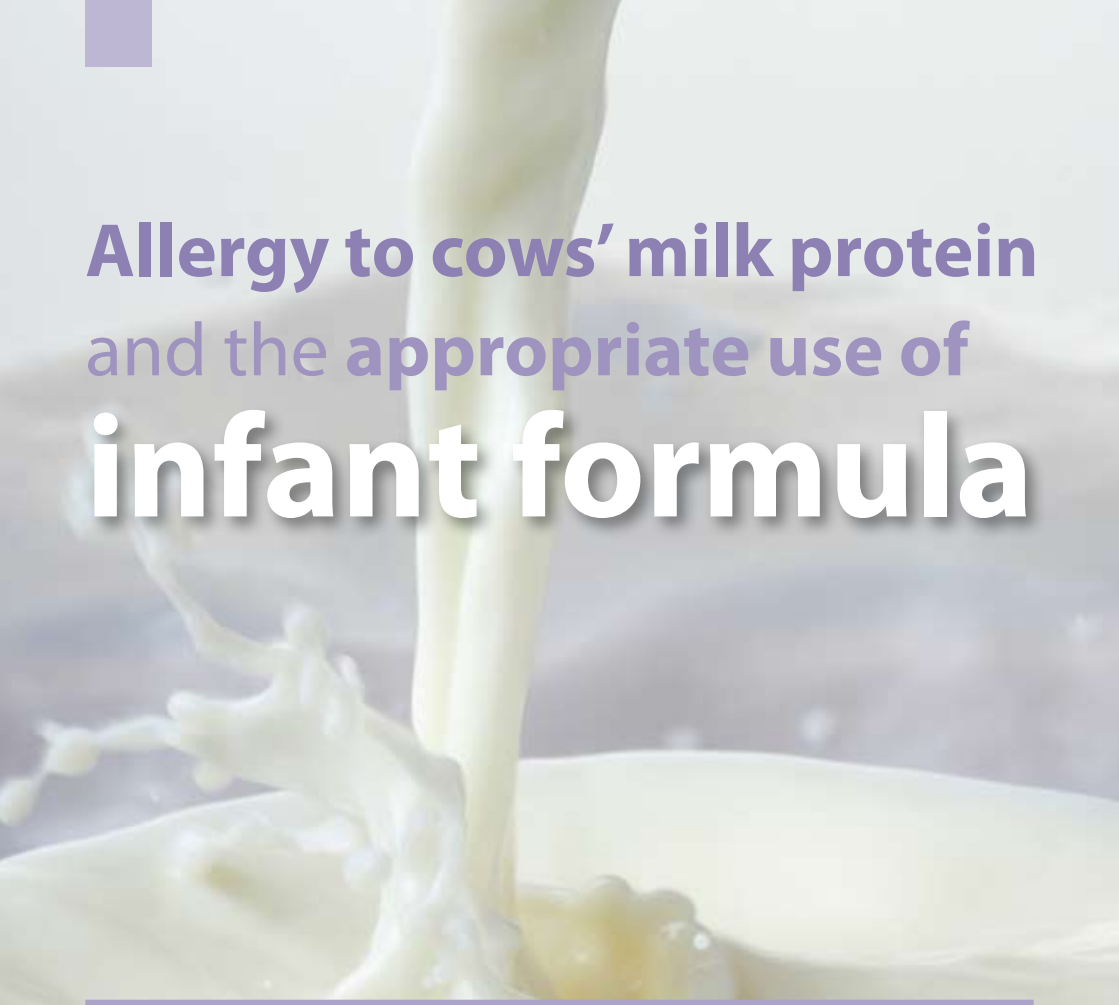
Allergy to cows' milk protein and the appropriate use of infant formula



