



REVIEW ARTICLE

Management of cow's milk protein allergy in infants and young children: An expert panel perspective

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Abstract: Cow's milk protein allergy is a condition commonly managed by general practitioners and paediatricians. The diagnosis is usually made in the first 12 months of life. Management of immediate allergic reactions and anaphylaxis includes the prevention of accidental food ingestion and provision of an adrenaline autoinjector, if appropriate. By contrast, the clinical course of delayed food-allergic manifestations is characterised by chronicity, and is often associated with nutritional or behavioural sequelae. Correct diagnosis of these non-IgE-mediated conditions may be delayed due to a lack of reliable diagnostic markers. This review aims to guide clinicians in the: (i) diagnostic evaluation (skin prick testing or measurement of food-specific serum IgE levels; indications for diagnostic challenges for suspected IgE- and non-IgE-mediated food allergy), (ii) dietary treatment, (iii) assessment of response to treatment, (iv) differential diagnosis and further diagnostic work-up in non-responders, (v) follow-up assessment of tolerance development and (vi) recommendations for further referral.

Key words: anaphylaxis; eosinophilic oesophagitis; food challenge; gastrointestinal; hypoallergenic formula; skin prick test.

Introduction

Cow's milk protein allergy (CMPA) affects approximately 2% of Australian infants and young children.¹ While its treatment is generally straightforward, mismanagement may result in significant morbidity, including anaphylaxis, as well as nutritional or psychosocial sequelae.² Due to the rapid increase of real and perceived food allergy, specialist allergist services are often overwhelmed.³ This may contribute to diagnostic delay and increase

the risk of severe allergic reactions or inappropriate dietary manipulations.

We have published guidelines for the use of infant formulas in the treatment of CMPA in Australia.⁴ However, detailed discussion of the ongoing and more complex management issues of CMPA was beyond the scope of that paper. The present review by the same expert panel⁴ is intended as a guide to clinicians, based on the best available evidence with regard to the practical aspects in the long-term management of CMPA.

Key Points

- 1 Management of IgE-mediated cow's milk allergy needs to ensure strict dietary avoidance of cow's milk protein and provide access to a written allergy action plan, as well as an adrenaline autoinjector, if appropriate.
- 2 Early diagnosis of non-IgE-mediated cow's milk allergy is essential in order to reduce the risk of adverse nutritional or behavioural outcomes.
- 3 If managed appropriately, the prognosis of cow's milk allergy in infancy is generally excellent.

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General Principles for the Management of CMPA

Two main types of CMPA, immediate and delayed, can be distinguished, based on the timing of the clinical reaction in relation to the ingestion of cow's milk protein (CMP).² Manifestations include reactions occurring within minutes (e.g. anaphylaxis, angioedema, urticaria and vomiting), and syndromes with delayed reactions that occur within hours to days (e.g. food protein-induced enteropathy, proctocolitis or eosinophilic oesophagitis). Some disorders, such as eczema have features of both immediate and delayed reactions (Table 1).

The key principle in the treatment of CMPA, irrespective of the clinical type, is the dietary elimination of CMP and replacement with hypoallergenic or soy formula.⁴ Maternal CMP elimination may be beneficial because breast milk can contain

