Guidelines on Diagnosis and Management of Cow's Milk Protein Allergy

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Justification: Cow's milk protein allergy (CMPA) is increasingly being diagnosed in the West, while there is scant data on the subject from India. There is low awareness among pediatricians about its diagnosis and management; leading to improper diagnosis. **Process:** A group of experts from the pediatric gastroenterology sub-specialty chapter of Indian Academy of Pediatrics (Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition) met at Mumbai on 26 October, 2018 and discussed various issues relating to the subject. A broad consensus was reached and a writing committee was formed. They met again on 11 August, 2019 at Chennai for a detailed discussion. The statement was sent to the entire group by e-mail and their approval obtained. **Objective:** To formulate a consensus statement enable proper diagnosis and management of Cow's milk protein allergy. **Recommendations:** Cow's milk protein allergy is most common in the first year of life. Gastrointestinal manifestations are usually non-IgE mediated and therefore skin prick test and specific IgE levels are not useful in diagnosis. Clinical response to elimination diet followed by a positive oral food challenge is diagnostic. In patients with only gastrointestinal manifestations, sigmoidoscopy and rectal biopsy may be considered as an alternative. Management involves strict avoidance of all forms of bovine milk protein. For infants who are artificially fed, an extensively hydrolyzed formula is the first choice. Soy formula is an alternative in those above six months of age. Since most infants outgrow the allergy, elimination diet is only for a limited period and re-evaluation should be done periodically.

Keywords: *Extensively hydrolyzed formula, Food allergy, Non-IgE mediated, Oral food challenge, Rectal biopsy*.

Food allergy is an adverse immunological response to proteins in food and must be differentiated from food intolerance, which is a general non-specific term for any adverse reactions to particular constituents of food. Cow's milk protein allergy (CMPA) is an immune- mediated reaction to various proteins in cow's milk. It is the most common food protein allergy in infants and children [1]. The reaction may be IgE-mediated, non-IgE mediated or mixed. CMPA may have cutaneous, respiratory and/or gastrointestinal manifestations.

In India, awareness among pediatricians is low leading to misdiagnosis or concurrence with parents that the child has allergy. This results in wrong dietary advice and unnecessary use of expensive formulas. The prevalence of CMPA peaks in infancy (1.5 -3 %) and falls to less than 1% at 6 years of age [2]. About 10 to 15% of children who have CMPA are also allergic to soy and the risk of cross- allergy is higher if symptoms begin below 6 months of age [3]. There are no epidemiologic studies on the prevalence of food allergy including CMPA in Indian children. Among hospital-based studies, CMPA was reported as a cause of malabsorption syndrome in 6% children of all ages and 13% of children below 2 years with chronic diarrhea [4]. CMPA was the cause in 35% children below 3 years of age presenting with chronic diarrhea in another study [5].

PROCESS

The pediatric gastroenterology sub-specialty chapter of Indian Academy of Pediatrics (Indian Society of Pediatric Gastroenterology, Hepatology & Nutrition) organized a meeting of select members of the group at Mumbai on 26 October, 2018. Brief presentations on various aspects of the topic were followed by a detailed discussion. A broad consensus was reached and a ten member writing committee was formed. This committee met again on 11 August, 2019 at Chennai for a detailed discussion. The statement was finalized and sent to the entire group by e-mail. Suggestions were incorporated and consent was obtained from all the members .

RECOMMENDATIONS

Diagnostic Modalities

A good reliable history and clinical examination are the cornerstones of diagnosis. Common differential diagnosis like infective colitis, celiac disease, gastro-esophageal reflux disease, eosinophilic esophagitis, immune deficiency and persistent diarrhea should be kept in mind. Empirical exclusion therapy without confirmation of diagnosis is unscientific and best avoided.

Diagnostic Elimination Trial

Current European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) practice guidelines suggest that the initial diagnosis of CMPA should be made on the basis of diagnostic elimination of cow's milk proteins from the diet and then it is to be confirmed by an oral challenge with CMP if there is a response to the elimination diet [6]. Elimination should be total, and particular attention should be paid to hidden sources of the antigen (*e.g*. avoiding biscuits or cake). If symptoms do not improve with strict elimination, the diagnosis of CMPA is unlikely.