Key Concepts

- Infants with cows' milk protein allergy (CMPA) can present with a range of syndromes. Definitive diagnosis can be difficult and specialist advice and/or referral may be necessary
- Three types of formula (soy, extensively hydrolysed protein and amino acid) are available for infants with CMPA
- Selection of the appropriate formula for CMPA depends on the allergy syndrome and the age of the infant
- For non-anaphylactic CMPA in infants aged under six months, extensively hydrolysed formula is recommended as first choice
- For non-anaphylactic CMPA in infants aged more than six months, soy formula can be trialled as first choice
- For infants with anaphylaxis due to CMPA or eosinophilic oesophagitis, amino acid formula is recommended as first choice
- If the first choice formula is not tolerated, an alternative formula can be trialled
- Other formula such as goats' milk-based, lactose-free and partially hydrolysed formula are not suitable for CMPA

Background to infant formula funding changes

Soy formula and elemental formula are the two main products used for infants with cows' milk protein allergy (CMPA). The two types of elemental formula available are extensively hydrolysed formula and amino acid based formula.

In New Zealand, more expensive and last-line amino-acid formula products, e.g. Neocate, are being prescribed as an early option. Pharmaceutical dispensing data indicate that 78% of infants with CMPA are being prescribed an amino acid formula without an initial trial of an extensively hydrolysed formula.

The use of amino acid formula as an early option is a concern on two fronts. Firstly, it is out of line with international guidelines which suggest that only approximately 5–10% of infants with CMPA require an amino acid formula.[1,2] Secondly, amino acid formula is significantly more expensive than other options (approximately five to six times the cost of extensively hydrolysed formula per 100 mL). The high cost and the high uptake of amino acid formula in New Zealand (the use of elemental formula is approximately 60% higher in New Zealand than in Australia on a per capita basis)[3] is causing expenditure growth in the Special Foods therapeutic group. In 2008/09 expenditure on elemental formula was $5.8 million, with approximately 38% annual growth (Figure 1).

Funding changes to infant formula

From April 1, 2011:

- Lactose free, soy (S26 Soy, Karicare Soy) and goats' milk infant formula will no longer be funded
- Special Authority approvals for the presently defined "elemental formula" will be split in to two groups:
  - Extensively hydrolysed formula, e.g. Pepti-Junior
  - Amino acid formula, e.g. Neocate, Elecare and Vivonex Pediatric

  Funding for amino acid formula will only be available to patients who have trialled the extensively hydrolysed formula or who have had anaphylaxis on exposure to cows' milk, or who have eosinophilic oesophagitis.
- Reassessment for continued funding, including assessment as to whether the infant can be switched to a less specialised formula will be required every six months instead of every 12 months.
- Patients who currently have a valid Special Authority will not be affected by these changes, until their current approval expires
- Extensively hydrolysed formula and amino acid formula will be fully funded (for eligible infants)

Given that clinical guidelines recommend the use of amino acid formula, only after a trial of an extensively hydrolysed formula (except for infants with anaphylaxis due to CMPA and in eosinophilic oesophagitis) and the unsustainable growth in expenditure, PHARMAC reviewed the access and funding of these products. This has resulted in modification of the access criteria so that:

- The less specialised products such as extensively hydrolysed formula should, in general, be trialled before funding is made available for the last-line amino acid formula
- Patients using these formulae should be reviewed regularly to determine if, as they get older, it is appropriate to transition them to cows' milk or less specialised products such as extensively hydrolysed or soy formula

PHARMAC also considered which of the milk-replacement options should be considered for funding versus which should be considered a private cost. PHARMAC concluded that the more specialised products, such as extensively hydrolysed formula and amino acid formula, should be fully subsidised (with Special Authority) and less specialised products that are available in supermarkets, such as lactose-free and soy formula, should not be funded (and be a private cost).

