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# Review:

# Gastrointestinal Issues In Pediatric Animal Protein Allergy (CMPA)

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**Abstract:**

Proper clinical history taking , examination, skin prick test, specific Ig E antibodies to cow's milk, diagnostic elimination trial, food Challenge test and endoscopic biopsy are the available diagnostic tools to diagnose and confirm Cow's milk allergy. Guidelines, consensus statements and position papers are published on diagnosis of CMPA. Holistic views of all have been considered and broad management principles are discussed.

**Keywords:** CMPA: Cow's milk protein allergy, Ig E: Immunoglobulin E, SPT: Skin Prick Test, CM: Cow's milk, sIgE: Specific Ig E,,OFC: Oral food Challenge,, DBPCFC : Double-blind placebo-controlled food challenge, FPIES: Food Protein-Induced Enterocolitis Syndrome

## Introduction:

Proper clinical history taking and examination is the cornerstone of diagnoses in food allergy. In Infants with Cow's milk protein allergy differential diagnosis includes causes like Infective colitis, Gastro-esophageal reflux disease and other organic diseases. Hence appropriate evaluation by diagnostic modalities is essential.

## Scoring System:

The Cow's Milk-related Symptom Score (CoMiSS)[1] is used to screen CMPA. The CoMiSS ranges from 0 to 33; 0 as complete absence of symptoms .Cut-off value of >= 12 is proposed as a "positive score "meaning the symptoms may be related to CMPA. In recently published study[2], in healthy infants less than 6 months, the median score CoMiSS is 3. Higher the score more likely is the shift towards the allergy. Sensitivity of CoMiSS is 77% and specificity is tested to be 66 % in one of the Indian study[3]. In conclusion the use of scoring system can be used as a tool when to suspect CMPA. It is not diagnostic but can be a good screening test but more studies are needed.

## Diagnostic elimination trial:

Diagnostic elimination of CMP (in the infant's/ child's diet or in the mother's diet in case of breast-feeding) irrespective of Ig E mediated CMPA or Non Ig E mediated CMPA can be considered for early and late reactions. For vomiting, atopic eczema one may consider trial for 1 - 2 weeks. For gastrointestinal symptoms i.e diarrhea/ constipation elimination of cow's milk for 2 - 4 weeks as per ESPGHAN guidelines.[4] In Non-I g E mediated CMPA, elimination diets and milk reintroduction remains the diagnostic test of choice.[5,6,8.] With improvement in clinical symptoms one may consider Open/blinded Food Challenge[7] for confirmation and start of therapeutic long term elimination diet.

In conclusion, diagnostic elimination trial is a cost effective measure to analyze CMPA. It is more useful in Non-Ig E mediated CMPA. In uncertain cases one should go ahead with Open /Blinded food challenge for definitive diagnosis.

**Food challenge test:**

Food challenge is an effective method to diagnose CMPA[8,9]. It can be Open food challenge (OFC) or Blinded food challenge. Double-blind placebo-controlled food challenge is the reference standard for the diagnosis of food allergy.[5,7,8] Open challenges can be used to confirm both IgE- and non- IgE-mediated reactions .These are usually adequate for clinical purposes[10,15]. Uncertain cases or for research blinded food challenge are required[9].

OFC (oral food challenge) is considered for making a diagnosis of IgE-mediated CMA (strong recommendation/very low-quality evidence) as per DRACMA guidelines .[11]

OFCs are more standardized for IgE- than for non-IgE mediated reactions. For Non Ig E mediated reactions prolonged observation may be required.

OFC[11] should be conducted under the observation of a team with specific expertise in pediatric allergy/Pediatrician/Pediatric Gastro-enterologist. Drugs for emergency treatment should be readily available. In cases with severe /near anaphylactic reactions to first of multiple introduced food where cow's milk is one component; OFC should be done in PICU (Pediatric Intensive care unit). If unifactorial etiology of Cow's milk exposure and anaphylaxis is clear one should not do OFC .Informed written consent is must. Histamine H1 receptor antagonists for 72 h, Leukotriene receptor antagonists for 24 h, b2 stimulants for 12 h ,Th2 cytokine inhibitors for 12 h, Theophylline for 48 h, Oral sodium cromoglycate (DSCG)for 48 h and Oral steroids 7-14 days should be discontinued before doing challenge test.[12]

Food tested and placebo should be tested on different days. Obvious symptoms induced within several hours after the administration in the OFC test, is interpreted as positive. In indeterminate cases, the OFC test can be repeated.[12] DBPCFC can be done to clarify delayed reactions [11].