Oral Food Challenge

A double blind placebo controlled food challenge is the gold standard for diagnosing CMPA, though it has the disadvantages of requiring a longer time to perform, needing patient and parents co-operation and being expensive [6]. Hence, in most instances (except in those with uncertain or questionable response to the initial oral challenge), an open food challenge is done, wherein the child is continued on a normal milk containing diet. If the patient remains without symptoms for two weeks, then CMPA is ruled out. However, if symptoms recur, then the diagnosis of CMPA is confirmed. Oral food challenge (OFC) is the most specific test for diagnosing food allergy and reliably distinguishes sensitization from clinical allergy. They are more standardized in IgE- mediated reactions, and should be done under medical supervision. However, in cases of severe anaphylaxis, the patient should be on a therapeutic elimination diet straightaway [6]. This test is required before re- introduction of the allergen after therapeutic elimination period is completed to confirm development of tolerance.

Endoscopy and Biopsy

An Indian study done on CMPA noted that sigmoidoscopy (82%) and rectal biopsy (97%) gave best information in patients with gastrointestinal manifestations of CMPA [7]. Histological changes are similar and non-specific in all food allergies and therefore should be interpreted only in the context of appropriate clinical setting. The most frequently seen endoscopic findings are focal erythema, erosions and nodular lymphoid hyperplasia in 40–90% of cases [8]. The presence of more than 60 eosinophils in six high power fields and/or more than 15–20 eosinophils per high power field is highly suggestive for CMPA .

Other Methods

Scoring system for screening: The Cow's milk-related symptom score (CoMiSS) has most commonly been used [9]. However, there is no agreement on cut-off values and it has poor sensitivity and specificity [10]. Until more studies are available from developing countries, CoMiSS cannot be recommended as a screening tool in our setting.

Specific IgE antibodies to cow milk: Specific IgE antibodies detect the presence of circulating antibodies against CMP. However, positive IgE neither confirms allergy nor differentiates between sensitization and clinical allergy [26]. Specific IgE tests are not useful in the diagnosis of non-IgE mediated CMPA .

Skin prick test: Skin prick tests are used to detect the presence of IgE tissue bound antibodies. It can be considered in IgE-mediated disease, but a positive test does not confirm allergy. Wheal size of ≥5 mm (≥2 mm in an infant <2 year) is associated with a higher specificity. 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 [11]. Infants are generally less responsive to skin prick tests. It is not validated in non-IgE mediated CMPA and may result in false positive or false negative diagnosis [12].

Approach to Diagnosis

CMPA is a clinical diagnosis, and there is no single test or biomarker that is pathognomonic of the condition. The ESPGHAN criteria of 2012 have done away with routine intestinal biopsy [6]. Allergen elimination followed by oral food challenge, has been advocated as the cornerstone of diagnosis.

A structured approach is needed for accurate diagnosis and should start with an allergy focused history (including family history) and physical examination. If the clinical features discussed earlier are present in an infant or young child, CMPA should be considered in the differential diagnosis. Clinical pointers that suggest IgE-mediated disease are the involvement of two or more systems, commonly the skin, gastrointestinal and respiratory tract. On the contrary, non-IgE mediated