Table 1 Clinical presentations and differential diagnosis of CMPA conditions

Condition	Timing of symptoms in relation to ingestion	Clinical features	Distinguishing features	Occurrence in exclusively breast fed infants	Differential diagnosis	Age of clinical resolution	Useful investigations
Acute allergic reaction (non-anaphylactic)	Immediate, up to 60 min	Periorbital angioedema/erythema. Generalised urticaria Vomiting, diarrhoea	No recurrence if avoidance complete	Possible	Idiopathic urticaria, insect bite	80% by 3 years	SPT, ImmunoCAP, oral food challenge
Anaphylaxis	Immediate, up to 60 min	Respiratory +/- cardiovascular involvement often associated with above features	As above. IM adrenaline treatment of choice	Extremely rare	Sepsis, acute cardiovascular or respiratory compromise, seizures	As above	SPT, ImmunoCAP
FPIES	Typically 2–4 h	Profuse vomiting +/- diarrhoea, sudden onset of pallor and floppiness. 20% present as hypovolaemic shock (with associated metabolic acidosis and methaemoglobinemia)	Responds to fluid resuscitation, adrenaline not required	No	Sepsis, gastroenteritis, malrotation, intussusception, metabolic disorder	Most by 3 years of age	History diagnostic, no laboratory markers available
Eczema	Min/h/days	Pruritic rash	Often generalised, onset at introduction of cow's milk	Yes	Seborrhoeic dermatitis, acrodermatitis enteropathica	Variable, tendency to improve with age	SPT, ImmunoCAP, elimination – re-challenge sequence
Eosinophilic oesophagitis	Days	Vomiting, feed refusal, FTT, oesophageal dysmotility	Histological diagnosis, 24 h pH monitoring usually normal, unresponsive to proton pump inhibitors	None reported	GORD, mucosal candidiasis (white plaques)	Unknown	Endoscopy
Cow's milk protein-induced GORD	h/days	Frequent regurgitation, poor feeding, feed aversion	Partially responsive to proton pump inhibitors when underlying mechanism related to CMPA	Yes	Idiopathic GORD, eosinophilic oesophagitis, malrotation	12–18 months	Clinical diagnosis. Requires endoscopy if haematemesis or significant FTT
Enteropathy	h/days	Vomiting, diarrhoea, severe irritability, FTT, iron deficiency anaemia, protein losing enteropathy	Receiving cow's milk in diet	Yes	Lactose intolerance, coeliac disease giardiasis, immune deficiencies, autoimmune enteropathy	Unknown	Small bowel biopsy for histology, duodenal disaccharidases and microscopy of duodenal aspirate for giardia
Proctocolitis	h/days	Low-grade rectal bleeding in a well infant	Normal perianal inspection, thriving	Yes	Constipation with anal fissure, infantile inflammatory bowel disease, chronic granulomatous disease, juvenile polyp	12 months	Rectal biopsy only if atypical features or non-responsive to treatment
Colic	h/days	Paroxysms of unexplained, inconsolable crying	Responds to dietary elimination, early onset soon after the introduction of cow's milk protein	Yes	Idiopathic colic, developmental disorders, urinary tract infection	4–6 months	Cow's milk elimination and re-challenge
Constipation	h/days	Passage of infrequent and/or hard stools	Responds to dietary elimination, early onset soon after the introduction of cow's milk protein	Yes	Hirschsprung's disease, slow transit constipation	12–18 months	Cow's milk elimination and re-challenge in conjunction with laxative treatment. Rectal biopsy in infants with early-onset severe constipation

CMPA, Cow's milk protein allergy; FPIES, food protein-induced enterocolitis syndrome; FTT, failure to thrive; GORD, gastro-oesophageal reflux disease; IM, intramuscular; SPT, skin prick test.

Table 2 Recommendations for further referral

Urgent referral
Anaphylaxis
Food protein-induced enterocolitis syndrome
Severe failure to thrive
Hypoproteinaemia/protein losing enteropathy
Referral if trial of cow's milk elimination fails
Haematemesis
Chronic diarrhoea
Persistent vomiting
Persistent rectal bleeding
Iron deficiency anaemia
Severe eczema

intact cow's milk antigens.⁵ However, as some CMPA conditions are not induced by trace amounts of CMP, continued maternal ingestion of dairy products may be tolerated by the infant. Cow's milk elimination diets need to be formally assessed for their nutritional adequacy with regard to protein, energy or micronutrient (e.g. calcium, vitamin D) contents.⁶