If symptoms occur after an open challenge test, DBPCFC is recommended in uncertain cases or cases with questionable symptoms and in cases of moderate to severe eczema.OFC may not be done in cases of severe anaphylaxis reaction with positive s Ig E levels and in cases with clear negative diagnostic elimination diet.

Most FPIES patients have negative skin prick testing .They also have undetectable specific IgE levels to the trigger food. Oral food challenges (OFCs) is needed if the diagnosis of FPIES is not clear. Vomiting in the 1–4 h period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms is the major criteria. Second (or more) episode of repetitive vomiting after eating the same suspect food, repetitive vomiting episode 1–4 h after eating a different food,extreme lethargy with any suspected reaction, marked pallor with any suspected reaction, need for emergency room visit with any suspected reaction, need for intravenous fluid support with any suspected reaction ,diarrhea in 24 h (usually 5–10h, hypotension and hypothermia are minor criteria The OFC will be considered diagnostic of FPIES, i.e. positive, if the major criterion is met with at least THREE minor criteria[13]

In conclusion DBPCFC is the most specific test for diagnosing food allergy and reliably distinguishes sensitization from clinical allergy. It should be used for uncertain cases and for research purposes. Open food challenge can substitute it for practical purposes in clinical settings.

**Specific Ig E antibodies to CM:**

Specific Ig E levels detect presence of circulating antibodies against CMP. But a positive Ig E level does not confirm an allergy[9,14]. It cannot differentiate between sensitization and clinical allergy[8]. sIgE e" 0.35 kU/L have been used to support a clinical diagnosis of Ig E mediated CMPA [5,15]. sIgE tests are not validated for the diagnosis of Non –Ig E mediated

CMPA and may result in false positive or false negative diagnoses[7,8,9]

CMPA likelihood is higher if testing for specific IgE is positive.[4] Patients with Low probability Oral food challenge test is must. Specific-IgEs for CMPA are sensitive, but not specific for diagnosis of food allergy[8,9,14] The magnitude of the sIgE titres is not associated to the severity of the symptoms in Ig E mediated CMPA . Positive sIgE titre in Food Protein-Induced Enterocolitis Syndrome is uncommon. But in atypical FPIES, sIgE titres positivity suggest more protracted course and an increased risk of immediate allergic reactions after ingestion of the offending food.[16]

In conclusion specific IgE for CMP test is not confirmatory test but it has supporting value. Their role in Ig E mediated CMPA is significant as compared to non Ig E mediated or mixed Food allergies.

**Skin prick test (SPT):**

SPT's are used to detect the presence of sIgE tissue bound antibodies.[5] In IgE-mediated CMA, the skin prick test can be considered[8, 12, 15] SPTs are not validated for the diagnosis of Non –Ig E mediated CMPA and may result in false positive or false negative diagnoses[7, 8] Positive Skin prick test does not confirm an allergy.[5, 6,8,9,12,14] If doubt persists on can consider food challenge in supervised settings. Antihistamines, antiallergics, and steroids should be withdrawn for at least 3 days[12] prior SPT. If blood test is negative for antigen-specific IgE antibodies, a positive SPT may provide helpful additional information[12, 17]. Infants are generally less responsive to SPT[17].

A wheal size of e" 5 mm (e" 2 mm in an infant d" 2 years) is associated with a higher specificity[5], [18, 19].Negative skin test results rules out IgE-mediated reactions [20], with negative predictive values of 95%.

SPT is recently studied as prognostic factor measure in CMPA. Wheal size is significantly larger in children with persistent CMPA compared to children outgrowing CMA.[21]

In conclusion, SPT are not confirmatory test but they do have supporting value. Their role in Ig E mediated CMPA is significant as compared to non Ig E mediated or mixed Food allergies. Larger the wheal diameter more significant is the association. Negative SPTs rule out association. If doubt persists on association one can consider food challenge in supervised settings.

