CMPA

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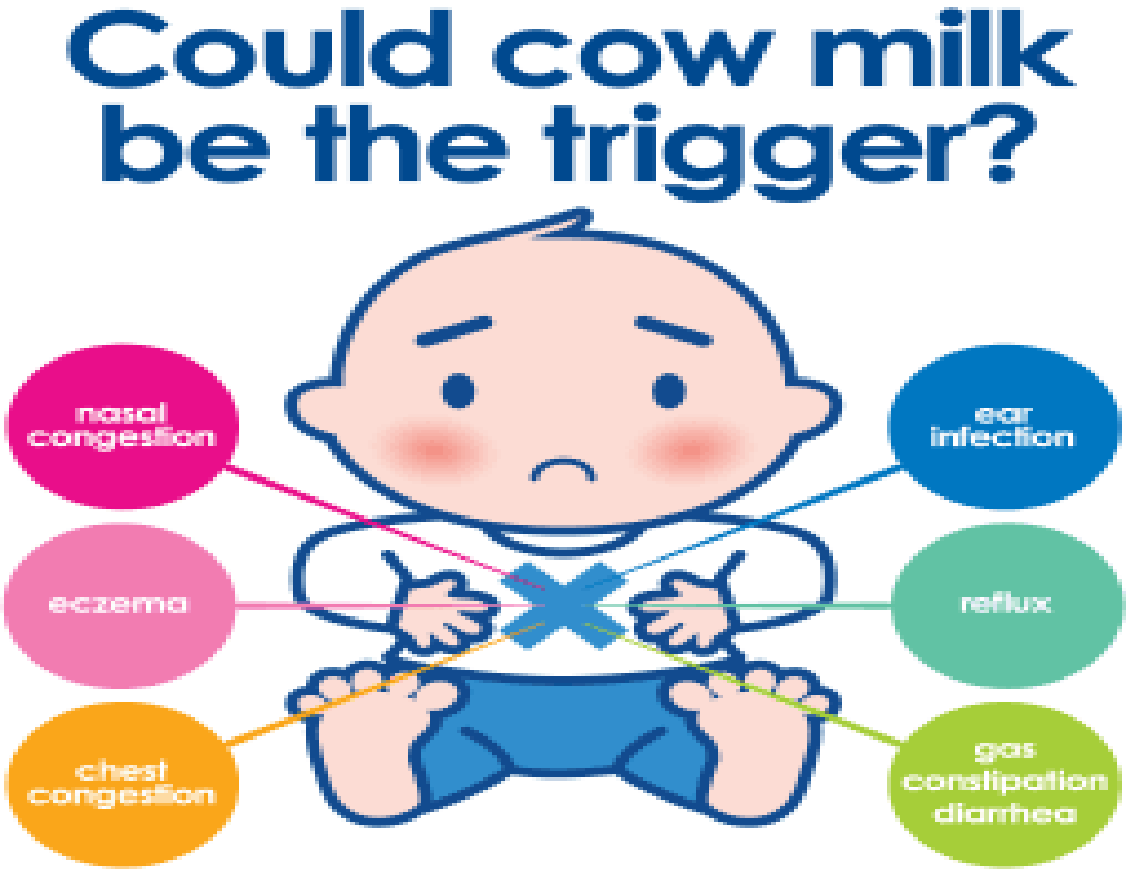
Cow Milk Protein Allergy



Objectives

- Introduction
- Epidemiology
- Clinical presentation
- Diagnostic procedures
- Treatment
- Prognosis
- Prevention
- Take home message

Introduction

- **Food allergy** is defined as an adverse health effect arising from a specific immune response that occurs following exposure to a given food.

- The immune reaction may be immunoglobulin (Ig)E mediated, non-IgE mediated, or mixed.

