Guidelines for the management of

cow's milk protein allergy in children 2012

(CMPA in children)

Malaysian Society of Allergy and Immunology

PERSATUAN PEDIATRIK MALAYSIA

Committee members

The following are members of the guideline committee:

Professor Dr Lee Way Seah (Chair)
Professor of Paediatrics and Consultant Paediatric Gastroenterologist and Hepatologist
Head, Department of Paediatrics
University of Malaya Medical Centre, Kuala Lumpur
Past President, College of Paediatrics, Academy of Medicine of Malaysia (AMMCOP)

Dr Alvin Khoh Kim Mun
Paediatrician and Fellow in Paediatric Gastroenterology
University of Malaya Medical Centre, Kuala Lumpur

Dr Amir Hamzah Abdul Latiff
Consultant Paediatrician and Consultant Clinical Immunologist/Allergist
Pantai Hospital Kuala Lumpur, Bangsar, Kuala Lumpur
President, Malaysian Society of Allergy and Immunology (MSAI)
Communications Council Member, World Allergy Organization (WAO)

Dr Chai Pei Fan
Consultant Paediatrician and Paediatric Gastroenterologist and Hepatologist
Pantai Hospital Kuala Lumpur, Bangsar, Kuala Lumpur

Dr Cheong Hon Kin
Paediatrician
Hospital Selayang, Batu Caves, Selangor Darul Ehsan

Dr Chong Sze Yee
Paediatrician and Fellow in Paediatric Gastroenterology
Hospital Selayang, Batu Caves, Selangor Darul Ehsan

Dr Kew Seih Teck
Paediatrician and Fellow in Paediatric Gastroenterology
Hospital Selayang, Batu Caves, Selangor Darul Ehsan

Dr Nazrul Neezam Nordin
Consultant Paediatrician and Paediatric Gastroenterologist and Hepatologist
Paediatric Institute, Hospital Kuala Lumpur, Kuala Lumpur

Dr Ng Ruey Terng
Lecturer in Paediatric Gastroenterology, Hepatology and Nutrition
University of Malaya Medical Centre, Kuala Lumpur

Dr Nur Atiqah Ng Abdullah
Consultant Paediatrician and Paediatric Gastroenterologist
Pantai Hospital Kuala Lumpur, Bangsar, Kuala Lumpur

Cik Siti Hawa bt Mohd Taib
Clinical Dietitian
Head, Department of Dietetics
University of Malaya Medical Centre, Kuala Lumpur

Datuk Dr Zulkifli Ismail
Consultant Paediatrician and Paediatric Cardiologist
KPJ Selangor Specialist Hospital, Shah Alam, Selangor Darul Ehsan
President Elect, Asia Pacific Paediatric Association (APPA)
Past President, Malaysian Paediatric Association (MPA)

Terms of reference

Target audience:

This guideline aims to cater mainly for paediatricians, primary care physicians and other frontline healthcare providers involved in providing care for children.

Format:

This guideline consists of easy-to-read information with appropriate flow charts. All facts are evidence-based as far as possible. Where evidence is not currently available, the combined and consensus opinion of the members with adequate consultation with senior colleagues prevailed.

1. The full guidelines on the management of cow's milk protein allergy may be obtained from the following websites:
   - Malaysian Paediatric Association (MPA)
     http://www.mpaweb.org.my
   - Malaysian Society of Allergy and Immunology (MSAI)
     http://www.allergymsai.org
   - Danone Dumex (Malaysia) Sdn Bhd
     http://www.dumex.com.my

2. A pocket reference guide which is a summary of the recommendations for the management of cow's milk protein allergy may be obtained from MPA, MSAI or Danone Dumex (Malaysia) Sdn Bhd.

Content:

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Disclaimer:

The content and recommendations made in this guideline is based solely on currently available scientific evidence and/or best clinical practice. The committee recognises the scarcity of published/available local data and the impact it might have on the recommendations made within this guideline. Healthcare professionals are encouraged to exercise their discretion when utilising the information contained within this guideline in their clinical practice.

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01 Introduction

Cow's milk protein allergy (CMPA) is the most common form of food allergy in infants. Local epidemiological data is limited; however, milk has been found to be the most common food allergen in Asia and in Malaysia.[1] The incidence of challenge-confirmed CMPA ranges between 5–8% worldwide,[2–6] while 5–15% of infants suffer from symptoms suggestive of adverse reactions to cow's milk protein (CMP).[7] However, the perception of CMPA is not uncommon; self-reported CMPA has been documented to be between 1.0–17.5% in preschoolers and 1.0–13.5% in children aged 5–16 years old.[8]

This discrepancy underlines the importance of accurate diagnoses, which will reduce the number of infants on inappropriate elimination diets. It also highlights the need for a local guideline for physicians to provide guidance in diagnosing and managing CMPA in infants in Malaysia, recognising issues unique to the local setting such as cost and availability of infant formulas, as well as religious dietary laws. This guideline was developed from discussion based on existing recommendations, clinical experience, and whenever possible, evidence from the literature, acknowledging the scarcity of available published local data.

