STANDARD TREATMENT GUIDELINES 2022

Cow’s Milk Protein Allergy

Lead Author
RK Gupta

Co-Authors
Soumya Nagarajan, Dhanesh Volvekar

Under the Auspices of the IAP Action Plan 2022

Remesh Kumar R
IAP President 2022

Upendra Kinjawadekar
IAP President-Elect 2022

Piyush Gupta
IAP President 2021

Vineet Saxena
IAP HSG 2022–2023
Food allergy is an emerging health issue in our country. It is an adverse effect arising from a specific immune response occurring on exposure to a particular food. Food allergy must be differentiated from food intolerance, which is a general nonspecific term for any adverse reaction to particular constituent of food.

Cow’s milk protein allergy (CMPA) is the most common food allergy in infancy, with reported prevalence of 1.5–3% in infancy and fall to <1% by 6 years of age.

Cow’s milk protein allergy is more likelihood of affecting children with other atopic conditions such as asthma, allergic rhinitis, and eczema among others, or with a family background of allergies. About 10–15% of children who have CMPA are also allergic to soy.

- Cow’s milk protein allergy can manifest in a varied clinical presentation and can be attributed incorrectly to many symptoms.
- As immediate symptoms of immunoglobulin E (IgE)-mediated CMPA can be readily recognized, timely recognition of non-IgE-mediated CMPA can be a diagnostic dilemma, due to delayed onset of presentation and overlapping with functional gastrointestinal (GI) disorders.
- IgE-mediated immediate food allergy reactions occur within minutes to 2 hours while in non-IgE-mediated or mixed type CMPA, symptoms occur after 2 hours up to 2 days or even 1 week (Table 1).
**What are the Symptoms?**

**TABLE 1: Symptoms and signs of CMPA.**

<table>
<thead>
<tr>
<th>IgE-mediated symptoms</th>
<th>Non-IgE-mediated symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Urticaria, angioedema, and rashes</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Wheezing, cough, running nose, conjunctivitis, and laryngeal edema</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Vomiting, GERD, dysphagia, pain abdomen, diarrhea, blood in stool, and oral allergy syndrome</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension and tachycardia</td>
</tr>
<tr>
<td>Systemic</td>
<td>Anaphylaxis</td>
</tr>
</tbody>
</table>

(CMPA: cow’s milk protein allergy; GERD: gastroesophageal reflux disease; IgE: immunoglobulin E)

Eosinophilic esophagitis, food protein enteropathy (FPE), food protein-induced enterocolitis syndrome (FPIES), and food protein-induced proctocolitis (FPIP) are distinct clinical entities associated with non-IgE-mediated CMPA.

**Well Baby with Blood in Stools**

Some exclusively breastfed, happy thriving infants may develop allergy to CMP due to protein transfer via breast milk with symptoms of blood and mucus streaking in otherwise normal stools. This settles within 48–72 hours of cow’s milk protein elimination from mother’s diet and generally resolves by 1 year of age.

With an extensive list of symptoms associated with CMPA, differential diagnosis includes other food allergies, lactose intolerance, immunodeficiency, infectious enterocolitis, irritable bowel syndrome, Meckel's diverticulum, cystic fibrosis, pancreatic insufficiency, etc.

Lactose intolerance is commonly confused with CMPA, presents with loose stool and flatulence but without vomiting, blood in stool or any other system involvement (Table 2). Most common variety is secondary lactose intolerance due to loss of brush border lactase expression secondary to inflammation or structural damage, usually gastroenteritis. Usually resolves by 2 weeks exclusion of lactase in diet. Primary and congenital variety is rare and permanent.
### Cow's Milk Protein Allergy

#### Differential Diagnosis

**TABLE 2:** Differences between CMPA and lactose intolerance.

<table>
<thead>
<tr>
<th></th>
<th><strong>CMPA</strong></th>
<th><strong>Lactose intolerance</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Types</td>
<td>IgE and non-IgE-mediated</td>
<td>Due to deficiency of lactase enzyme in intestinal brush border</td>
</tr>
<tr>
<td>Mechanism</td>
<td>It is an immune-mediated reaction to milk protein, so even small exposure may cause features</td>
<td>Quantity-dependent so small amount may be tolerated</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Multisystem involvement (GIT, respiratory, skin, and CVS)</td>
<td>Only gastrointestinal (diarrhea, flatulence, and pain)</td>
</tr>
<tr>
<td>Natural history</td>
<td>Recovers by 4–5 years of age in majority of people</td>
<td>Recovers in days/weeks in secondary, permanent in congenital and primary types</td>
</tr>
</tbody>
</table>

(CMPA: cow's milk protein allergy; CVS: cardiovascular system; GIT: gastrointestinal tract; IgE: immunoglobulin E)

Cow’s milk protein allergy is a clinical diagnosis, and there is no single test or biomarker that is pathognomonic of the condition. Clinical clues that suggest IgE-mediated disease are the involvement of two or more systems, commonly the skin, GI, and respiratory tract. On the contrary, non-IgE-mediated disease (which is more common in India) may manifest with only GI symptoms.

