



How to Diagnose and Manage Cow Milk Protein Allergy?

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Introduction

Ingestion of cow's milk can cause adverse reactions that may occur at any age, including exclusively breast fed infants, but not all reactions are allergic. These reactions range from non-allergic hypersensitivity, traditionally termed cow's milk protein intolerance (CMPI) to allergic milk hypersensitivity traditionally termed cow's milk protein allergy (CMPA). The latter requires the activation of an underlying immune mechanism. In many children with CMPA, the condition is IgE-mediated and is thought to manifest as a phenotypical expression of atopy (urticaria and angioedema), with or without atopic eczema, allergic rhinitis, asthma and anaphylaxis. A large subset of patients have non-IgE mediated allergy and present mainly with gastrointestinal (GI) symptoms. These conditions are very different from lactose malabsorption.

Children allergic to cow's milk are allergic to its proteins. The major cow milk allergens belong either to the casein fraction (α_{s1} -, α_{s2} -, β -, and κ -casein) or to whey proteins (α -lactalbumin and β -lactoglobulin).

The prevalence of CMPA is 0.5% in exclusively breastfed infants and increases to 2–3% in formula fed. It may be higher in those infants fed with cow milk. There is limited data from India about its prevalence but there are reports of 13% among children less than 2 years of age with malabsorption and a 30% prevalence in children with chronic diarrhea.

Clinical Manifestations

CMPA is mostly a disease of infancy and early childhood and presents with a wide variety of symptoms including gastrointestinal in 32 to 60% of cases, cutaneous symptoms in 5 to 90% and anaphylaxis in 0.8 to 9% of cases. Respiratory symptoms are not rare. In most of the populations studied, there are overlapping presenting symptoms.

Conditions associated with IgE-mediated allergic reaction to cow's milk include vomiting, diarrhea and rash with or without respiratory symptoms.

Although isolated IgE mediated gastrointestinal symptoms are rare in the first month of life, non-IgE mediated, bloody stools in newborn infants within the first 24 hours of life has been described.

Several studies including ones from India noticed the diversity of conditions associated with non-IgE mediated reaction to cow's milk. It can present with

1. Diarrhea—bloody and non-bloody; proctocolitis in a well appearing breastfed or formula fed baby is the most common manifestation of non-IgE mediated CMPA.

2. Gastroesophageal reflux disease especially if not responding to acid blockers and associated with poor weight gain or eczema.
3. Infantile colic that is extreme and poor response to anti-reflux measures especially associated with eczema.
4. Cow's milk protein-induced enteropathy manifested by diarrhea, failure to thrive, vomiting, hypoproteinemia.
5. Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated gastrointestinal food hypersensitivity that manifests as profuse, repetitive vomiting, sometimes with diarrhea, leading to dehydration and lethargy in the acute setting, or weight loss and failure to thrive in a chronic form. Skin rash and other manifestations of IgE-based allergies are not seen. FPIES has not been seen in exclusively breastfed infants. FPIES usually begins in early infancy within one to four weeks of introduction of cow's milk or soy protein, which are the most common offending agent for FPIES. It, however, may also be induced by other solid foods such as rice, oats, barley, poultry, certain fruits, vegetables or legumes. Mean onset of solid food FPIES is later than CMPA as these foods are introduced at a later age, typically around 4–7 months.
6. Allergic eosinophilic esophagitis characterized by swallowing difficulty, food impaction and dysphagia.
7. Constipation not resolving with standard measures.
8. Rarely, it can present with chronic pulmonary infiltrates known as Heiner's syndrome.

Unfortunately, there is no one symptom that is pathognomonic for CMPA. The timing and pattern of these symptoms aid in the diagnosis and help differentiate between IgE and non-IgE mediated forms of allergy (Table 1.1). Symptoms of CMPA occur often, but not always, within the first 6 weeks after the introduction of cow milk protein.

How to Diagnose it?

The diagnosis of CMPA is usually clinical. It is based upon the history and sometimes laboratory testing, when available. Diagnostic tests for non-IgE mediated manifestations of CMPA are limited. For IgE mediated reactions, milk sensitization may be determined by:

- Skin testing, including skin prick test (SPT), and atopy patch test (APT).
- The evaluation of serum food-specific IgE using one of the several available methods.