**Endoscopy and Biopsy:**

Endoscopy and biopsy findings do contribute in allergy diagnosis .The most frequently encountered findings are focal erythematic, erosions and nodular lymphoid hyperplasia in 40–90% on endoscopic morphology.[22] The presence of more than 60 eosinophils in six HPFs and/or more than 15–20 eosinophils/HPF is highly suggestive for CMPA . In Infants with Cow's milk protein allergy differential diagnosis includes other causes like Infective colitis, Gastro-esophageal reflux disease and other organic diseases. Appropriate Pediatric Gastroenterologist referral for endoscopy helps in diagnosis and to rule out other etiologies. Endoscopy and biopsy are useful in atypical cases and in ruling out other etiologies.

**Other advanced testing:**

Component-resolved diagnostics (CRD) has been used for food allergy diagnosis[23,24] CRD can improve diagnostic accuracy. Allergen extracts contain a complex mixture of allergen components. This molecular test can be used prior to open food challenge. It tests sIgE test to allergen component in cow's milk. sIgE testing to allergen components can be performed using single-plex IgE antibody assay and multiplex IgE antibody assay in microarrays. CRD or molecular-based allergy can help to explain the cross-reactivity between allergens. Components studied are betalactoglobulin (Bos d 5), and alphalactoglobulin (Bos d 4). Casein has the highest diagnostic accuracy for cow's milk allergy. Bos d 4 for cow's milk has sensitivity of 62.0% and specificity of 87.5% [24] Cow milk contains nearly 200 proteins.[25] Targeted mass spectrometry (MS) is one of the most important techniques in

proteomics used for identification, confirmation and characterization of proteins responsible for CMPA. Different clinical phenotypes of CMA can be further classified with the help of Proteomics. Prognostic biomarkers related to oral food challenge response can be identified with advanced proteomics.[26] More studies are needed before their wider clinical application.

**Challenges:**

In a cohort,[27] 41% of patients with CM FPIES transformed into an IgE-mediated phenotype. IgE-mediated food allergy association with FPIES has also been reported.[28] Hence fluidic approach with open mind to avoid cognitive bias is equally important while handling CMPA.

**Management of cow's milk protein allergy:**

Once the diagnosis is established strict avoidance of all cow's milk/animal protein protein[9,15] in food is necessary. Maternal elimination diet of trigger food in breast-fed infants should be considered. Elimination diets may adversely affect nutritional outcomes hence appropriate monitoring and supplementation of calcium and other nutrients is essential. Extensively hydrolyzed formulae, amino-acid based formula are available for children less than 2 years of age. Amino acid formulas may be more useful for the subgroup of patients with more severe symptoms or severe anaphylaxis reactions[4,7,11] For Cow's milk allergy persisting beyond 2 years, milk free diet should be considered. Soy formulae should avoided before 6 months of life.[4,11] Oral immunotherapy (OIT) has mixed success and need further validation.[11,29,30] 10% and 14% of affected Cow's milk allergy infant's cross- react to soy protein[31,32]. Phytate content[33] of soya formula make them nutritional disadvantageous as it interferes with mineral absorption. Isoflavones[33] with a weak estrogenic action that can lead to undesirable side-effects in infants less than 6 months.

Dietetic counseling by a trained dietitian with competencies in food allergy, and regular monitoring of growth is essential in Long term. Probiotics supplements cannot be recommended for the management of food allergy and needs further studies.[34]Patient education and use of emergency medications by care givers is equally important.

Short-term management of acute reactions, anaphylaxis is vital in management. The patient at risk of severe reactions should be properly and timely identified and treated. EACCI guidelines are against prophylactic use of antihistamines[7] .Mast cell stabilizers are not recommended for the prophylactic treatment of food allergy.[7]

Cow's milk allergy is rarely permanent. About 50% of affected children develop tolerance by the age of 1 year,>75%by the age of 3 years, and>90% are tolerant at 5-10 years of age.[35] Appropriate diagnosis and treatment with growth monitoring and patient education; forms the cornerstone in management of CMPA.

**Key learning points:**

1. Cow's Milk Allergy is being diagnosed commonly in developing countries. Cognitive bias, over-investigation or under treatment should be avoided.
2. Diagnostic Elimination trial is a cost effective measure to analyze CMPA. DBPCFC is the most specific test for diagnosing food allergy. Specific IgE and Skin prick test for CMPA are not confirmatory tests but have supporting value.
3. Strict avoidance of all cow's (Animal) milk protein in food is necessary. Immunotherapy needs further validation.

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