02 Summary of the guidelines

CMPA is defined as an immune-mediated hypersensitivity to CMP. Although local epidemiological data is limited, milk has been recognised as the most common food allergen in Asia and Malaysia.[1] Although the prevalence of CMPA generally peaks at 1 year of age and usually resolves in 3–4 years,[9–11] it may persist up till the age of 18 years in a small minority of individuals.[12] Patients with CMPA may present with a wide variety of gastrointestinal, cutaneous and respiratory symptoms. Up to 9% of patients may experience anaphylaxis.[13] Immunoglobulin E (IgE)-mediated CMPA is characterised by an immediate onset of reactions that occur within minutes of ingestion of cow's milk while non-IgE-mediated CMPA is characterised by late-onset symptoms that typically develop within one to several hours or after several days following ingestion of cow's milk.[13]

Although a medical history alone cannot be considered diagnostic of CMPA, it is likely to determine the type of diagnostic testing necessary when CMPA is suspected. The double-blind placebo-controlled food challenge (DBPCFC) is considered the 'gold standard' for diagnosing food allergies. However, an open oral food challenge (OFC) represents a more practical approach. A negative DBPCFC should always be followed by an open OFC. When dealing with IgE-mediated acute reactions with objective signs, a positive open OFC may be sufficient. Open OFCs are done in the annual assessment of tolerance onset of CMPA. However, food challenges should not be performed in children or adults with a history of severe systemic reaction or anaphylaxis. In the workup of CMPA, a skin prick test (SPT) should be considered, particularly when it is impractical or impossible to conduct an OFC. A wheal diameter cut-off of ≥ 6 mm (≤ 2 years of age) and ≥ 8 mm (> 2 years of age) generally defines CMPA. When an OFC and an SPT are not possible, serum cow's milk-specific IgE test may be considered. However, test results should be interpreted within the context of clinical presentation.

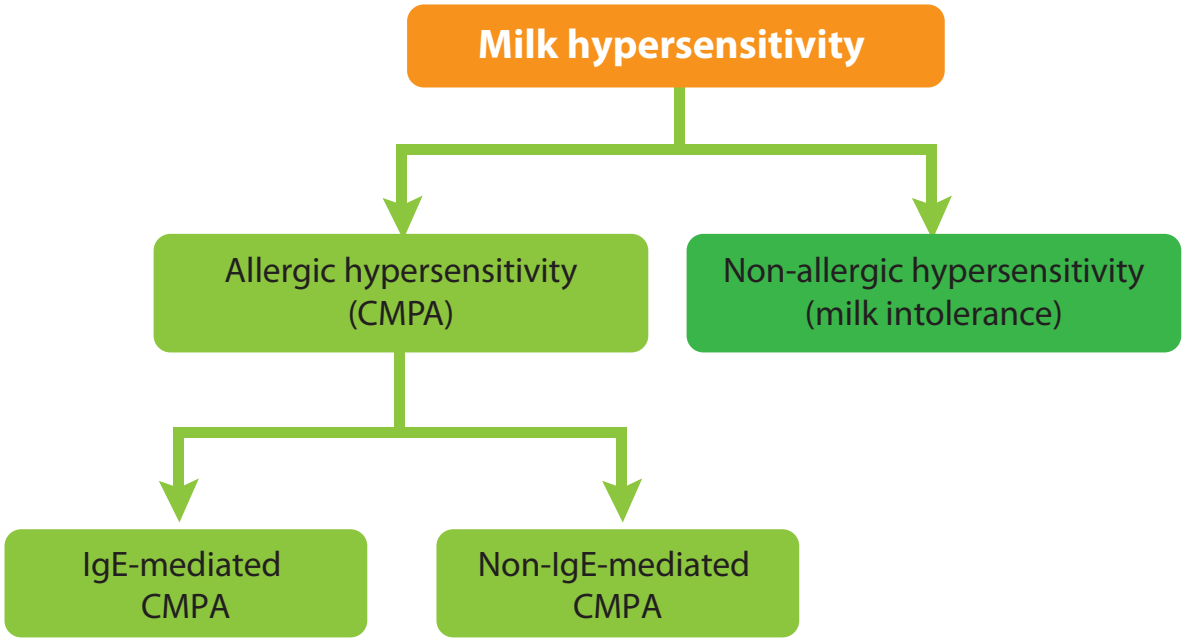
The key principle in the management of CMPA is the dietary elimination of CMP. A substitute formula may not be necessary in infants who are breastfed and children above the age of 2 years. In exclusively breastfed children, continuation of breastfeeding with maternal elimination of CMP is recommended. For children below the age of 2 years and non-breastfed children, replacement of cow's milk with a substitute formula is recommended, with the first and second option being extensively hydrolysed formula (EHF) and amino acid formula (AAF), respectively. In all cases of CMPA, a periodical re-evaluation of cow's milk tolerance every 6 months with an open OFC is recommended.