However, both these methods help in prognosis rather than diagnosis and there is no consensus statement on routine usage of these tests. The classic method for diagnosing CMPA is by elimination, provocation and re-elimination, using for the

Table 1.1: Basic differences between IgE and nonIgE mediated CMPA

<i>Clinical presentation</i>	<i>IgE-mediated CMPA</i>	<i>NonIgE-mediated CMPA</i>
Exposure to reaction time	Minutes to a couple of hours	Several hours to days
Severity	Mild to anaphylaxis	Mild to moderate
Duration	Often persists beyond 1 year of age	Usually resolves by 1 year of age
Diagnosis	Serum IgE, skin prick test (SPT)	Oral challenge

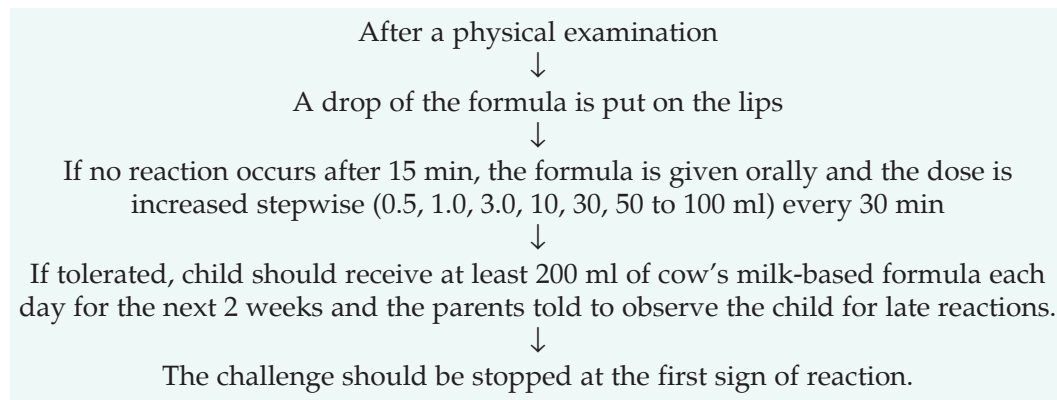
Source: Adapted from *Eur J Pediatr* (2015) 174:141–150.

provocation phase a double blind, placebo-controlled food challenge protocol (DBPCFC). This form of challenge is considered the gold standard as up to 70% of the positive test results obtained with open provocation are not confirmed at a follow-up DBPCFC. Thus, in a setting when oral food challenge cannot be performed, SPT (>3 mm) and Cow's milk specific IgE (≥ 0.35 IU/L) may be of benefit.

More often the child has only milk or milk and soy allergy. Some children may have multiple food allergies one of them being dairy. This is less common in our population for the present.

Keep in mind that though milk allergy presents most commonly during early infancy, older children can also present with milk allergy. Figure 1.1 gives the ESPGHAN practical guidelines for diagnosis of CMPA.

How to Perform an Oral Food Challenge?



Endoscopic Evaluation

Flexible sigmoidoscopic or colonoscopic evaluation with biopsy is a useful tool for further evaluation of selected patients. This test is usually reserved for patients with

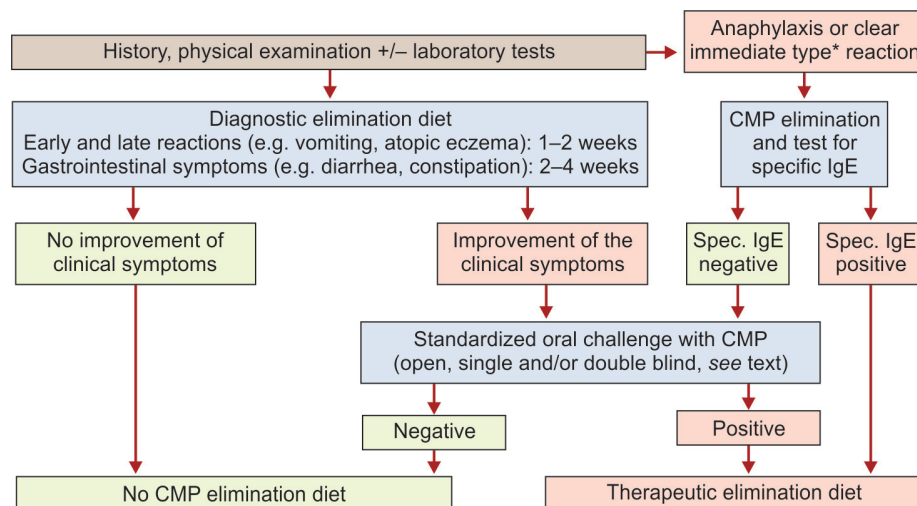


Fig. 1.1: ESPGHAN guidelines on diagnosis of CMPA

*Acute urticaria, stridor, wheeze, anaphylaxis.