Cows' milk protein allergy – a spectrum of syndromes

CMPA is an immunologically mediated adverse reaction to cows' milk protein, with a prevalence of approximately 2% in infants aged under two years.[1] Allergic reaction to cows' milk protein can be IgE or non-IgE mediated, and the spectrum of reactions ranges from immediate anaphylaxis and food allergy reactions to delayed effects such as atopic

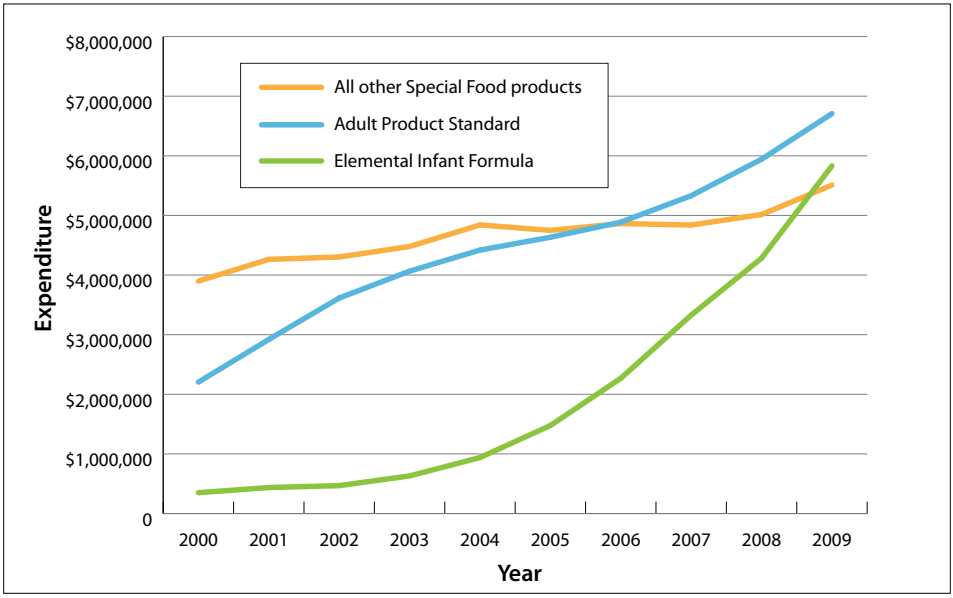


Figure 1: Special Foods expenditure in the Pharmaceutical Budget (main categories)

eczema. Table 1 (over page) provides a summary of the various clinical presentations of CMPA, including key differential diagnoses.

Immediate and delayed CMPA can be differentiated by the timing of the reaction in relation to the intake of cows' milk. Immediate reactions, such as anaphylaxis, angioedema, urticaria and vomiting, occur within minutes. In contrast, delayed reactions, such as food protein enteropathy, proctocolitis and eosinophilic oesophagitis, can manifest over hours or days. Some disorders have features of both immediate and delayed reactions, e.g. in eczema caused by CMPA, the pruritic rash can occur within minutes, hours or days. CMPA can also occur in exclusively breastfed infants due to allergens present in breast milk from maternal ingestion of dairy products.

Immediate allergic reactions

The most serious form of immediate reaction is anaphylaxis with respiratory tract involvement and/or hypotension. In infants the features of anaphylaxis are not always apparent and they may present with coughing, wheezing, severe distress, floppiness or collapse. Anaphylaxis due to CMPA is extremely rare in exclusively breastfed infants.

CMPA allergy can also present with an acute allergic (non-anaphylactic) reaction with erythema, angioedema, urticaria or vomiting. Infants with CMPA are often allergic to other foods such as eggs and peanuts. Immediate allergic reactions are possible in exclusively breastfed infants.

About 80% of cases of immediate CMPA reactions resolve by age three years.[2]

Food protein-induced enterocolitis syndrome

This syndrome is a relatively uncommon non-IgE mediated reaction. Infants usually present with rapid onset of projectile vomiting, floppiness, pallor and possibly diarrhoea, one to three hours after ingestion of cows' milk. The differential diagnosis may include gastroenteritis, sepsis or intestinal obstruction. Food protein-induced enterocolitis syndrome usually occurs when cows' milk is first introduced and can also be caused by other food allergies such as soy, wheat, rice and chicken. In most infants, symptoms resolve completely by age three years.[2]

Atopic eczema

CMPA or allergy to other foods (particularly egg, milk and peanuts) should be considered as a possible cause of eczema in children (**that is not responding to appropriate treatment**), especially if symptoms are moderate to severe.