03 Definitions and terminology

Adverse reactions to cow's milk can occur at any age from birth, but not all such reactions are allergic in nature. Terms such as milk allergy, milk intolerance and milk hypersensitivity are often used interchangeably, despite representing different conditions. A recent revision of the allergy nomenclature, endorsed by the World Allergy Organization, defines any adverse reactions to milk as milk hypersensitivity and can be divided into immune-mediated hypersensitivity (milk allergy) and non-immune-mediated hypersensitivity (milk intolerance). CMPA can be further divided into IgE-mediated CMPA and non-IgE-mediated CMPA (Figure 1).[14] IgE-mediated CMPA is thought to manifest as a phenotypical expression of atopy; it may co-exist with atopic eczema, allergic rhinitis and/or asthma. Non-IgE-mediated CMPA, however, is probably cell-mediated and presents mainly with gastrointestinal symptoms.[13]

***Hypersensitivity**: objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons.*[14]

***Allergy**: a hypersensitivity reaction initiated by specific immunologic mechanisms.*[14]



CMPA = cow's milk protein allergy.

Figure 1. Classification of milk hypersensitivity

04 Natural history of cow's milk protein allergy

CMPA can develop from the neonatal period, peak by 1 year of age and remit in childhood. Onset of symptoms is related to antigen exposure and generally occurs within the first 2 months of life.[15–17] Referral studies suggest that CMPA usually resolves in about 3–4 years.[9–11] However, a recent study involving 807 children with CMPA found that CMPA can persist into adolescence.[12] The condition persists beyond 12 years of age in approximately one third of these children, while 12% of them remained allergic to cow's milk until the age of 18 years (Figure 2).[12]