Confirmation of the diagnosis relies on the resolution or significant improvement of symptoms following CMP elimination. Persistence of symptoms despite strict CMP elimination may occur because of unrecognised co-existing food allergies (e.g. egg, peanut, wheat) or a condition masquerading as CMPA (e.g. lactose malabsorption, idiopathic urticaria). Tolerance development is usually assessed at least annually by history of accidental exposure, skin prick test (SPT), measurement of cow's milk-specific serum immunoglobulin E (IgE), or food challenges.^{7–9} In IgE-mediated CMPA, challenges are generally conducted in hospital due to the risk of anaphylaxis. In non-IgE-mediated allergies, challenges usually do not require hospitalisation, with the exception of food protein-induced enterocolitis syndrome (FPIES).

Management Principles for Specific Conditions in Infants with CMPA

The management of immediate and delayed allergic manifestations of CMPA is discussed in separate sections below. Table 2 offers recommendations for further referral in difficult-to-manage clinical scenarios of suspected CMPA syndromes. Table 3 outlines areas in the clinical management of CMPA that require clarification and would benefit from further research.

Specific issues in immediate or acute allergic reactions

Management of CMPA *without* anaphylaxis

In infants with an immediate allergic reaction (e.g. generalised urticaria, angioedema or acute vomiting), but no cardio-respiratory involvement, CMP should be strictly eliminated and replaced with an extensively hydrolysed formula (eHF).⁴ A soy-based formula may be considered in infants above 6 months of age.¹⁰ The rationale against the use of soy as a first-line treat-

Table 3 Areas requiring further research

- (1) Standardisation of specific IgE testing (skin prick tests and food-specific serum IgE).
- (2) Criteria to predict patients at high risk of future anaphylaxis
- (3) Development of appropriate diagnostic markers for non-IgE-mediated CMPA
- (4) Strategies to promote tolerance development in children with CMPA
- (5) Clarification of the role of CMPA in infantile colic, GORD and constipation

CMPA, Cow's milk protein allergy; GORD, gastro-oesophageal reflux disease.

ment formula in infants under 6 months of age with CMPA is based on a variety of factors, including a higher rate of concurrent soy allergy in this age group (25% under 6 months vs. 5% between 6–12 months of age),¹¹ as well as nutritional and safety considerations which are reviewed in detail elsewhere.¹² Mothers should be encouraged to continue breastfeeding and generally do not require dietary CMP restriction, unless the infant has residual manifestations (e.g. eczema) while being breastfed. About 10% of infants do not tolerate eHF and require transition to an amino acid-based formula (AAF).¹²

In infants who have commenced eHF or AAF before 6 months of age, a transition to soy formula may be considered after 6 months of age, particularly if the SPT and/or serum specific IgE are negative to soy. A negative skin prick test is defined as a wheal diameter of 0 mm, in the context of a positive histamine control. A positive skin prick test is defined as a wheal diameter of 3 mm or greater, in the context of a negative saline control. Wheal diameters of 1 or 2 mm are regarded as equivocal. A specific serum IgE to cow's milk of <0.35 kU_A/L is regarded as negative. The reliability of these tests depends on the pre-test probability of a positive test result.

Patients are usually reviewed around 12 months of age to assess for tolerance development to CMP or other food allergens by careful history and measurement of food-specific serum IgE levels^{7,8} or SPT.⁹ If these are negative, or levels have decreased substantially, a cow's milk challenge is often considered. If acute allergic symptoms recur upon challenge, this procedure may be repeated after 6–12 months. Most children with non-IgE-mediated CMPA will develop tolerance by 5 years of age,¹³ whereas only 42–85% of children with IgE-mediated CMPA outgrow their allergy by 8 years.^{13,14}

Management of CMPA *with* anaphylaxis

Anaphylaxis to CMP is an uncommon presentation of CMPA and typically occurs after the first exposure to cow's milk-based formula. Clinical features suggestive of anaphylaxis in infancy include coughing, wheezing, severe distress, pallor, floppiness and/or collapse.² Anaphylaxis to eHF has been described.¹⁵ Amino acid-based formula (AAF) is therefore suggested as the first-line treatment choice in infants with previous cow's milk anaphylaxis while awaiting further specialist assessment. In this setting, use of AAF is recommended as a safer alternative until

challenges with ehF or soy can be performed under specialist supervision.⁴ These considerations are not currently reflected in the guidelines of the Australian Pharmaceutical Benefits Scheme (PBS).

