, and allergic urticaria in childhood.

CMPA Prevention

- However, no studies have been published that demonstrate that this also occurs with PHF supplemented with prebiotics.
- Nevertheless, these data suggest that **prebiotics and probiotics are safe** and that some evidence indicates that they can reduce the incidence of allergy even though more testing is needed to make them a routine recommendation.
- modulating CMPA is to **induce changes** in the structure of cow's milk proteins through **thermal treatments of cow's milk (**in vitro, results not conclusive)
- Consequently, it is **not advisable** to offer dairy products that are boiled, baked or cooked for long periods of time since they do not offer any demonstrated benefit in terms of tolerance to cow's milk protein

Referral

- All patients with food allergy and their families would benefit from referral to a **registered dietitian nutritionist** (RDN) to learn how to avoid their allergens and how to substitute the eliminated food while minimizing the social impact of the allergy.
- Children in particular are at increased nutritional risk, and parents will need to plan avoidance strategies for a variety of settings, including those where the **parent may not be present (eg, school, camps).**

Referral

- Of note, an RDN has completed a minimum of a bachelor's degree from an Accreditation Council for Education in Nutrition and Dietetics (ACEND) approved program, an ACEND-approved internship, passed a written exam, and completed continuing professional education credits needed to maintain credentials.
- The term "nutritionist" is often free from governmental regulation and can be used by anyone without proof of qualification.
- Children with **multiple food allergies or cow's milk allergy** (CMA) appear to be at **greatest nutritional risk**, with a higher proportion exhibiting poor growth or overt malnutrition.

Conclusions

- CMPA can occur in exclusively **breastfed infants and formula-fed** infants.
- Since its manifestations are **not pathognomonic**, a complete **medical history** with a thorough examination is the basis of diagnosis.
- Confirmation using a **skin prick test, serum-specific IgE, or atopic patch test** lacks specificity, so placebo-controlled double-blind dietary challenges remain the reference treatment.
- Breastfeeding is the best and cheapest option for feeding healthy children and those with CMPA.
- Meanwhile, EHF based on cow's milk remains the recommended and preferred therapeutic option while AAF are reserved for the most severe cases.

Monitoring growth

- Growth in children is a good indicator of adequate energy and protein intake.
- **Weight** is the most sensitive measure of energy intake and is affected earlier and to a greater extent than stature by dietary inadequacies.
- However, stature may be negatively affected by food allergy even prior to changes in weight velocity.
- Children with food allergies are at greater risk of inadequate growth and suboptimal nutrition than those without food allergies

Cow's milk allergy

- Adults with CMA are at risk of **vitamin D and calcium** deficiency because it is difficult to meet calcium needs through nondairy sources without careful substitution.
- The nutritional impact of cow's milk elimination **in children is even greater** since milk and milk products are the primary source not only of calcium and vitamin D, but also fat and protein for young children.
- Milk also provides **vitamin B12, vitamin A, pantothenic acid (vitamin B5), riboflavin, and phosphorus**.
- Finding a nutritionally dense substitute for cow's milk in the pediatric diet is essential.

Breastfed infants

- The nutritional adequacy of the maternal diet may need to be assessed since complete milk elimination can compromise maternal nutrient intake.
- Maternal concentrations of vitamin D, vitamin A, vitamin B6, vitamin B12, thiamin, niacin, selenium, iodine, and choline, in addition to the types of fatty acids present in the maternal diet, are reflected in breast milk.
- Repletion in the maternal diet with a complete **multivitamin mineral** supplement can increase the content of these nutrients in breast milk when the maternal diet is otherwise deficient.
- Calcium content of breast milk is not affected by maternal calcium intake.
- However, maternal dietary calcium replacement or calcium supplementation (**1000 mg/day**) is recommended to maintain maternal stores.


Thank you