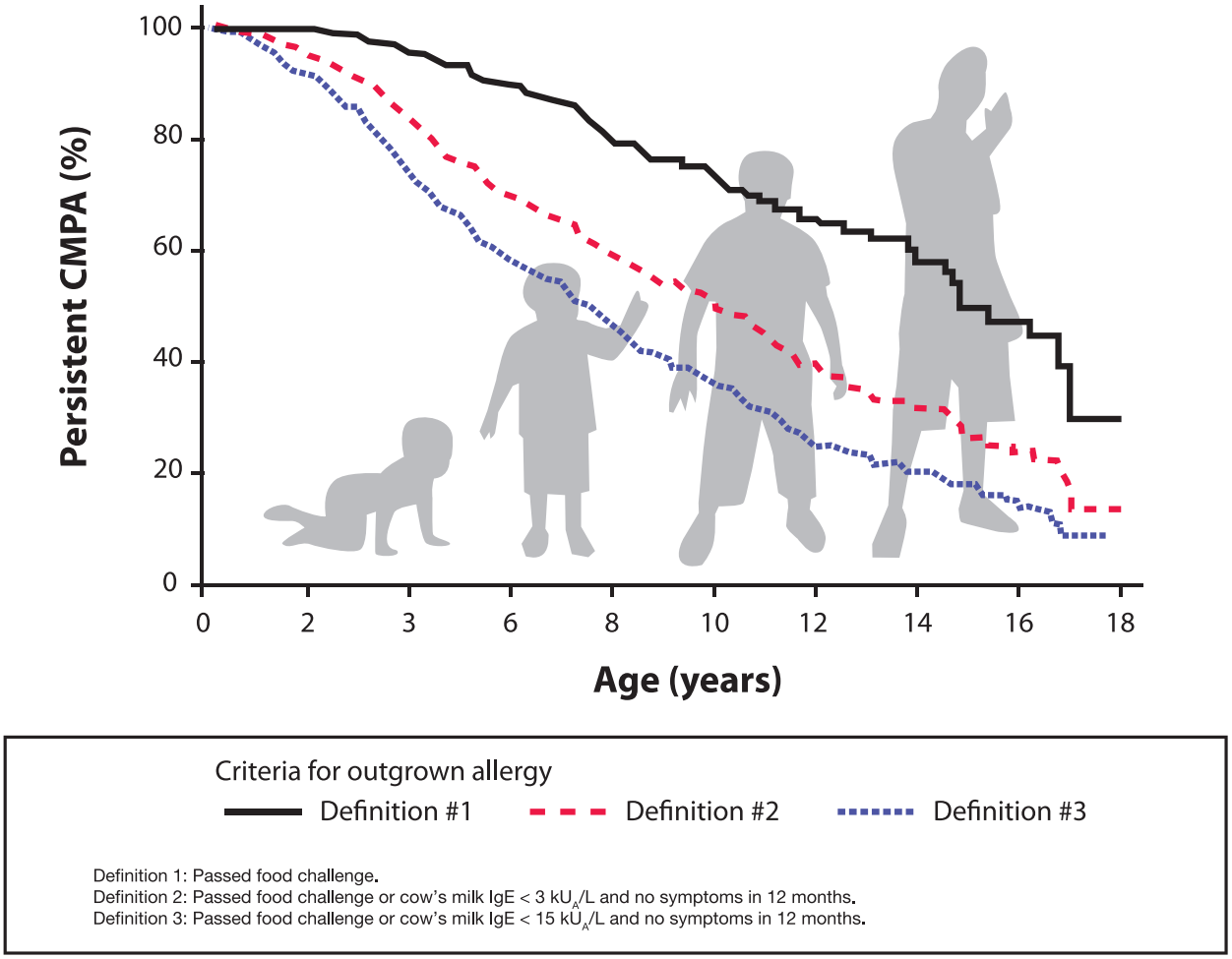


Figure 2. Incidence of CMPA resolution. Adapted from Skripak JM *et al.*, 2007.[12]

Risk factors for persistent CMPA may include:

- A clinical diagnosis of asthma, rhinitis, eczema, early respiratory symptoms with skin and/or gastrointestinal symptoms, and a positive family history of atopic disease [9,12]
- Severe symptoms at the time of diagnosis[9,18–20]
- Larger wheal diameter at SPT with fresh milk – each 1 mm increment in wheal diameter is associated with longer duration of disease[9]
- Clinical type of CMPA – several studies found that 15% of children with IgE-mediated CMPA remained allergic after 8.6 years while all children with non-IgE-mediated CMPA outgrew their allergy after 5 years[2,21,22]

05 Clinical history and symptoms

Individuals with CMPA may present with a vast array of symptoms. Patients with CMPA develop gastrointestinal symptoms in 32–60% of cases, cutaneous symptoms in 5–90% of cases, respiratory symptoms in 15–30% of cases and anaphylaxis in 0.8–9.0% of cases.[13] Thus, knowledge of the various CMPA disorders and a detailed medical history (Table 1) is vital in arriving at an accurate diagnosis.

5.1 Clinical history

Table 1. Medical history in a workup for CMPA

1. Is this CMPA?	• What is the nature of the symptoms? – Gastrointestinal, respiratory, cutaneous or generalised
2. Has the child been exposed to CMP?	• What is the timing of the reaction post-exposure? – IgE-mediated reactions usually occur within 20 minutes to 2 hours following ingestion of cow's milk – Non-IgE-mediated reactions are usually more delayed in onset – In a minority of infants who are exclusively breastfed, CMP may be transmitted via human milk, and thus maternal diet should be investigated[7]
3. Consider other differential diagnoses	
4. Consider other food protein allergy	
5. Consider family history	
6. Are there any other concomitant atopic condition?	• The majority of children with CMPA also have eczema, while 25% of them will go on to develop other food allergies. These children are at risk of developing asthma. Additionally, asthma is a risk factor for more severe food-induced reactions

05 Clinical history and symptoms

5.2 IgE-mediated CMPA reactions

IgE-mediated CMPA is characterised by an immediate onset of reactions that occur within minutes of ingestion of cow's milk (Table 2).[13]

Table 2. Conditions associated with IgE-mediated reactions[13]

1. IgE-mediated systemic reactions (anaphylaxis)	• The most severe manifestation of immediate CMPA and is potentially fatal • Reactions involve the skin and mucosa, respiratory symptoms (dyspnoea, bronchospasm, stridor, reductions in peak expiratory flow, hypoxaemia), fall in blood pressure, organ dysfunction symptoms, gastrointestinal symptoms (colic, vomiting) and shock[13] • Immediate-onset reactions (symptoms develop within minutes of ingestion) • Late-onset reactions (symptoms develop from one hour to several days after ingestion)
2. IgE-mediated gastrointestinal reactions	• **Oral allergy syndrome** – Less prominent in paediatric populations than in adults, but lip swelling is often observed in children during food-challenge procedures[23] • **Immediate gastrointestinal allergy** – Symptoms include vomiting and diarrhoea[13]
3. IgE-mediated respiratory reactions	• Severe clinical manifestations include anaphylaxis, asthma attack and rhinitis[24–29] • Although rare, asthma and rhinitis secondary to inhalation of cow's milk proteins have been reported[30,31]
4. IgE-mediated cutaneous reactions	• **Immediate-onset reactions** – Acute urticaria or angioedema – Contact urticaria • **Late-onset reactions** – Atopic dermatitis