The main feature of eczema due to CMPA is pruritic rash, which can be severe. Most, but not all, reactions are IgE mediated. The condition tends to improve over time, though the age of clinical resolution is variable.[2]

Gastrointestinal syndromes

There are a wide range of gastrointestinal syndromes due to CMPA. CMPA may present with vomiting, chronic diarrhoea, malabsorption and failure to thrive. Multiple food allergies are sometimes involved.

Gastro-oesophageal reflux disease (GORD)
In approximately 40% of infants referred for management of GORD, the underlying cause is CMPA.[1] The typical symptoms are frequent regurgitation, poor feeding and aversion to feeding. The reaction is not usually IgE-mediated. In GORD caused by CMPA, symptoms may partially improve with a protein pump inhibitor (PPI) and usually resolve by age 12 – 18 months.[2]

Allergic eosinophilic gastroenteritis
This condition is characterised by weight loss and failure to thrive associated with vomiting, diarrhoea, severe irritability and sometimes blood loss in the stool after feeding. Iron deficiency and protein-losing enteropathy can occur in severe cases.[1]

Food protein-induced enteropathy
Infants with allergic enteropathy presents with persistent diarrhoea, perianal excoriation, failure to thrive and vomiting. The infant may have anaemia

Table 1: Clinical presentations and differential diagnosis of CMPA conditions (Adapted from Allen et al, 2009)[2]

Condition	Timing of symptoms in relation to ingestion	Clinical features	Distinguishing features
Acute allergic reaction (nonanaphylactic)	Immediate, up to 60 min	Perioral/orbital angioedema/ erythema. Generalised urticaria Vomiting, diarrhoea	No recurrence if avoidance complete. Incidence approximately 2% in infants.
Anaphylaxis	Immediate, up to 60 min	Respiratory +/- cardiovascular involvement often associated with above features	As above. IM adrenaline treatment of choice. Rare manifestation of CMPA.
Food protein-induced enterocolitis syndrome	Typically 2–4 hours	Profuse vomiting +/- diarrhoea, sudden onset of pallor and floppiness. 20% present as hypovolaemic shock (with associated metabolic acidosis and methaemoglobinaemia)	Responds to fluid resuscitation, adrenaline not required. Unknown incidence but thought to be approximately 0.3%.
Eczema	Min/hours/days	Pruritic rash	Often generalised, onset at introduction of cows' milk. Incidence due to CMPA unknown.
Eosinophilic oesophagitis	Days	Vomiting, feed refusal, failure to thrive, oesophageal dysmotility	Histological diagnosis, 24 hours pH monitoring usually normal, unresponsive to proton pump inhibitors. Incidence approximately 0.04% in infants.
Cows' milk protein-induced GORD	hours/days	Frequent regurgitation, poor feeding, feed aversion	Partially responsive to proton pump inhibitors when underlying mechanism related to CMPA. Up to 40% of infants with GORD have CMPA.
Enteropathy	hours/days	Vomiting, diarrhoea, severe irritability, failure to thrive, iron deficiency anaemia, protein losing enteropathy	Receiving cow's milk in diet. Unknown incidence due to CMPA.
Proctocolitis	hours/days	Low-grade rectal bleeding in a well infant	Normal perianal inspection, thriving. CMPA is the most common cause.
Colic	hours/days	Paroxysms of unexplained, inconsolable crying	Responds to dietary elimination, early onset soon after the introduction of cows' milk protein. May be caused by CMPA in some cases.
Constipation	hours/days	Passage of infrequent and/or hard stools	Responds to dietary elimination, early onset soon after the introduction of cow's milk protein. Unknown incidence due to CMPA.