- **Cow's milk protein allergy (CMPA)** is a disease of infancy which is due to allergy against lactoglobulin, or one or more milk proteins contained in cow's milk

- Should not be confused with lactose intolerance

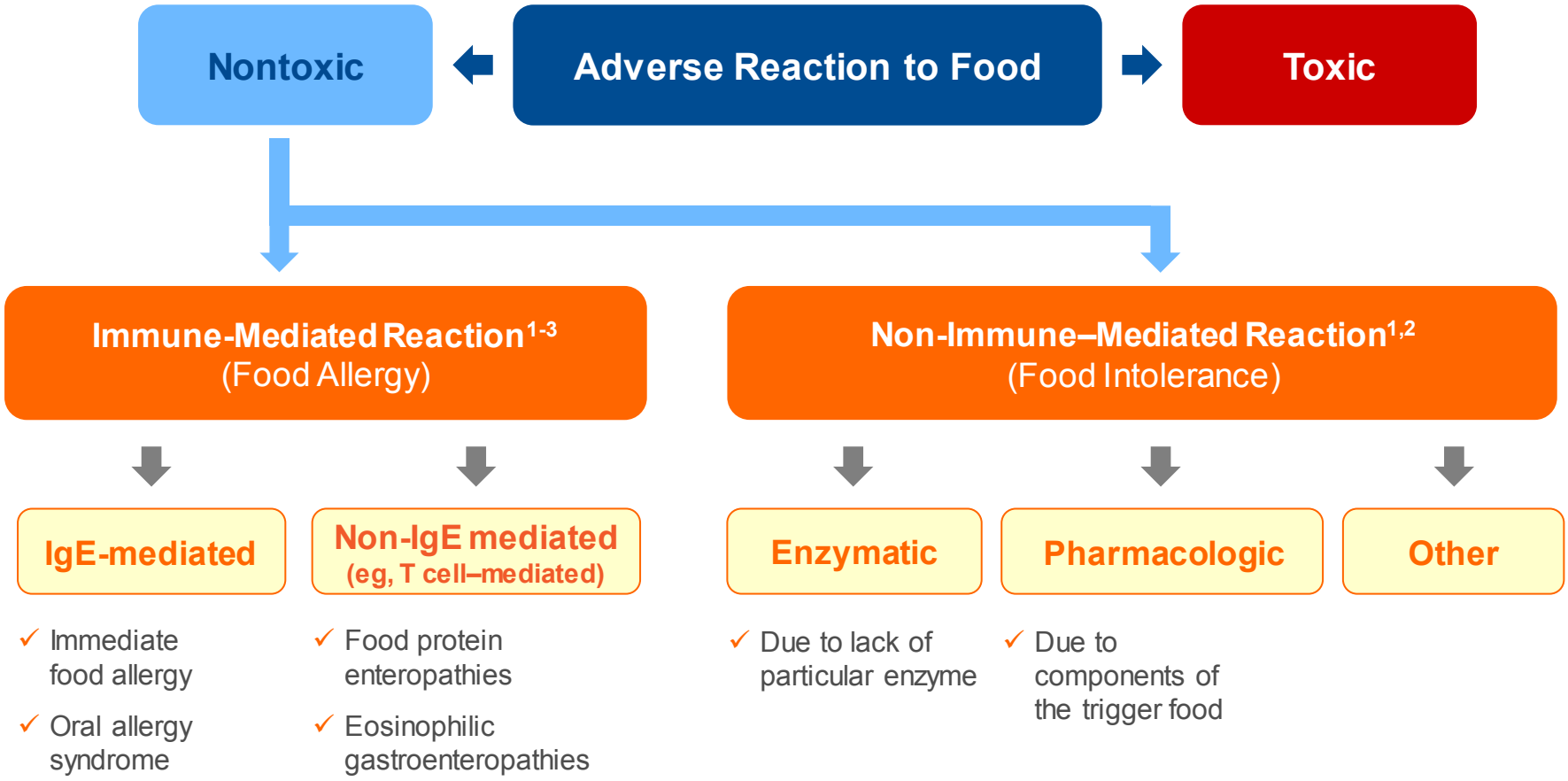
- It is the leading cause of food allergy in infants and young children younger than 3 years.