05 Clinical history and symptoms

5.3 Non-IgE-mediated CMPA reactions

Non-IgE-mediated CMPA is characterised by late-onset symptoms (Table 3) that typically develop one to several hours or after several days following ingestion of cow's milk.[13]

Table 3. Conditions associated with mixed and non-IgE-mediated reactions[13]

1. Atopic dermatitis	• A chronic, relapsing, pruritic inflammatory disease of the skin.[32] CMPA-associated atopic dermatitis can occur even in extremely low-birthweight infants[33] • Early age of onset and greater severity of eczema have been linked with greater frequency of associated high levels of cow's milk-specific IgE[34] • Immediate-onset reactions • Late-onset reactions
2. Non-IgE-mediated gastrointestinal reactions	• **Gastro-oesophageal reflux disease (GERD)** – 40–56% of infants referred for specialist management of GERD have CMPA[35] – Cow's milk can induce severe gastric dysrhythmia and delayed gastric emptying[36] • **Cricopharyngeal spasm** • **Pyloric stenosis** • **Allergic eosinophilic oesophagitis (EoE)** – Characterised by swallowing difficulty, food impaction, food refusal, difficulty in infant feeding, poor weight gain and poor response to standard anti-reflux treatment[37] – Recognised by symptoms such as postprandial vomiting, diarrhoea and blood loss – Hypersensitivity to multiple foods may be observed • **Food protein-induced gastroenteritis and proctocolitis** – Symptoms usually present by the second month.[38] It can also occur in the early neonatal period, sometimes mimicking Hirschsprung's disease[39,40] – Presentations include relatively normal stools or mild diarrhoea and low-grade rectal bleeding, but be otherwise well and thriving.[38] Other systemic features are usually absent[41] • **Food protein-induced enterocolitis syndrome (FPIES)** – An uncommon disorder which presents 1–3 hours following ingestion of CMP[42] – Symptoms include repeated projectile vomiting, hypotonia, pallor and diarrhoea; may progress to dehydration and cause shock in 20% of cases[42] – May be caused by other food proteins and has not been reported in exclusively breastfed infants[42]

	• **Cow's milk protein-induced enteropathy** – A more chronic spectrum of FPIES which may cause diarrhoea (with or without blood), failure to thrive, vomiting, hypoproteinaemia and anaemia[43,44] – Clinical signs of secondary lactose intolerance may be present[45] – Soy milk, hydrolysed casein protein and maternal dietary proteins transferred through breast milk have also been implicated[46] • **Severe irritability (colic)** – Unexplained paroxysms of irritability, fussing or crying that persists for more than 3 hours per day, on more than 3 days per week for at least 3 weeks[47] – In most cases colic is caused by multiple factors which may include gastroesophageal reflux and oesophagitis[48] • **Constipation** – The possible association between CMPA and constipation in infants and young children remains controversial[49] – Removal of CMP from the diet has been shown to benefit children suffering from chronic constipation and has been reported in numerous publications, including a systematic review[50–52]
3. Non-IgE-mediated respiratory reactions	• **Heiner's syndrome** – A very rare form of chronic pulmonary disease characterised by recurrent pulmonary infiltrates associated with chronic cough, recurrent fever, tachypnoea, wheezing, rales, failure to thrive and family history of CMPA[53] – Should be considered in infants with unexplained chronic pulmonary infiltrates

06 Investigation/diagnostic testing in cow's milk protein allergy

Although a detailed medical history often provides evidence for the type of food-induced allergic reaction and the potential causative allergen involved, history alone cannot be considered diagnostic of CMPA. Nonetheless, clinical history is likely to determine the type of diagnostic testing required in a child with suspected CMPA.

6.1 Oral food challenges

Although an elimination diet can be started in patients with suggestive medical histories, an OFC is an integral component of diagnosis, with the exception of patients with previous systemic or anaphylactic reactions. An OFC is the most valuable diagnostic tool for confirming suspected CMPA. The DBPCFC is considered the 'gold standard' for diagnosing food allergies – it has the ability to minimise false positive diagnoses.