Breastfeeding can be continued as anaphylaxis to CMP via breast milk is rare, and it is not usually necessary for mothers to restrict their dietary intake of cow's milk.¹⁶ Infants with anaphylactic reactions to CMP should be formally reviewed by a paediatrician with expertise in food allergy, ideally within 6–8 weeks. An anaphylaxis action plan is available at <http://www.allergy.org.au>. An adrenaline autoinjector (Epipen or Epipen junior, CSL, Australia) should be provided at the time of the acute episode, along with demonstration of its correct use. According to the anaphylaxis guidelines of the Australasian Society of Clinical Immunology and Allergy (ASCIA), children with a body weight between 10–20 kg should have access to an Epipen junior 150 µg, and children and adults >20 kg be provided with an Epipen 300 µg. (These ASCIA guidelines differ from the product information provided by the manufacturers.) The Australian PBS prescription guidelines for Epipen junior and Epipen are available at <http://www.pbs.gov.au/html/healthpro/search/results?term=epipen&scope=PBS+STATIC&form-type=simple>. The provision of an adrenaline autoinjector for infants under 10 kg needs to be assessed on a case-by-case basis, in consultation with a paediatric allergy specialist. Parents should be trained in anaphylaxis recognition and receive information on strict dietary CMP avoidance.

FPIES

FPIES is a non-IgE-mediated food allergic manifestation that typically presents in infancy.¹⁷ The most common causes are cow's milk, soy and rice,¹⁸ but can also be associated with meats and cereals.¹⁹ Failure to recognise FPIES is common and infants may be misdiagnosed as having septic shock, surgical conditions (e.g. malrotation or intussusception), gastroenteritis or inborn errors of metabolism. The following diagnostic criteria have been proposed: (i) repetitive vomiting and/or diarrhoea within 4 h of ingestion (following first exposure to a food) without other identifiable cause, (ii) symptoms limited to gastrointestinal tract, (iii) complete resolution of symptoms on avoidance and (iv) recurrence of symptoms upon challenge.¹⁹ Hypovolaemic shock has been described in up to 20% of cases.¹⁷ There are no useful diagnostic tests for FPIES, and the diagnosis relies on recognition of clinical features. The role of atopy patch testing and SPT in FPIES is unclear,^{19,20} although SPT is often undertaken to exclude IgE-mediated CMPA.

Treatment involves a strict CMP-free diet, and usually replacement with ehF because of the common co-existence of FPIES to cow's milk and soy.⁴ FPIES has not been reported in exclusively breastfed infants, and no maternal elimination of CMP is necessary while breast-feeding. Diagnostic challenges for FPIES should be deferred until 2–3 years of age at which time FPIES is most likely to have resolved. Some centres obtain intravenous access prior to a challenge due to the risk of hypovolaemic shock. There are no published food challenge protocols for FPIES, and challenges should only be undertaken by clinicians experienced in their administration.

Specific issues in the management of delayed allergic conditions

The management of non-IgE-mediated or delayed CMPA poses diagnostic challenges as, apart from food elimination and re-challenge, no reliable diagnostic tests are available. There is clinical overlap with other food-associated disorders, such as lactose malabsorption, coeliac disease or idiosyncratic reactions to foods. Management of delayed CMPA conditions in breastfed infants can be further complicated by incomplete cow's milk elimination from breast milk, mainly due to maternal intake of unrecognised sources of CMP.