- **Without an appropriate diagnostic** workup, there is a high risk of both over and under diagnosis and thus over and under treatment.

- A **correct diagnosis** allows the appropriate diet to be given to affected infants, thus supporting normal growth and development.

Introduction

Classification of Adverse Reactions to Food



IgE=immunoglobulin E.

1. Burks AW, et al. *Pediatrics*. 2011;128(5):955-965.
2. Burks AW, et al. *J Allergy Clin Immunol*. 2012;129(4):906-920.
3. Spergel JM. *Allergy Asthma Clin Immunol*. 2006;2(2):78-85.

EPIDEMIOLOGY

Upto 6 % of the children experience food allergic reactions in first 3yrs of life

- CMPA seem to peak in the **first year** of life, with a prevalence of approximately **2% to 3%** of total food allergy
- This prevalence then falls to **<1%** in children 6 years of age and older .

- A few **exclusively breast-fed** infants may also develop clinically significant CMPA via dairy protein transfer into human breast milk.

- In developing countries, such as India, it is believed that CMPA is a disease of the developed world .

- This assumption is mainly due to lack of awareness and diagnostic facilities (endoscopic biopsies).

- In India, cow's milk is used as frequently as in the West and a recent study from the UK has shown that food allergy, including CMPA, is more frequent in non-Caucasians (majority were Asian) than in Caucasians.

- Therefore, there is no reason why it should not occur in India. However, information about this disease from India is scanty and only one study by Yachha et al has highlighted a prevalence of 13% among children < 2 years of age with mal absorption.

- There is no study from India that has prospectively established the presence and frequency of CMPA in children.

CLINICAL PRESENTATION

- CMPA can induce a diverse range of symptoms of variable intensity in infants.

- Can be classified into 2 types –

- ❑ Immediate reactions
- ❑ Delayed reactions

- **Immediate reactions** occur from minutes up to 2 hours after allergen ingestion and are more likely to be IgE mediated

- **Delayed reactions** manifest up to 48 hours or even 1 week following ingestion.

  Involves non–IgE-mediated immune mechanisms(T cell mediated immunity)

- **Combinations of immediate and delayed reactions** to the same allergen may occur in the same patient.

- Symptoms and signs related to CMPA may involve many different organ systems, mostly the **skin and the gastrointestinal and respiratory tracts**.

- The involvement of 2 systems increases the probability of CMPA.

TABLE 1. Some symptoms and signs related to CMPA

	Infants and toddlers	Older children	Immediate reaction (within min–2 h after ingesting CMP)
Digestive	Dysphagia	Dysphagia	Vomiting
	Frequent regurgitation	Food impaction	
	Colic, abdominal pain	Regurgitation	
	Vomiting	Dyspepsia	
	Anorexia, refusal to feed	Nausea, vomiting	
	Diarrhea ± intestinal protein or blood loss	Anorexia, early satiety	
	Constipation ± perianal rash	Diarrhea ± intestinal protein or blood loss	
	Failure to thrive	Constipation	
	Occult blood loss	Abdominal pain	
	Iron-deficiency anemia	Occult blood loss	
		Iron-deficiency anemia	
Respiratory	Runny nose	Runny nose	Wheezing or stridor
	Wheezing	Wheezing	Breathing difficulties
	Chronic coughing (all unrelated to infections)	Chronic coughing (all unrelated to infections)	
Skin	Urticaria (unrelated to infections, drug intake, or other causes)	Urticaria (unrelated to infections, drug intake, or other causes)	Urticaria
	Atopic eczema	Atopic eczema	Angioedema
	Angioedema (swelling of lips or eyelids	Angioedema (swelling of lips or eyelids)	
General	Anaphylaxis	Anaphylaxis	Anaphylaxis
	Shock-like symptoms with severe metatobolic acidosis, vomiting, and diarrhea (FPIES)		FPIES

CMPA = cow's-milk protein allergy; FPIES = food protein–induced enterocolitis syndrome.