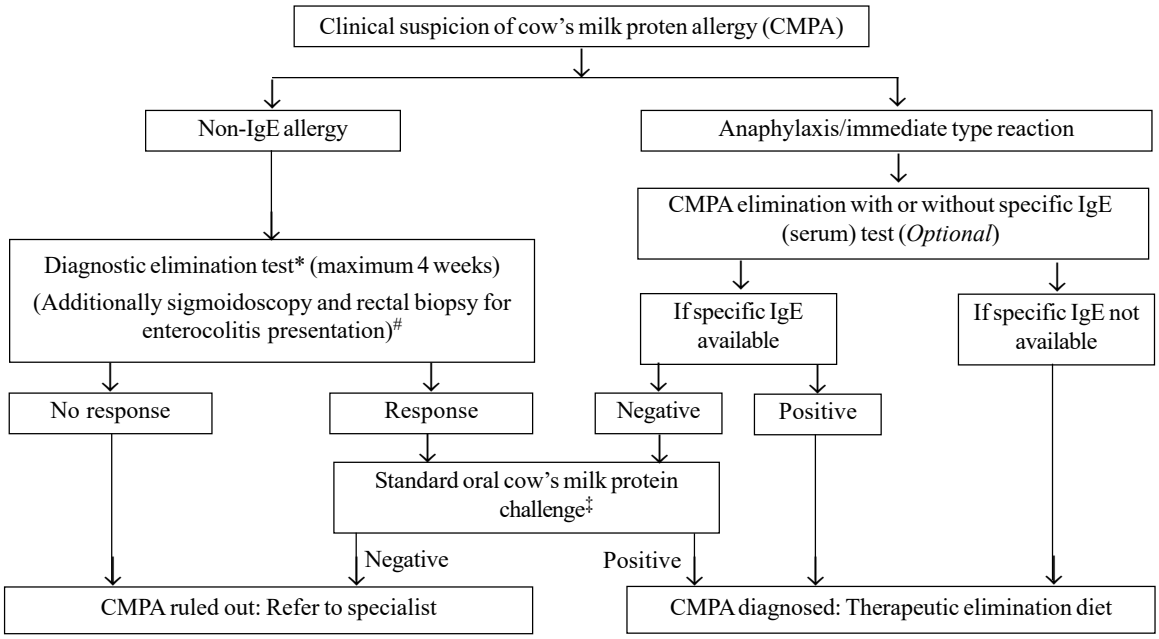
disease (which is more common in India) may manifest with only gastrointestinal symptoms. The expert group does not advocate testing for cow's milk protein (CMP) - specific IgE in serum as a routine, considering the high cost and as it indicates only sensitization (food elimination and challenge needs to be done for diagnosis). However, It may be useful with acute/ life threatening symptoms such as stridor, wheeze, angioedema and anaphylaxis. Here, the food challenge may be delayed by a year if CMP- specific IgE is positive and there is symptom resolution with an elimination diet. Approach to a child with suspected CMPA is given in ***Fig*.1**.

The initial diagnosis of CMPA should be made on the basis of a diagnostic elimination test. 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 [13]. If the child does not show any improvement during this time period, a diagnosis of CMPA is ruled out on most occasions. A few exceptions are: some children have associated soy protein allergy or allergy to other components of the extensively hydrolyzed formula (eHF) that has been used during milk restriction; some sick infants may also have multiple food protein allergies (such as egg, wheat, soy, nuts, sea fish). In both these situations, an amino-acid based formulation (AAF) should be used during the allergen elimination, and if there is no improvement in symptoms on this too, then CMPA is ruled out as a cause for the child's symptoms [6].

For those on exclusive breastfeeding, elimination requires excluding milk and milk products from the mother's diet (while she continues to breast feed the infant). Care must be taken to remove sources of CMP from the breast-fed infants being given supplementary feeds in addition. For non-breast fed patients, all sources of milk protein should be stopped and infants should be started on an extensively hydrolyzed formula. Soy formula may be used beyond 6 months of age. For older children, all forms of milk and milk products should be stopped as part of the elimination [6].

Patients who show an improvement of symptoms with allergen elimination (as above) should be subjected to an oral milk challenge after 2-4 weeks of a CMP free diet in the asymptomatic period to confirm the diagnosis [13].

Procedure for oral food challenge: CMP either as 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, 30



*#Subset of patients with enterocolitis: sigmoidoscopy and rectal biopsy is useful; *Exclusively Breast Feeding (EBF) infant: Eliminate all Cow's Milk Protein containing food in mother; Mixed/ Formula fed: Eliminate all Cow's Milk Protein food/ formula in mother & infant. eHF/ soy trial; Symptoms with first CMP feeds: return to EBF (maternal restriction of milk protein not required) (Elimination duration: 1-2 weeks for most, 2-4 weeks for chronic symptoms); ‡Exclusively Breast Fed: Mother returns to normal CMP diet; Mixed/ Formula Fed: Home challenge with CMP formula/ milk*

Fig. 1 *Approach to a child with suspected cow's milk protein allergy.*

mL, 100 mL (given every 30 minutes), which can be done on an out-patient basis [14]. 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. 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 two weeks to look for any delayed manifestations.