6.1.1 Selection of patients for oral food challenges

For patients of any age with a history of adverse reaction to a food:[54]

- For establishment or exclusion of the diagnosis of food intolerance/allergy
- For assessment of tolerance. Once diagnosed, when a patient is supposed to have outgrown his clinical allergy – especially in children, whose food allergies normally outgrow during childhood

For patients without specific history of adverse reaction to a food:[54]

- If any chronic symptom is suspected by the patient or the physician to be food-related
- If a patient is on an inappropriate elimination diet – without a documented history of adverse food reaction. If the food has to be reintroduced into the diet and there are reasons to suspect that an adverse reaction is possible
- If a sensitisation to a food is diagnosed and tolerance is not known (e.g. sensitisation to cross-reactive foods that have not been eaten after the adverse reaction)

OFCs should not be performed in the following:

- Repetitive reactions with minimal quantities of food with positive SPT/serum food-specific IgE
- Recent severe systemic reaction (in children) or anaphylaxis (in adults)
- Patients with chronic atopic disease, such as asthma or atopic eczema, should only be challenged when disease activity is at a stable and low level

6.1.2 Double-blind placebo-controlled food challenge

DBPCFC is the 'gold standard' for the diagnosis of CMPA. It is the most specific test for diagnosing CMPA and may be performed in ideal circumstances. However, due to the cost and inconvenience of DBPCFCs, open challenges may be sufficient in most clinical settings.

DBPCFC may be performed:

- To establish or exclude diagnosis in patients suspected of immediate, systemic allergic reaction to a food
- In infants and children ≤ 3 years of age, however, an open OFC controlled and evaluated by a physician is most often sufficient

Recommendations:

- DBPCFC is useful when studying delayed reactions or chronic symptoms (e.g. atopic eczema, isolated gastrointestinal late reactions, chronic urticaria)
- DBPCFC is required for subjective food-induced symptoms (e.g. migraine, chronic fatigue syndrome, joint complaints)
- When the result of an open food challenge is uncertain, DBPCFC is recommended

6.1.3 Open oral food challenge

- For practical reasons, an open OFC can be the first approach when the probability of a negative outcome is estimated to be very high
- A negative DBPCFC should always be followed by an open OFC
- A positive open OFC could be sufficient when dealing with IgE-mediated acute reactions manifesting with objective signs
- In infants and children ≤ 3 years of age, an open, physician-controlled OFC is often sufficient for suspected immediate type reactions (unless parental bias is anticipated)

Recommendations:

- An open OFC can be considered as an alternative to DPBCFC
- A negative DBPCFC should be followed by an open OFC
- Open OFCs are done in the annual assessment of tolerance onset of CMPA

6.1.4 Single-blind challenge

Single blind challenges carry the same difficulties for blinding foods as for DBPCFCs and introduce subjective bias of the observer.

Recommendations:

- Single-blind challenges do not offer any advantages over DBPCFC and is not recommended in the diagnosis of CMPA

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6.2 Skin testing

6.2.1 Skin prick test

An SPT can be used to screen patients with IgE-mediated CMPA, where glycerinated standardised extracts (1:10 or 1:20 dilution) and positive (histamine) and negative (saline) controls are applied by the prick of puncture technique. Traditionally, a wheal diameter that is at least 3 mm greater than the negative control is indicative of a positive response. Positive predictive accuracies of SPTs are less than 50%. Positive SPTs do not prove a causal relationship, but merely suggest the presence of clinical food allergies. On the other hand, negative predictive accuracies of SPTs are generally greater than 95% and may be used to exclude IgE-mediated food allergies. It has been reported that a wheal diameter cut-off of at least 6 mm and 8 mm is more than 95% predictive of reactivity in infants less than 2 years of age and 3 years of age, respectively.[55]

Limitations:

- Lack of standardised extracts for many potential food allergens
- There is a tendency for false positive results in children less than 1 year, presumably due to immaturity of the immune system, and in atopic individuals
- The use of antihistamines may result in false negative results

Recommendations:

- SPT should be considered in the workup of CMPA, particularly when it is impractical or impossible to conduct an OFC (e.g. anaphylaxis)
- Results of an SPT should be interpreted within the context of clinical presentation
- Generally, a wheal diameter cut-off of ≥ 6 mm (≤ 2 years of age) and ≥ 8 mm (> 2 years of age) defines CMPA

6.2.2 Other skin tests

- Atopy patch test (APT) and intradermal skin testing are not recommended for the evaluation of CMPA

Recommendations:

- Atopy patch test and intrademal skin testing are not recommended for the evaluation of CMPA

06 Investigation/diagnostic testing in cow's milk protein allergy

6.3 Evaluation of serum food-specific IgE

Serum food-specific IgE determination (fluorescence enzyme immunoassay with the ImmunoCAP assay)* may also be used to screen patients suspected of IgE-mediated CMPA (Table 4). However, for the same allergen extract used, it is generally less sensitive than skin tests. With a positivity limit of 0.35 kU_A/L (on the ImmunoCAP assay), it has greater negative predictive value than positive predictive value. It may be used in the following clinical situations:

- Significant dermatographism
- Severe skin diseases
- Use of antihistamines
- Suspected exquisite sensitivity to certain foods

*At time of publication, the ImmunoCAP assay (Thermo Fisher Scientific (previously Phadia), Waltham MA) is the most widely used assay in Malaysia. Other available assays include CLA Allergen Specific IgE Assay (Hitachi Chemical Diagnostics Inc, Japan), Turbo-MP (Agilent Technologies Co, Santa Clara, CA) and 3gAllergy on the Immulite 2000 (Siemens medical Solutions Diagnostics, Tarrytown, NJ). Results from the different assays are not interchangeable. All values mentioned in this publication are made with reference to the ImmunoCap assay.