Diagnosis

- Diagnosis is difficult due to the wide range of possible symptoms that may occur and in a clinical context diagnosis of CMPI is based either on repeated withdrawal of and challenge with cow's milk, or by demonstration of histological changes on repeated endoscopic biopsies.

- The double-blind, placebo controlled food challenge is the best way to diagnose but it is difficult to perform and interpret.

DIAGNOSTIC PROCEDURES

- The **first step** is a thorough **medical history and physical examination**.

- Allergen elimination and challenge procedure is gold standard

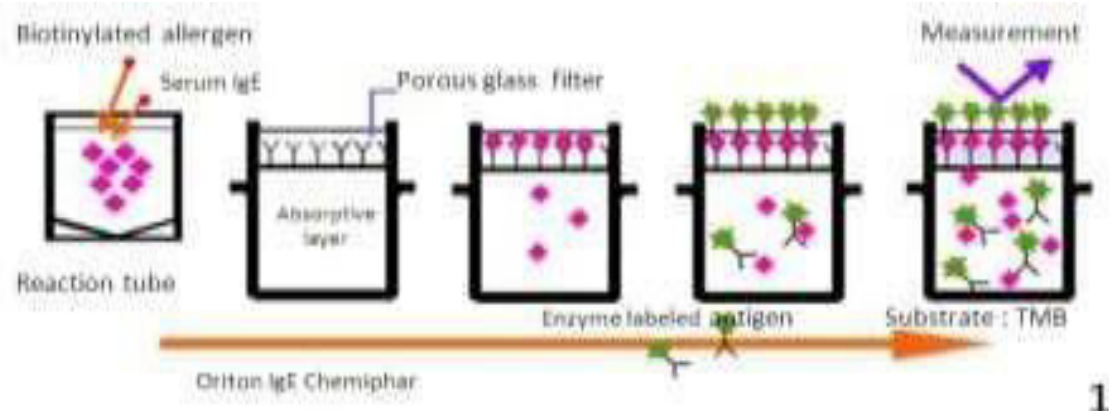
- Determination of specific IgE and skin Prick(SPT) test

  - Serum IgE – sensitivity 87%, specificity – 48%
  - SPT – sensitivity 88% , specificity – 68%
  - Not of much help due to it's low specificity

Determination of Specific IgE and Skin Prick Test

- For clinical practice, the determination of **specific IgE in a blood sample and the skin prick test (SPT)** are useful diagnostic tests at any age.

- The higher the antibody titer and the larger the diameter of the SPT reaction, the greater is the probability of having a reaction to CMP and allergy persistence.



- Sigmoidoscopy showing aphthous ulcers is seen in 82% of cases and rectal biopsy(>6 eosinophil /HPF) is positive in 97% of infants with allergic colitis which provide an initial clue in diagnosis.