	Occurrence in exclusively breast fed infants	Differential diagnosis	Age of clinical resolution	Useful investigations
	Possible	Idiopathic urticaria, insect bite	80% by 3 years	Skin prick test, IgE antibodies, oral food challenge
	Extremely rare	Sepsis, acute cardiovascular or respiratory compromise, seizures	As above	Skin prick test, IgE antibodies
	No	Sepsis, gastroenteritis, malrotation, intussusception, metabolic disorder	Most by 3 years of age	History diagnostic, no laboratory markers available
	Yes	Seborrhoeic dermatitis, acrodermatitis enteropathica	Variable, tendency to improve with age	Skin prick test, IgE antibodies, elimination – re-challenge sequence
	None reported	GORD, mucosal candidiasis (white plaques)	Unknown	Endoscopy
	Yes	Idiopathic GORD, eosinophilic oesophagitis, malrotation	12–18 months	Clinical diagnosis. Requires endoscopy if haematemesis or significant failure to thrive
	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
	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
	Yes	Idiopathic colic, developmental disorders, urinary tract infection	4–6 months	Cow's milk elimination and re-challenge
	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

and hypoproteinaemia. Chronic malabsorption occurs due to intestinal villous damage.[2] An association with soy allergy or secondary lactose intolerance is common. If CMPA and lactose intolerance co-exist, a lactose free formula will ameliorate the osmotic diarrhoea but continued exposure to cows' milk protein will worsen intestinal damage.[2]

Constipation and infantile colic

The role of CMPA is controversial in these disorders and unequivocal diagnosis is difficult. Both conditions are common in infancy and the causes are multi-factorial, although elimination of cows' milk from the diet may resolve symptoms. Colic usually resolves by age four to six months and constipation by age 12 – 18 months.[2]

Food protein-induced proctocolitis

Infants with food protein-induced proctocolitis usually present with mild diarrhoea and low-grade rectal bleeding (often with mucous and flecks of blood) within the first three months of life and most develop tolerance to CMPA by 12 months.[2] Although CMPA is most often implicated, other food proteins such as soy, rice and wheat may contribute and this condition can also occur in infants who are breast fed. Infants are otherwise generally well although in prolonged or severe cases there may be failure to thrive or anaemia.[2]

Eosinophilic oesophagitis

This condition is more common in older children than infants. In infants, the usual features are refusal of food, failure to thrive, vomiting, reflux and poor response to anti-reflux treatments. Diagnosis requires endoscopy and is based on histological finding of eosinophilia of the oesophagus. Infants with eosinophilic oesophagitis may have hypersensitivity to multiple foods.[1]

Recommendations for referral for investigation of CMPA[2]

Urgent referral is required for infants with:

Anaphylaxis

Severe failure to thrive

Hypoproteinaemia/protein losing enteropathy

- Clinical features include; vomiting, diarrhoea, severe irritability, failure to thrive, iron deficiency anaemia

Food protein induced proctocolitis

- Low grade rectal bleeding in an otherwise well infant

Referral is required for infants with the following conditions if a trial of cows' milk elimination has failed:

Haematemesis*

Chronic diarrhoea

Persistent vomiting

Persistent rectal bleeding*

Persistent iron deficiency anaemia

Severe eczema

* Apply clinical judgement – these conditions would often warrant urgent referral.

Diagnosis of cows' milk protein allergy can be challenging

As CMPA is not a single, uniform entity, making a clear diagnosis can often be difficult. Many of the symptoms observed in CMPA syndromes are non-specific, e.g. diarrhoea, reflux, constipation and other allergies, and can be caused by other common clinical conditions or allergies. Generally, there is limited evidence for switching formula when infants experience symptoms such as vomiting, spilling, crying, diarrhoea or constipation, unless they are severe or persistent, when further investigation is warranted. There is significant potential for incorrect or over-diagnosis of CMPA, exacerbated by misinformation about the significance of milk and food allergies, targeted marketing of infant formula and a trend for avoidance of cows' milk products and use of hypoallergenic infant formula. Conversely, under-diagnosis of CMPA may increase the risk of adverse nutritional or behavioural outcomes.

A correct diagnosis is critical and this may often require referral for immunological or other investigations such as biopsy or specialist gastrointestinal examination (see sidebar Page 10).