Eczema

CMPA may play a role in infantile eczema. Eczema flares may occur over a variable period of time following CMP ingestion, ranging from hours to days. Despite the delayed onset between allergen exposure and exacerbation, eczema is often associated with IgE-mediated food allergy, and SPT or food-specific serum IgE testing is helpful in predicting response to elimination of CMP and other food allergens.²¹ Infants with early onset eczema (within the first 6 months) of at least moderate severity have a high incidence of food allergies, including CMPA.²²

The duration of CMP elimination trials in infants and mothers of breastfed infants is usually a minimum of 2–4 weeks, and an observable clinical response would be expected within 2 weeks. Elimination diets should be undertaken in addition to optimisation of eczema care, including topical steroids, emollients and treatment of staphylococcal skin infections. Clinical response to CMP elimination can be variable, and elimination of other foods should be guided by IgE-based testing to other foods such as egg and wheat. In the absence of immediate-type symptoms, a positive SPT to a food reflects allergic sensitisation that may, or may not, be causally related to eczema exacerbations. As such, interpretation of positive SPT results in the context of eczema may require confirmatory elimination and rechallenge sequences, including formal inpatient food challenges. In a small proportion of cases, infantile eczema may respond to CMP elimination despite a negative SPT. In children with eczema, the reintroduction of foods, such as cow's milk, after a period of elimination should best be performed under medical supervision as severe allergic reactions or anaphylaxis may occur (even if the food had previously not caused any acute allergic reactions, except for eczema exacerbations).

Eosinophilic oesophagitis

Eosinophilic oesophagitis (EO) is a histological diagnosis characterised by 15 or more intraepithelial eosinophils per high power field in oesophageal biopsy specimens, absence of significant gastro-oesophageal reflux and/or lack of response to proton pump inhibitors.²³ Although sometimes used in the diagnostic work-up, oesophageal 24-h pH monitoring is not generally required for making a diagnosis of EO. Infants and toddlers usually present with unremitting vomiting and regurgitation, feeding intolerance or aversion, severe irritability and may develop failure to thrive. Some experts use SPT and atopy patch testing to guide elimination diets,²⁴ while others empirically

remove common foods allergens (cow's milk, soy, egg, wheat, peanuts and tree nuts).²⁵

When CMP is implicated in the pathogenesis of EO, an amino acid-based formula is recommended as first line therapy. Endoscopies are required to monitor response to dietary elimination or challenge that minimises unnecessary dietary restrictions. In infants and young children who have failed to respond to dietary elimination, consideration is usually given to treatment with swallowed corticosteroid aerosols.²³

Cow's milk protein-induced gastro-oesophageal reflux disease (GORD)

Although up to 40% of infants with symptoms of GORD are thought to have CMPA.²⁶ There are no clear distinguishing features to identify diet-responsive infants with GORD. Most infants with CMP-induced GORD usually present within the first weeks of CMP exposure. The diagnosis of CMP-induced GORD is made by strict CMP elimination for a minimum of 2–4 weeks, and subsequent re-challenge. The prognosis of CMP-induced GORD in infancy is excellent, and reintroduction of CMP is usually successful by 12–18 months of age.

Cow's milk protein-induced enteropathy

Non-IgE-mediated enteropathy is characterised by chronic malabsorption due to small intestinal villous damage.²⁷ This disorder mainly occurs in formula-fed infants. Clinical features include persistent diarrhoea, perianal excoriation, vomiting, abdominal pain and failure to thrive. Oedema and ascites may be present in severe cases due to enteric protein loss. Secondary lactose malabsorption is common, and micronutrient deficiencies (e.g. iron, folate and fat-soluble vitamins) can occur. Diagnosis may be delayed in those patients mislabelled as lactose intolerant, because partial improvement may occur on a lactose-free (but CMP-containing) formula. However, while a lactose-free diet reduces the osmotic diarrhoea, the continued CMP exposure perpetuates the villous damage.