Since non-IgE mediated gastrointestinal symptoms appear to be the commonest manifestation of CMPA in India, sigmoidoscopy and rectal biopsy can also be considered for confirmation of diagnosis in children whose parents do not give consent for oral food challenge. In children with no response to diagnostic elimination diet or those in whom alternative diagnosis is strongly considered, further investigations are necessary.

Management

The safest strategy for the management of CMPA is the strict avoidance of CMP for a defined period [6]. A delay in diagnosis may result in failure to thrive, anemia, and hypoproteinemia; however, there is ample evidence that over-diagnosis or wrong diagnosis results in unnecessary dietary restrictions, increased risk of rickets, decreased bone mineralization and great economic burden [15]. The choice of an appropriate substitute to fulfill the nutritional requirements during the time of CMP avoidance is crucial. There are some variables which should be considered before recommending alternatives to milk feeds (***Box* II**).

Exclusively Breast-fed Infants

CMPA in an exclusive breast-fed infant is usually mild and majority of these infants do not have anemia or failure to thrive. Breastfeeding is continued till at least 6 months of age and the mother is advised to avoid bovine milk and all dairy products (cheese, yogurt, paneer, butter, ghee) as well as milk containing foods in her diet. It may take up to 72 hours for the antigens to disappear from breast milk and for clinical response after withdrawal of milk and milk products [16]. The maternal elimination diet is maintained for 3 to 6 days in those with IgE-mediated allergy, while in non-IgE mediated it is two weeks in those without atopy, and 4 weeks in those with atopic dermatitis or allergic

Box I Clinical Manifestations of Cow's Milk Protein Allergy

IgE mediated syndromes (Onset- immediate to <1 h)

Immediate food hypersensitivity, perioral utricaria/ erythema, angioedema/ anaphylaxisGeneralized rash, vomiting, wheezing, cough

***Non-IgE mediated* (Onset - late >24 h, usually after 5-7 d)**

Proctocolitis: Fresh bleeding per rectum, constipation

Enteropathy: Watery diarrhea, failure to thrive, protein losing enteropathy, occult gastrointestinal bleeding

Enterocolitis: Bloody diarrhea, anemia/hypo-proteinemia

Esophagitis: Reflux like symptoms, vomiting/feed refusal, dysphagia

Gastritis/Gastro-duodenitis: hematemesis, occult gastrointestinal bleed

Atopic dermatitis

Mixed (Onset-intermediate, <24 h)

Food Protein Induced Enterocolitis syndrome (FPIES): Vomiting/diarrhea/colitis, shock like symptoms with severe vomiting, diarrhea, neutrophilic leukocytosis and metabolic acidosis

Table I Differentiation Between Cow's Milk Protein Allergy and Lactose Intolerance

	Cow's milk protein allergy	*Lactose intolerance*
Types	IgE and Non-IgE mediated	Congenital, primary (age-dependent decline in lactase enzyme) and secondary (mucosal damage after severe gastroenteritis or other causes)
Mechanism	All or none phenomenon, is an immune reaction to milk protein	Quantity-dependent, due to deficient lactase enzyme in brush border
Symptoms	Multisystem (gastro-intestinal/skin/ respiratory	Only gastrointestinal (diarrhea, flatulence, pain)
Natural history	Recovers by 4-5 y of age in majority	Recovers in days-weeks in secondary, permanent in congenital and primary

colitis [6]. If symptoms persist even after this period, other allergens or a different etiology should be considered. If the symptoms improve or disappear, CMP may be reintroduced as a challenge in the maternal diet. If symptoms recur then CMP should be avoided as long as she is breast-feeding. Calcium supplementation (1000 mg per day in divided doses) is essential for the mother during the period of elimination. Very strict elimination diets that exclude not only milk but also fish, soy, wheat and gluten products may cause unnecessary nutritional imbalance in the mother and are best avoided.