unusual or atypical symptoms, such as constipation, diarrhea with mucus-streaked stools but without grossly visible bleeding, or severe rectal bleeding or anemia despite a trial of cow's milk elimination diet.

Although infrequently used as a tool for diagnosing CMPA the characteristic findings are:

- Sigmoidoscopic appearance of aphthous ulcers and rectal biopsy with >6 eosinophils/hpf without much change in crypt architecture (unusual for IBD).
- Isolated nodular lymphoid hyperplasia on colonoscopy.
- Duodenal nodularity and eosinophilia.

If the patient is in the appropriate age range and the history and symptoms are consistent with the diagnosis of CMPA, an open or single-blind challenge is often sufficient to make the diagnosis. However, a double-blind, placebo-controlled oral food challenge remains the gold standard for the diagnosis of food allergy.

How is Cow Milk Protein Allergy Different from Lactose Intolerance?

Table 1.2 shows the difference between cow milk protein allergy and lactose intolerance.

Lactose breath test is available but is difficult to do in very young children, in older children, lactose breath test is a definitive way to diagnose this condition though experimenting with lactose containing and lactose free foods is often adequate.

How to Treat it?

Avoidance of cow milk protein in any form is the only available treatment.

Breastfed Infants

- The mother should eliminate all dairy products from her own diet. This would include foods to which dairy has been added.
- It may take up to 72 hours to clear cow milk protein antigens ingested by the lactating woman from breast milk.
- Calcium supplements should be added to the mother's diet to replace milk intake.
- Complementary foods when started need to be dairy free.

Table 1.2: Difference between cow milk protein allergy and lactose intolerance

	<i>Cow milk protein allergy</i>	<i>Lactose intolerance</i>
Type of adverse reaction	Allergy—immunological	Intolerance—non-immunological
Pathological molecule	Bovine milk protein	Lactose—carbohydrate
Organ involvement	GI tract, skin, respiratory	GI tract
Common GI symptoms	Vomiting, colic, small or large bowel diarrhea, GI bleed	Small bowel diarrhea, colic, flatulence, perianal excoriation
Age group affected	Infancy and toddler	All age groups
Treatment	Stoppage of all dairy products, change to non-dairy protein or hydrolyzed formula	Reduction of lactose, can continue dairy protein, including lactose-free milk, lactose-free yoghurt or ice cream
Result of treatment	Qualitative—all-or-none phenomenon	Quantitative—response as per reduction of lactose

Non-breastfed Children

- Need extensively hydrolyzed 100% bovine casein infant formulas or elemental amino acid formulae.
- Soy formulations are not recommended, particularly in those below 6 months of age.

The DRACMA guidelines clearly suggest extensively hydrolyzed formula (eHF) as the first-line treatment for the majority of situations. In general, eHFs are nutritionally adequate and well tolerated but their main drawbacks are a bitter taste, cost and availability. There is a little use in shifting from one cow milk-based formula to another cow milk-based formula if the consideration is CMPA.

Which Formula and for Whom?

Soy Protein Formula

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and ESPGHAN recommendations agree that soy formulas should not be used in infants with food allergy under 6 months of age. Because of their lower cost and better palatability than extensively hydrolyzed formulas, soy protein formulas could be considered for use in patients with food allergy older than 6 months of age. In such cases, however, tolerance to soy protein should first be established by clinical challenge. Infants with IgE-mediated CMPA allergy are more likely to tolerate soy formula than those with non-IgE-mediated CMPA. Many nutritional pitfalls with these formulae have been implicated in the past, the majority of which have been corrected by manufacturers. It is less expensive and readily available and may be the first line formula for some families. Practitioner and parent should be aware that 25–40% cross reactivity exists with cow milk protein allergy but mostly for non-IgE mediated allergy.