Table 4. Cut-off values for food-specific IgE levels[56]

Allergen	Decision point (kU_A/L)	Positive predictive value
Egg **(infants < 3 years)[a]**	7 (2)	98 95
Milk[b] **(infants < 3 years)[c]**	15 (5[b])	95 95
Peanut	14	100
Soybean	30	73
Wheat	26	74

Adapted from Sampson HA, 2001.[56]

[a] From Boyano Martinez T *et al.*, 2001.[57]

[b] Although casein-specific IgE test is available, it has no advantage over milk-specific IgE test in the consideration of CMPA.

[c] From Garcia-Ara C *et al.*, 2001.[58]

Limitations:

- A positive result may be due to cross-reactivity with other similar allergens and not to the test allergen (Table 5)
- Reference sera for most allergens are not available, leading to issues in quality assurance
- The arbitrary units used to assess the test may be misinterpreted by clinicians
- In tissues, most IgE is bound to mast cell surfaces and are not present in serum. Furthermore, the amount of IgE binding does not necessarily reflect the serum level at a given dilution of serum
- The presence of specific IgE does not indicate significant clinical allergy, but merely prior sensitisation to the allergen
- The cut-off values in different populations may differ

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Table 5. Clinical cross-reactivity of foods[59]

Food	Cross-reactivity	Percentage (%)
Egg	Chicken meat	< 5
Cow's milk	Beef/veal Goat's milk	≈ 10 ≈ 90
Beef/veal	Lamb	≈ 50
Fish	Other fish species	> 50
Peanut	Legumes (except lentil) Tree nuts	< 10 ≈ 35
Soybean	Legumes	< 5
Wheat	Other cereal grains	≈ 25
Tree nuts	Other nuts	> 50

Adapted from Sampson HA, 1999.[59]

Recommendations:

- Serum cow's milk-specific IgE test is a useful diagnostic tool for symptomatic CMPA when an SPT or OFC is not possible
- Results of a serum cow's milk-specific IgE test should be interpreted within the context of clinical presentation
- Generally, a cow's milk-specific IgE (via fluorescence enzyme immunoassay with the ImmunoCAP assay) ≥ 15kU$_A$/L is predictive of a positive diagnosis of symptomatic CMPA

07 Management of CMPA

7.1 Principles of management

Key principles in the management of CMPA:

- The key principle in the management of CMPA, regardless of the clinical type, is dietary elimination of CMP
- A substitute formula may not be necessary in infants who are breastfed and children above the age of 2 years
- Replacement of cow's milk with a substitute formula is recommended for children below the age of 2 years and non-breastfed children

7.2 Elimination and avoidance of cow's milk protein

Avoidance of CMP is not limited to exposure via the oral route; CMPs may be encountered in inhalant or contact forms and must be avoided as they may trigger severe reactions.[60–62] Avoidance of other bovine proteins should be evaluated on a case-by-case basis; while practically all children allergic to beef are allergic to milk,[63] the opposite is not true.[64] Attention must be paid to the prescription of a nutritionally safe and balanced diet. Compliance with dietetic advice should be verified throughout the therapeutic phase. As the natural history shows that many children with CMPA outgrow their condition (Table 6), a periodical re-evaluation of cow's milk tolerance every 6 months with an open OFC (until tolerance develops) is recommended. Different types of formulas are available to replace cow's milk in managing CMPA (Table 7). The choice of substitute formula should take into account the patient's preferences, dietary requirements and individual circumstances, as well as cost and availability of the formula. Goat's milk-based formula and fresh goat's milk are not recommended for the management of CMPA. Unmodified goat's milk is high in sodium and low in folic acid, increasing the risks of hypernatraemia[65] and megaloblastic anaemia.[65] Also, they may be allergenic in children with CMPA (approximately 90% cross-reactivity).[59]

Table 6. Prognosis of CMPA diagnosed in a 1-year birth cohort of newborns[2]

Age (years)	Recovery rate	95% confidence interval
1	56	40–72%
2	77	61–89%
3	87	73–96%
5	92	79–98%
10	92	79–98%
15	97	87–100%

Adapted from Host A *et al.*, 2002.[2]