- Milk elimination and challenge to be done to confirm the diagnosis

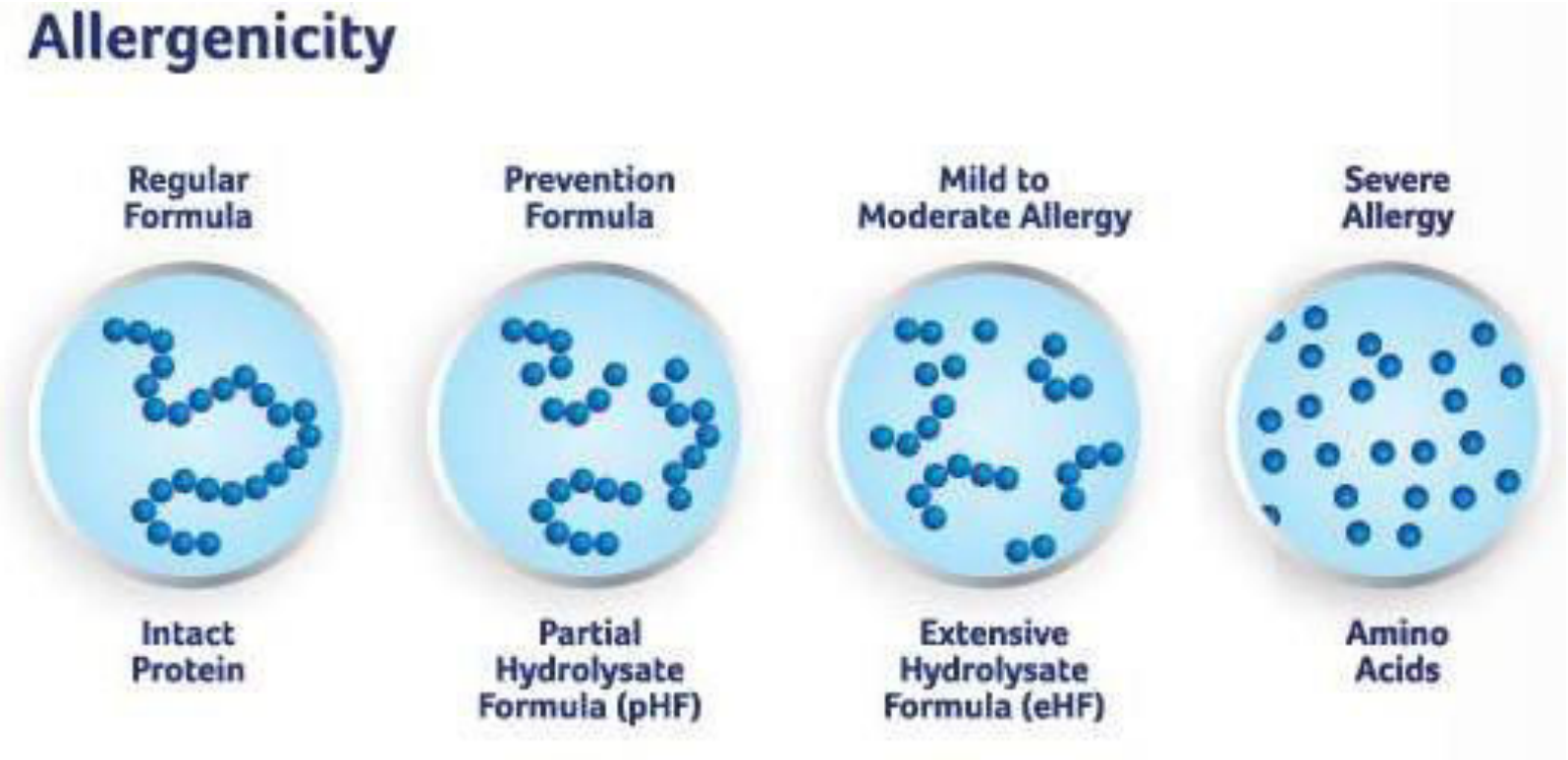
Endoscopy and Histology

- In patients with otherwise **unexplained significant and persistent gastrointestinal symptoms**, failure to thrive, or iron deficiency anemia, upper and/or lower endoscopies with multiple biopsies are appropriate;

- Neither sensitive nor specific for CMPA.

- The diagnostic yield of these procedures is higher for finding diagnoses **other than CMPA.**

Formula feed: Allergenicity decrease with decreasing chain length



Important Information

Cow's-milk protein (CMP)

Diagnostic Elimination of CMP

- If symptoms are relevant and CMPA is likely, a **diagnostic elimination** of CMP should be initiated for a limited period of time.
- This ranges from **3 to 5 days** in children with immediate clinical reactions (eg, angioedema, vomiting, exacerbation of eczema within 2 hours)
- **1 to 2 weeks** in children with delayed clinical reactions (eg, exacerbation of eczema, rectal bleeding).
- In patients with gastrointestinal reactions (eg, chronic diarrhea, growth faltering), it may take **2 to 4 weeks** on a CMP-free diet to judge the response.
- If there is **no improvement** in symptoms within these timelines, then CMPA is unlikely.