Extensively Hydrolyzed Formulas (eHF)

The American Academy of Pediatrics defines “extensively hydrolyzed formula” as those containing only oligopeptides that have a molecular weight <3,000 Da to which at least 90% of infants do not manifest any clinical symptoms in controlled double-blind studies. Initial exclusive feeding of an extensively hydrolyzed formula is the treatment of choice for infants suspected of having CMPA suffering from mild to moderate disease (*see below*). Because of its taste, some children may refuse to take the needed quantities for growth in which case an amino acid-based formula may be needed as their organoleptic characteristics are not as unpleasant.

There is no role for partially hydrolyzed formulas or pre and probiotics in the management of CMPA.

Amino Acid Formulas

These formulas, as the name indicates, provide protein only in the form of free amino acids and no peptides. Although in theory, amino acid formulas may be used as first-line treatment for CMPA, their high cost may be a limiting factor.

British Society of Allergy and Clinical Immunology recommendations for amino acid formulas include the following:

1. Severe CMPA (failure to thrive and abundant blood in stools),
2. Multiple food allergies,

3. Allergic symptoms or severe atopic eczema when exclusively breastfed,
4. Severe forms of non-IgE-mediated CMPA, such as eosinophilic esophagitis, enteropathies, and food protein-induced enterocolitis syndrome,
5. Growth faltering, and/or
6. Infants at nutritional risk with reactions to or refusal to ingest appropriate amounts of extensively hydrolyzed formula.

Rice Hydrolyzed Formula

An alternative would be to use rice-based formulas. Rice is one of the less allergenic staple foods, reacting in <1% of allergic children. It has no lactose and no phytoestrogens. For this reason, it has been developed as a non-allergenic product in the form of rice protein hydrolysates. These formulae are now in use for more than 10 years in many European countries and proven to be safe and effective.

Alternative Milk Source

Other mammalian sources, such as goat, sheep, buffalo milk, have shown a high degree of cross-reactivity and hence not recommended. There are chicken-based formulas also available and theoretically they should be safe to use (diet C used in the past for intractable diarrhea of infancy was chicken based), but there is limited data.

Does Heating the Milk Alter its Allergenicity?

Casein is thermostable, and hence heating or baking (when temperatures exceed 400°C) is not sufficient to break it down. Whey proteins are thermolabile and baking breaks it down making it less allergenic. It is estimated that only about 20% of the allergy is from the whey component.

Duration of Milk Exclusion Diet

Once an infant is diagnosed as having CMPA and is placed on an exclusion diet, reevaluation needs to be performed every 6 months if the child is under 1 year of age and every 6–12 months from 1 year of age onward, to determine if the child is a candidate for reintroducing cow's milk. The BSACI has suggested an escalation of products, a so-called "milk ladder," starting with baked milk products, as thermal processing reduces allergenicity. If well tolerated, more allergenic products can be reintroduced progressively leaving for the end uncooked cheese and fresh cow's milk, which should only be introduced in children with demonstrated full tolerance to baked milk products. In a breast fed baby, baked foods can be introduced in the mother's diet first.

Prognosis and Natural History

Tolerance is achieved by the majority of children with cow's milk protein allergy. Non-immunoglobulin E (IgE)-mediated CMPA tends to resolve more quickly than IgE-mediated CMPA. This is achieved in >75% by 3 years of age and >90% by 6 years of age when taken as a whole, but almost 85% of non-IgE mediated allergy resolves by the end of the first year.

Conclusion

CMPA is common in India and needs to be differentiated from lactose intolerance. It often presents with gastrointestinal symptoms such as diarrhea and rectal bleed but

can have varying clinical presentations. Strict diagnostic criteria should be applied to minimize misdiagnosis including over diagnosis. In the absence of reliable objective diagnostic tools, clinical assessment with CMP elimination and challenge within 4 weeks remains a fundamental for the accurate diagnosis of CMPA. Elimination of dairy products remains the cornerstone of treatment. In non-breastfed children, extensively hydrolysed formula is the recommended dairy substitute. So as not to prolong unnecessary dietary restrictions, supervised CMP challenges are required, although the optimal interval for reevaluation depends on the clinical scenario. It is important to note that if the child is not improving with eHF by 4 weeks, switch to an amino acid base formula and other diagnoses should be considered.

SUGGESTED READING

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