CMP-induced enteropathy in infancy may have symptoms similar to coeliac disease. However, the onset of symptoms often coincides with the dietary introduction of CMP, prior to wheat exposure. Infants with significant failure to thrive may require specialist referral for consideration of a small bowel biopsy. This should ideally occur before an hypoallergenic formula is commenced to allow correct histological characterisation of the intestinal lesion.

Proctocolitis

Food protein-induced proctocolitis is an allergic inflammatory process involving the distal colon and usually presents in the first 3 months of life with low-grade rectal bleeding in an otherwise thriving infant. CMPA is the most common cause, although other food proteins (e.g. soy, rice, wheat) have been implicated²⁸ and it occurs in breast fed infants.

The majority of breastfed infants with allergic proctocolitis respond to maternal elimination of CMP, although some require the additional elimination of soy²⁹ or conversion of the infant to eHF if unresponsive to maternal dietary elimination within

2 weeks. In refractory cases, transition from ehF to an AAF may be required. The majority of infants with allergic proctocolitis develop tolerance to CMP by 12 months. Monitoring of iron status and haemoglobin is required in infants with prolonged symptoms. Consideration of endoscopic examination is recommended in infants with protracted rectal bleeding or associated complications such as failure to thrive or anaemia.

Controversial manifestations of CMPA

Infantile colic

Colic is a multi-factorial condition which typically occurs in infants between 3 to 6 weeks, with remission occurring by 4 months of age.³⁰ The causal relationship of colic and CMPA is controversial, although several trials have demonstrated a significant clinical improvement in response to CMP elimination.^{31–33} Persistence of irritability beyond 4 months may suggest an organic aetiology, including CMPA. Most infants with colic have no associated atopic disorders, and IgE-based tests for food allergy are not helpful. Most diet-responsive infants will reduce colic behaviour within 1 week of dietary modification.^{31,32} Mothers of breastfed infants should consider strict CMP elimination for 2–4 weeks. If this fails referral for a trial of multiple food protein, elimination under dietetic supervision may be considered if food allergy is still in question. Formula-fed infants with persistent irritability and suspected CMPA should be changed to an ehF for 2–4 weeks,³³ and a trial of AAF may be appropriate if no significant improvement has occurred within 4 weeks of ehF. According to the current Australian PBS guidelines, ehF cannot be accessed for uncomplicated infantile colic unless other clinical features of CMPA are present.

In infants who respond to dietary elimination, rechallenge to the allergen in question is recommended after 4–6 weeks to confirm the diagnosis, although in practice parents are often reluctant to undertake this diagnostic step. Re-introduction of eliminated food proteins should be undertaken cautiously because some infants with colic who responded to cow's milk elimination may develop acute allergic reactions when subsequently re-challenged with CMP.

Constipation

CMPA in infancy may present with constipation.³⁴ However, in the absence of clear diagnostic markers, there are significant difficulties in making an unequivocal diagnosis of CMP-induced constipation. There is a wide range of normal stool frequency in infancy.³⁵ Minor constipation at the time of weaning from breast milk to CMF is relatively common and usually due to non-allergic mechanisms such as co-incident introduction of solids. Clinical features suggestive of CMP-induced constipation include onset in close relationship to the first dietary introduction of CMP. There is no diagnostic test for CMP-induced constipation, other than CMP elimination for 2–4 weeks followed by CMP re-challenge. Infants with severe constipation require specialist referral to exclude anorectal malformations or Hirschsprung's disease. Increased eosinophils on rectal biopsy support the diagnosis of CMP-induced constipation^{34,36} and management involves strict dietary CMP elimination and occasionally

soy. Laxatives should be continued and gradually weaned, as tolerated.

Summary

Improved recognition of food allergic manifestations in infancy and access to sophisticated treatment formulas have significantly reduced the morbidity associated with CMPA. The long-term management of CMPA involves prevention of inadvertent allergen exposure, and implementation of precautions against anaphylaxis. Patients require at least annual reassessment for tolerance development, as well as monitoring of dietary intake and growth parameters. If appropriately managed, the prognosis of CMPA is excellent.

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