- **In non–breast-fed infants**, cow's-milk–based formula and supplementary foods containing CMP or other unmodified animal milk proteins (eg, goat's milk, sheep's milk) should be strictly avoided.

- **If the first feeds with cow's-milk–based formula in a breast-fed infant** cause symptoms, the infant should return to exclusive breast-feeding.

- An elimination diet in formula-fed infants usually starts with an **extensively hydrolyzed infant formula (eHF)**
-
- In infants with extremely severe or life-threatening symptoms, an **Amino acid formula** may be considered as the first choice.

- **Soy protein–based formula** may be an option in infants older than 6 months who do not accept the bitter taste of an eHF, or in cases in which the higher cost of an **eHF** is a limiting factor, provided that the tolerance to soy protein has been established.

- If there is no improvement **within 2 weeks**, then an allergic reaction to the remaining peptides in the eHF must be considered, particularly in infants with sensitization against multiple foods.

- In these cases, an **AAF** should be tried before CMPA is ruled out as cause of the symptoms.

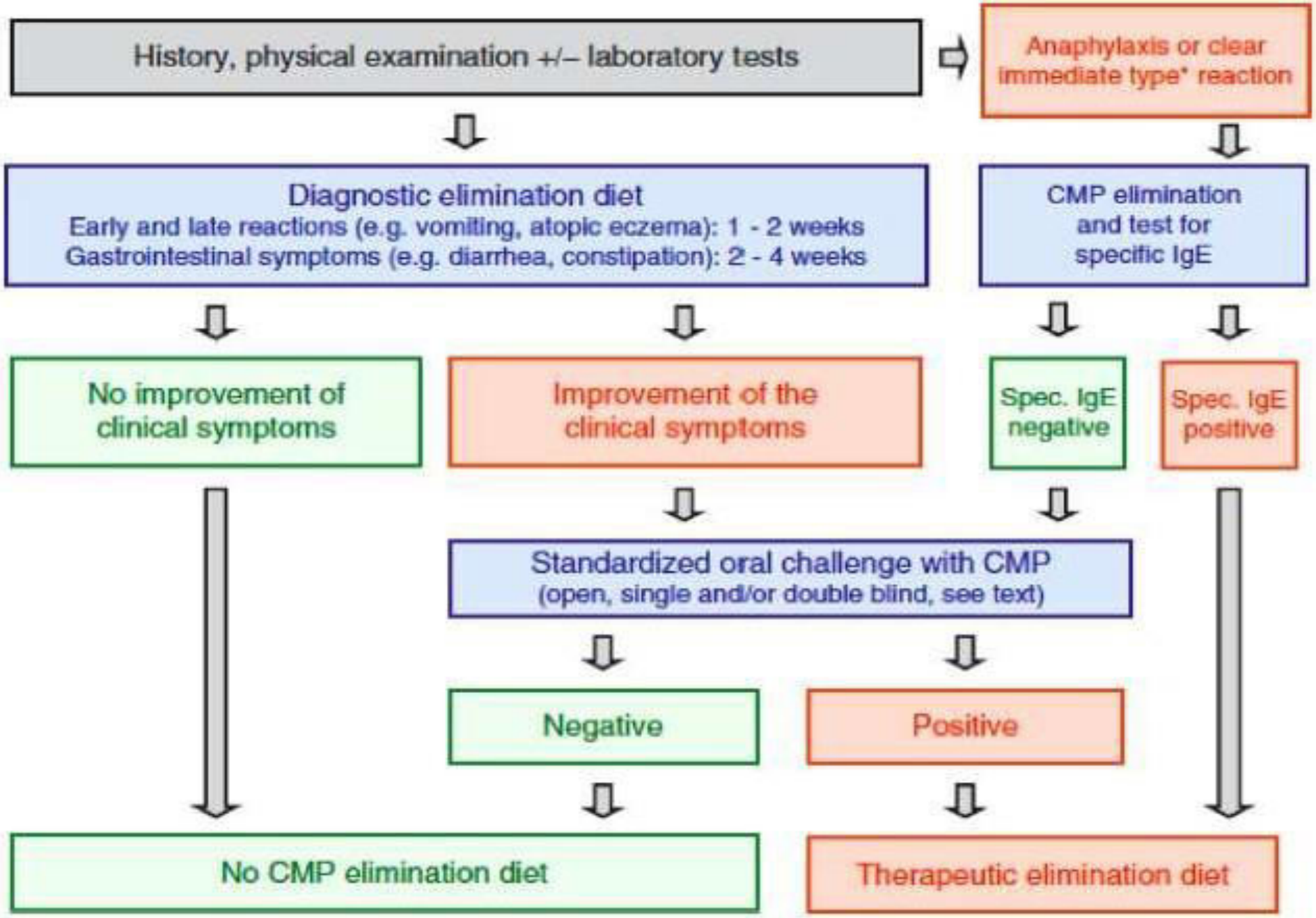
Oral Food Challenge Procedure With CMP Open and Blind Challenges