In all cases, diagnosis is usually confirmed by complete elimination of cows' milk from the diet for two to three weeks and observing if the symptoms resolve.[1] In some situations, a rechallenge to see if symptoms recur may be indicated to confirm a diagnosis. As CMPA may naturally remit over time, a rechallenge after a period of avoidance might be useful to ascertain tolerance.[1]

Persistence of symptoms after elimination of cows' milk from feeds can indicate the possibility of other food allergies, e.g. peanut, egg or wheat, or another condition with similar symptoms, such as lactose intolerance or idiopathic urticaria.[2]

Infant formula for treatment of CMPA

Soy

Soy-based infant formula is not appropriate for infants aged under six-months as cross-reactivity or concurrent soy allergy is much higher in this group – 25% under age six months versus only 5% between age 6 – 12 months.[2] Some infants aged over six months find soy-based formula more tolerable than extensively hydrolysed formula.

Although soy-based formula are not subsidised, these products remain an option for treatment of CMPA in infants aged over six-months and are comparably priced to standard cows' milk formula.

Extensively hydrolysed formula

Partially or extensively hydrolysed formula contains cows' milk protein that has been broken down into peptides. In general, the more extensive the hydrolysis of the protein, the less likely it is to cause an allergic response. Only about 10% of infants do not tolerate extensively hydrolysed formula and require progression to amino acid formula.[2]

Amino acid formula

These are the most hypoallergenic formula and should only be considered as first line options for less common, specific types of CMPA or if extensively hydrolysed formula has been trialled and not tolerated.

Table 2: Syndromes associated with cows' milk protein allergy and appropriate choice of formula feed (adapted from Kemp et al, 2008).[1]

		Choice of Formula		
Syndrome	Onset of reaction	First Choice	Second (if first not tolerated)	Third (if second not tolerated)
Immediate Reaction				
Immediate Food Allergy	< 1 hour	Extensively hydrolysed formula (< 6 months)	Amino acid formula	
		Soy (> 6 months)	Extensively hydrolysed formula	Amino acid formula
Anaphylaxis	< 1 hour	Amino acid formula with urgent referral		
Food protein-induced enterocolitis syndrome	1 – 3 hours	Extensively hydrolysed formula	Amino acid formula	
Delayed reaction				
Atopic eczema	Hours to days	Extensively hydrolysed formula (< 6 months or > 6 months with failure to thrive)	Amino acid formula	
		Soy (> 6 months, no failure to thrive)	Extensively hydrolysed formula	Amino acid formula
Gastrointestinal syndromes.	Hours to days	Extensively hydrolysed formula (< 6 months or > 6 months with failure to thrive)	Amino acid formula	
GORD, allergic eosinophilic gastroenteritis, food protein-induced enteropathy, constipation, severe irritability (colic)		Soy (> 6 months, no failure to thrive)	Extensively hydrolysed formula	Amino acid formula
Food protein-induced proctocolitis	> 24 hours	Extensively hydrolysed formula	Amino acid formula	
Eosinophilc oesophagitis in infants	Days to weeks	Amino acid formula		

Management of CMPA

Irrespective of the cause and clinical type of CMPA in an infant, cows' milk should be removed from the diet and replaced with an elemental or soy based formula.

Mothers should be encouraged to continue breast-feeding whenever possible.[2] Cows' milk should be eliminated from maternal diets where the infant has immediate reactions such as anaphylaxis.[1] In cases of delayed reaction, maternal intake of cows' milk is often tolerated, and avoidance is usually only necessary if there are residual symptoms after elimination of cows' milk from the infant's diet.[2]

If the allergy is IgE mediated, avoidance of cows' milk should be strictly enforced with provision of an allergy action plan and adrenaline autoinjector if appropriate.[2]

See "Management of anaphylaxis in primary care", BPJ 18 (Dec, 2008).