Infants on Mixed Feeds

CMP is completely withdrawn along with all unmodified animal (goat/sheep/buffalo/camel) milk proteins. However, breastfeeding should be continued without any elimination in the maternal diet [6]. In infants less than 6 months of age with mild to moderate reaction, extensively hydrolyzed formula (eHF) with proven efficacy is recommended [17]. There is safety concern regarding use of soy in infants less than 6 months of age and cross-allergy to soy is seen in in 10-15 % of infants with CMPA. Soy is however cheaper and more palatable than eHF and these factors should be weighed when alternate formula is recommended. Children with IgE-mediated CMPA tolerate soy protein better than non-IgE mediated CMPA. In infants more than 6 months of age with mild to moderate reaction, soy protein formula can be used instead of eHF if there are financial constraints [18]. If the diagnosis is reasonably certain, but there is no improvement within 2 weeks of eHF, then amino acid formula (AAF) should be tried before CMPA is ruled out. In infants who are sick or have severe or life threatening symptoms AAF should be the first choice rather than eHF [6].

Exclusive Formula Fed Infants

Breast feeds must be started if they were stopped only recently. Rest of the management protocol is the same as in group II.

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

A simple algorithm for management of infants with non-IgE mediated CMPA is shown in ***Fig.* 2**.

Management of IgE-mediated CMPA

When an infant with CMPA presents with classical symptoms of IgE-mediated allergy such as angioedema, urticaria or anaphylaxis, emergency care should be provided as for any allergy, and all forms of CMP should be immediately withdrawn. In mild to moderate allergy, eHF is the first choice. Only those who do not respond to the above measures should be switched to AAF. Those with severe allergy require hospitalization and should be given only AAF. OFC should be done with caution only in a hospital setting between 12 to 18 months. In those with severe IgE mediated allergy, OFC should be done only with eHF [16].

The elimination diet should be continued for atleast one year and re-evaluation done every 6 months subsequently [40]. The prognosis of infants and children with CMPA is good as 50% will tolerate CMP by 1 year, >75% by 3 years and >90% by 6 years of age [19]. Only 5 % would continue into adulthood. High total IgE and specific IgE levels correlate with a higher age of acquiring tolerance [20].

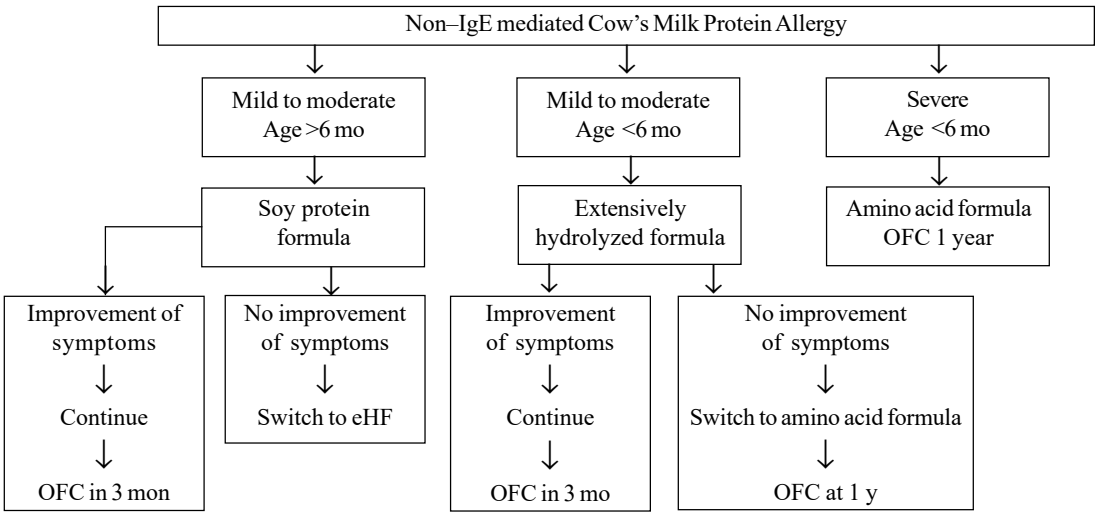
Prevention

Primary prevention aims to delay the first exposure of infants to cow's milk protein, while secondary prevention involves avoiding antigen exposure in high-risk atopic infants. Tertiary prevention is when clinicians advise cow's milk avoidance as a means of treatment after confirmation of diagnosis.