- After documentation of significant improvement on the diagnostic elimination, the diagnosis of CMPA should be confirmed by a **standardized oral challenge test** performed under medical supervision.

- This allows documentation of any signs and symptoms and the milk volume that provokes symptoms, and allows symptomatic treatment as needed.

Dose of Milk

- Stepwise doses of 1, 3.0, 10.0, 30.0, and 100mL may be given at 30-minute Intervals.
- **If severe reactions are expected**, then the challenge should begin with minimal volumes (eg, stepwise dosing of 0.1, 0.3,1.0, 3.0, 10.0, 30.0, and 100mL given at 30-minute intervals).
- **If no reaction occurs**, then the milk should be continued at home every day with at least 200 mL/day for at least 2 weeks.


History, physical examination +/– laboratory tests
Anaphylaxis or clear immediate type* reaction
Diagnostic elimination diet
Early and late reactions (e.g. vomiting, atopic eczema): 1 - 2 weeks
Gastrointestinal symptoms (e.g. diarrhea, constipation): 2 - 4 weeks
CMP elimination and test for specific IgE
No improvement of clinical symptoms
Improvement of the clinical symptoms
Spec. IgE negative
Spec. IgE positive
Standardized oral challenge with CMP
(open, single and/or double blind, see text)
Negative
Positive
No CMP elimination diet
Therapeutic elimination diet

TREATMENT

- The strict avoidance of CMP is presently the safest strategy for managing CMPA.

- substitute formula is needed to fulfill nutritional requirements in an individual child with CMPA and the best choice of such a formula depends mostly on the age of the patient and the presence of other food allergies.

Infants Up to Age 12 Months

- If the diagnosis of CMPA is confirmed, then the infant should be maintained on an elimination diet using a therapeutic formula for at least **6 months or until 9 to 12 months** of age.

- Infants/children with **severe immediate IgE- mediated reactions** may remain on the elimination diet for 12 or even 18 months before they are rechallenged after repeated testing for specific IgE.

- **The factors that determine the choice of formula used in an individual infant include**:
- residual allergenic potential
- formula composition
- costs
- availability
- infant's acceptance

- **Infants should grow and thrive normally** when treated with either **eHF or AAF formula** .

eHF Based on CMP

- The majority of infants and children with CMPA tolerate an **extensively hydrolyzed formula** with whey or casein as a nitrogen source.

- American Academy of Pediatrics (**AAP**) defines an extensively hydrolyzed formula as a formula containing only peptides that have a molecular weight of <3000 Da.