In cases where IgE-mediated variety is suspected, skin prick testing (SPT) and/or blood test for specific IgE can be considered. When non-IgE-mediated case is suspected, elimination of milk protein from diet and oral challenge after improvements in clinical symptoms confirms the diagnosis (Flowchart 1).

**Oral Challenge Test**

- Cow milk either as formula or pasteurized milk (in <12 months age) is administered cautiously in the following manner: 1 mL, 3 mL, 10 mL, 30 mL, and 100 mL (given every 30 minutes), which can be done on an outpatient basis. The child should be observed for 2 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 2 weeks.

- For those with severe reactions on initial presentation (IgE-type), the milk challenge is administered in hospital setup in more graded fashion (0.1 mL, 0.3 mL, 1 mL, 3 mL, 10 mL, 30 mL, and 100 mL: given every 30 minutes) as an inpatient 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 2 weeks to look for any delayed manifestations.
Cow’s Milk Protein Allergy

**Diagnosis**

Double-blind Placebo-controlled Food Challenge

Although being reference standard for diagnosis is limited to research as they are time consuming and expensive. Endoscopy/histopathology will be of help in unexplained cases only.

What is not Required for Diagnosis?

No role for total eosinophil count, vacuolated eosinophil count, and total IgE levels. As of now, atopic patch test is not recommended by any standard guidelines. Basophil histamine release assay and lymphocyte stimulation are used in research setup. Component resolved diagnosis (CRD) or molecular level antigen testing should not be used in routine.

**Flowchart 1:** Algorithm for infants and children with symptoms suggestive of CMPA.

History and physical examination

- Anaphylaxis/type 1 immediate IgE reaction
  - Cow’s milk elimination diet and testing after 4 weeks
    - Skin prick test or blood specific IgE to milk does not show sensitization
      - No elimination diet
    - Skin prick or blood specific IgE to milk shows sensitization
      - Continue elimination diet of cow’s milk
  - Elimination diet: Diagnostic (for 2–4 weeks)
    - Improvement in clinical symptoms
    - No improvement in clinical symptoms
      - Oral food challenge with milk for diagnosis
        - Positive
          - Continue elimination diet of cow’s milk
        - Negative
          - No elimination diet
      - To stop elimination of cow’s milk in the diet of the baby/mother

(CMPA: cow’s milk protein allergy; IgE: immunoglobulin E)
Cow’s Milk Protein Allergy

**Flowchart 2:** Treatment of cow’s milk protein allergy.

(AAF: amino acid formula; CMP: cow’s milk protein; eHF: extensively hydrolyzed formula)

- **Strict avoidance of CMP for a defined period and reintroduction at right time is the key to management. Early and accurate diagnosis is important, as delayed diagnosis may result in failure to thrive and anemia while overdiagnosis results in unnecessary dietary restrictions and economic burden.**

- **Treatment of CMPA includes removing cow’s milk protein from your child’s diet (elimination diet). Elimination diets are usually started with extensively hydrolyzed formula (eHF), with improvement in about 90% of children with CMPA. Amino acid formula (AAF) is used in severe CMPA or when child is not responding to eHF even after 14 days. Elimination diet should be continued for at least 1 year and reevaluation done every 6 months.**

- **Buffalo’s, goat’s, or sheep’s milks generally elicit the same reaction as cow’s milk, so using these as a substitute is not likely to improve symptoms.**

- **Soy protein-based formulae are tolerated by the majority of infants with CMPA, but about 10% of affected infants react to soy protein, with higher proportions in infants younger than 6 months so not to be used in <6 months age.**
In the case of immediate reaction CMPA that causes anaphylaxis, intramuscular (IM) epinephrine (1:1,000) should be used immediately. Patients with anaphylaxis need to be evaluated and monitored in an emergency room, even if the symptoms improve with epinephrine. This is because there is a risk of a “second wave” of symptoms occurring after the epinephrine wears off.

Once CMPA is confirmed (encourage breastfeeding at all levels)

- In formula feed
  - Elimination diet
    - IgE-mediated reaction keep off for 12–18 months
    - Non-IgE-mediated reaction keep off 6–12 months

- In breastfeed
  - Continue breastfeeding
    - Mother to avoid CMP in all form (and take calcium 1000 mg + vitamin D 400 IU/10 µg daily)

The best way to prevent CMPA is exclusive breastfeeding for 4–6 months (17–27 weeks). The incidence of CMPA is lower (0.5%) in exclusively breastfed infants compared to formula-fed or mixed-fed infants.

About 50% will develop tolerance by 1 year, 75% by 3 years, and 90% by 6 years. Other food allergy can come up in 50% and to inhalants by 50–80% before puberty.
Further Reading