Exclusively Breast-fed Infants

The best way to prevent CMPA is exclusive breast-feeding for 4-6 months (17-27 weeks)[21]. The incidence of CMPA is lower (0.5%) in exclusively breast-fed infants compared to formula-fed or mixed-fed infants. The reproducible clinical reactions to CMP are mild to moderate in the majority. A plausible explanation is that the level of CMP in breast milk is 100, 000 times lower than that in cow's milk and is in the form of peptides and not as intact protein [22]. Breast milk also contains proteases a digesting protein. The other protective factors in breast milk are maternal antibodies and chemokines which reduce the development of allergy, hormones and growth factors which potentiate maturation of gut associated lymphoid tissue (GALT), polyunsaturated fatty acids (PUFAs), glycoproteins, oligosaccharides and micro RNAs which exhibit immune function.

There is no evidence that modification of maternal diet during pregnancy or lactation has any protective effect



OFC: Oral food challenge; eHF: Extensively hydrolyzed formula.

Fig. 2 *Management of infants with non-IgE mediated cow's milk protein allergy.*

against allergy in at-risk infants. Moreover an exclusion diet may cause nutritional deficiencies in the lactating mother and infant [23]. Allergen avoidance should be advised only when the breast-fed infant has proven CMPA. There is no evidence to suggest that delaying introduction of solid foods, or even potentially allergenic foods, beyond age 4-6 months offers any protective effect. Supplementary foods should be introduced one at a time in small quantities, preferably while the mother is still breastfeeding but not before the infant is at least 17 weeks of age to prevent other allergies [24].

Infants Not Exclusively Breast-fed

There is no role for milk formula with intact protein from other animals or soy protein in the prevention of allergy. The role of hydrolyzed formulae (both partial and extensively) in prevention of CMPA is still debated. If there is a family history of allergic disease in both parents, there may be some justification in using partially hydrolyzed formula with whey protein as a starter formula, if exclusive breastfeeding is not possible. However, a recent meta-analysis concluded that there is no benefit of using hydrolyzed formula to prevent CMPA [25].

CONCLUSION

CMPA is primarily a disease of infancy with increasing incidence. While manifestations of IgE- mediated disease is immediate with multi system involvement, non-IgE disease is delayed with symptoms related to the GI tract. Clinical response to an elimination diet followed by an oral food challenge is the cornerstone of diagnosis. In children with persistent diarrhea and colitis, sigmoidoscopy and biopsy are useful in diagnosis. Breastfeeding should be continued and all cow's milk protein should be stopped. Most children will outgrow the allergy between 12 and 18 months of age.

Contributors: JM: coordinated and edited the paper; SKY: verified the scientific content; ASr and RM: authored the segment on prevalence and clinical features; AS and YW: the segment on diagnostic modalities; UP,GR: the segment on approach to diagnosis, MS,GS: the segment on management and prevention. All authors participated in finalizing the paper.
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RECOMMENDATIONS

- In non-IgE mediated cows' milk protein allergy (CMPA), milk specific-IgE and skin prick tests are not useful in diagnosis.
- Oral food challenge following a clinical response to elimination diet is mandatory in diagnosis. In those with only gastrointestinal manifestations, sigmoidoscopy and rectal biopsy should be considered
- Duration of diagnostic milk protein elimination needed to observe clinical response varies from 3-5 days in IgE-mediated allergy and 2-4 weeks in others.
- Unmodified mammalian milk (cow, buffalo, donkey, goat or camel) should not be used in infants with proven CMPA.
- In artificially-fed infants with CMPA, extensively hydrolyzed formula is the first choice. Soy formula may be considered above 6 months of age. Amino acid formulas are needed only in a small subset of infants.
- Delaying introduction of solid foods, or even potentially allergenic foods, beyond 4-6 months of age has no protective effect in high risk infants.

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