AAF

- Formulae containing free amino acids as the only nitrogen source are the best option in infants reacting to **eHF**.
- This risk is estimated to be **<10%** of all infants with CMPA, but it may be higher in the presence of severe enteropathy or with multiple food allergies.
- For that reason, AAF may be considered a **first-line treatment in infants with**

➢ **severe anaphylactic reactions** and

➢ **infants with severe enteropathy** indicated by hypoproteinemia and faltering growth.

Soy protein–based formulae

- Soy protein–based formulae are tolerated by the majority of infants with CMPA, but between **10% and 14%** of affected infants react to soy protein, with higher proportions in infants younger than 6 months.

- **The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the AAP** recommend that cow's-milk–based formulae should be preferred over soy formula in healthy infants, and soy protein– based formulae **should not** usually be used during the **first 6 months** of life.

❑ Soy formulae have nutritional disadvantages because:

- their absorption of minerals and trace elements may be lower because of their phytate content , and
- they contain appreciable amounts of isoflavones with a weak estrogenic action that can lead to high serum concentrations in infants.

- however, a **soy formula may be considered** in an infant with CMPA:

- **older than 6 months if eHF is not accepted or tolerated by the child,**
- **if these formulae are too expensive for the parents, or**
- **if there are strong parental preferences (eg, vegan diet).**

Weaning Food

- **weaning food** should be free of CMP until a supervised successful oral challenge indicates the development of tolerance.

- **Delaying introduction of weaning foods** with a higher allergenic potential such as egg, fish, or wheat has no proven beneficial effect for allergy prevention and should be avoided unless there is a proven allergy to any of them .

REEVALUATION

- There is insufficient evidence to recommend an optimal interval before reevaluation.

- The **duration of exclusion** will depend on the age, severity of a child's symptoms, and positivity of specific IgE for CMP.

- Convention is that a challenge with cow's milk may be performed after maintaining a therapeutic diet for at least 3 months or maximum up to 12 months to avoid continuing a restrictive diet for an unnecessarily long time.
- Such restrictions may result in improper growth.

➢ **If a challenge is positive, then the elimination diet is usually continued for between 6 and 12 months.**

➢ **If the challenge is negative, then cow's milk is fully reintroduced into the child's diet.**

Prognosis

- The prognosis for CMPA in infancy and young childhood is good.

➢ Approximately **50%** of affected children develop tolerance by the age of 1 year,

➢ **>75%** by the age of 3 years, and

➢ **>90%** are tolerant at 6 years of age.

CMPA: Is there potential for primary prevention?

- The increasing incidence of pediatric allergies including CMPA calls for new primary **prevention** strategies.

- ***Exclusive breastfeeding*** *is recommended for at least 4 months and up to 6 months of age.*
- Advantages-

✓ To possibly reduce the incidence of atopic dermatitis in children younger than **2 years**.

✓ To reduce the early onset of wheezing before **4 years of age**

✓ To reduce the incidence of cow's milk protein allergy in the **first 2 years** of life.

- If an infant is not breastfed or is partially breastfed, commercial infant **formula should be used until 12 months of age.**

- **Complementary foods** can be introduced between 4 and 6 months of age, when an infant is developmentally able to sit with support and has sufficient neck control.
- Most pediatric guidelines suggest first introducing single ingredient food after ***6 months*** of age, with one new food every 3 to 5 days.

- **Probiotic supplementation:**

- It is known that oral probiotic supplementation can reduce the prevalence of atopic disease by:

✓ **stabilizing intestinal integrity,**

✓ **increasing numbers of specific intestinal flora**

✓ **reducing intestinal inflammation**

Take home message

Cow's milk protein allergy is an important cause of food allergy in infants and young children.

- More than two organ system can be involved and the reactions may be IgE or non IgE mediated one.

- Clinical symptoms may vary in severity and may be non specific at times.

- Early recognition of signs and symptoms is essential to have a favourable outcome.

- High index of suspicion, clinical improvement on milk withdrawal and reappearance of symptoms on challenge remain the gold standard test in diagnosis.

- Exclusive breast feeding, avoidance of early introduction of allergenic items are likely to reduce the condition.

THANK YOU