When eliminating cows' milk, dietary intake should be assessed for nutritional adequacy of the recommended amounts of protein, calories and micronutrients, such as vitamin D and calcium. This also applies to the maternal diet if cows' milk avoidance is necessary.

Infant formula for CMPA

There are three types of formula available for CMPA; soy-based formula, extensively hydrolysed formula and amino acid formula (see sidebar Page 11).

There has been a trend in New Zealand and overseas to prescribe the most hypoallergenic formulas, especially amino acid formula, first line for CMPA.[3] This is an expensive option and in most cases not necessary.

The type of infant formula most appropriate as the initial option for CMPA should be determined by the age of the infant and the clinical characteristics of the CMPA. Amino acid formula should only be considered as a first line option in infants with CMPA with anaphylaxis and in infants with a confirmed

Nutritional adequacy of cows' milk (dairy) free diets

All food groups provide a variety of nutrients. When a whole food group is removed from an individual's diet there is a risk of an inadequate intake of one or more nutrients. When dairy products are avoided, the nutrients most at risk are protein and calcium.

Adequate amounts of energy in a dairy free diet can be obtained by ensuring a varied intake of breads, cereals and carbohydrate-rich vegetables while protein needs can be met by regular consumption of meat, fish, chicken, eggs and meat alternatives (nuts, seeds, legumes and pulses), providing there are no other allergies that indicate such foods should be avoided. In children the adequacy of these nutrients is best assessed by monitoring growth.

Consumption of a calcium fortified cow's milk alternative (soy, extensively hydrolysed formula or amino acid formula) will provide an additional source of calcium. Other dietary sources of calcium should also be encouraged, providing they are age appropriate and the individual does not have a proven allergy to them. Examples of other calcium containing foods* include:

- Canned fish where the bones are eaten, e.g. salmon, sardines
- Tahini (sesame paste)
- Almonds, brazil nuts, hazelnuts
- Figs
- Some breakfast cereals, check food label for calcium content

*check products are dairy free or suitable for other concurrent allergies.

diagnosis of eosinophilic oesophagitis.[1, 2] In the majority of cases of CMPA, extensively hydrolysed formula, (or soy if the infant is aged more than six months) should be considered first. In some cases failure to thrive affects the choice of formula.[1] These recommendations are summarised in Table 2 (Page 12) and form the basis of the current funding pathway.

Infants should be reviewed regularly (every six months) to check if tolerance to cows' milk protein has developed. This can be done by taking a history of accidental ingestion of cows' milk, skin prick testing, measurement of cows' milk specific serum IgE or food challenges.

In an infant with severe IgE mediated CMPA, tolerance should only be assessed in hospital because of the risk of anaphylaxis.

Other infant formula are not recommended

Soy-based, extensively hydrolysed formula and amino acid formula are the only infant formula recommended for the treatment of CMPA. The following are not recommended or contraindicated; Lactose-free cows' milk, (e.g. Karicare De-Lact), partially hydrolysed cows' milk (e.g. Karicare SensiKare), Goat's milk based formula and other mammalian milks, rice milk and oat milk.[1]

Monitoring and re-evaluation

Expert guidelines recommend regular monitoring of growth for children with food allergy in combination with nutrition counselling.[4] There are, however, no clear guidelines on when re-evaluation of CMPA or other allergies should occur. In practice re-trialling allergenic foods depends on clinical judgement, taking into consideration the severity of symptoms, the age of the child and other medical and social circumstances.[4] For infants with anaphylaxis, food challenges should be performed in hospital.[2]

There are also no clear guidelines on when an infant with CMPA should be weaned off a formula and when consideration should be given to changing to a less hypoallergenic formula, e.g. amino acid formula, to extensively hydrolysed formula, or extensively hydrolysed formula to soy-based, or for how long the effect of a switch should be evaluated for. However, given that most CMPA syndromes resolve over time, the requirement for on-going formula should be regularly reviewed.

Re-assessment should be on a case by case basis and it may be appropriate to consult with a paediatrician or dietitian with expertise in the management of CMPA for further advice.

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