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Table 7. Substitute formulas for CMPA

Formula	Common brands available in Malaysia[a]	Indicated age range for CMPA	Protein source	Comments
EHF	Alimentum® Mamex® Gold Pepti Pregestimil® LIPIL	Birth to 1 year	Cow's milk	• Less palatable than other formulas • Most are non-halal, with the exception of Mamex® Gold Pepti
AAF	Comidagen Neocate®	< 1 year	Amino acids	• Recommended in: – Severe CMPA – Persistent symptoms with EHF – Refusal of EHF by the child • Cost-benefit ratio should be considered • Has a less bitter taste than EHF
	Comidagen Plus Neocate® Advance	> 1 year		
SBF	Enfalac A+ ProSobee® Isomil® Mamex® GOLD Soya Step 1 Nursoy®	6 months–1 year	Soy	• Absolute indications: – Galactosaemia – Hereditary lactase deficiency – Vegetarian diet • Not recommended for preterm babies • Cross-sensitisation to soy has been reported[66,67]; no advantage over cow's milk formula to supplement breast milk • There are concerns about unsuitability for use in infants < 6 months of age due to unknown long-term effects of the high aluminium and phytoestrogen content in SBF
	Mamex® GOLD Soya Step 2	> 6 months		
	Isomil® Plus	1–3 years		

The term milk loosely refers to any whitish beverage that is used to provide nutrition. However, when considering the nutritional needs of young infants the formulas listed in this table are recognised as treatment options for CMPA.

AAF = amino acid formula; EHF = extensively hydrolysed formula; SBF = soy-based formula.

[a] At date of publication.

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Table 8. Options for substitute formula based on phenotypic presentation of CMPA

Clinical presentation	Options		
	First option	Second option[a]	Third option[b]
Immediate onset reactions (< 1 hour)			
Anaphylaxis	AAF	EHF	SBF[c]
Acute urticaria or angioedema	EHF	AAF / SBF[c]	–
Asthma/rhinitis	EHF	AAF / SBF[c]	–
Immediate gastrointestinal allergy including oral allergy syndrome	EHF	AAF / SBF[c]	–
Delayed onset reactions (> 1 hour)			
Allergic EoE	AAF	–	–
Atopic dermatitis	EHF	AAF / SBF[c]	–
Gastroesophageal reflux disease	EHF	AAF	–
Cow's milk protein-induced enteropathy	EHF	AAF	–
Food protein-induced enterocolitis syndrome	EHF	AAF	–
Cow's milk protein-induced gastroenteritis and proctocolitis	EHF	AAF	–
Severe irritability (colic)	EHF	AAF	–
Constipation	EHF	AAF	–
Heiner's syndrome	EHF	AAF	SBF[c]

Adapted from Fiocchi A *et al.*, 2010 and Kemp A *et al.*, 2008.[13,68]

AAF = amino acid formula; EHF = extensively hydrolysed formula; EoE = eosinophilic oesophagitis; SBF = soy-based formula.

[a] If first option is not tolerated.

[b] If second option is not tolerated.

[c] For infants above 6 months of age.

07 Management of CMPA

7.3 Strategies for the management of cow's milk protein allergy

7.3.1 Exclusively breastfed children

The incidence of CMPA in exclusively breastfed children is very low; approximately 0.5% of breastfed children have CMPA.[7] As with all cases of CMPA, avoidance of CMP is essential. Continuation of breastfeeding with maternal elimination of CMP (with calcium supplementation) is recommended. In infants presenting with food protein-induced enterocolitis syndrome, maternal elimination of CMP may not be necessary. It takes an average of 2–4 weeks for symptoms to improve or disappear. If symptoms do not improve after 2–4 weeks, an alternative diagnosis should be considered. If symptoms improve or disappear during maternal elimination diet, an open OFC can be performed 6 months later. If symptoms do not reappear during OFC, elimination of CMP can be discontinued. On the other hand, if symptoms reappear, CMP should be eliminated from the mother's diet for the entire period of breastfeeding (Figure 3).[69]

7.3.2 Formula-fed children

Avoidance of CMP from the diet is essential. EHF is recommended as a substitute to cow's milk formula in mild-to-moderate cases. AAF is recommended for infants presenting with anaphylaxis, allergic eosinophilic oesophagitis or if the symptoms in mild-to-moderate cases do not improve on EHF after 2–4 weeks. If symptoms improve on EHF or AAF, an open challenge should be performed under clinical observation. Children who do not develop symptoms during challenge and up to 1 week after follow-up can resume CMP in their diet, although they should be monitored. On the other hand, if symptoms reappear during challenge, the child should be maintained on a CMP-free diet until the child is between 9–12 months of age, and for at least 6 months (Figure 3).[69]

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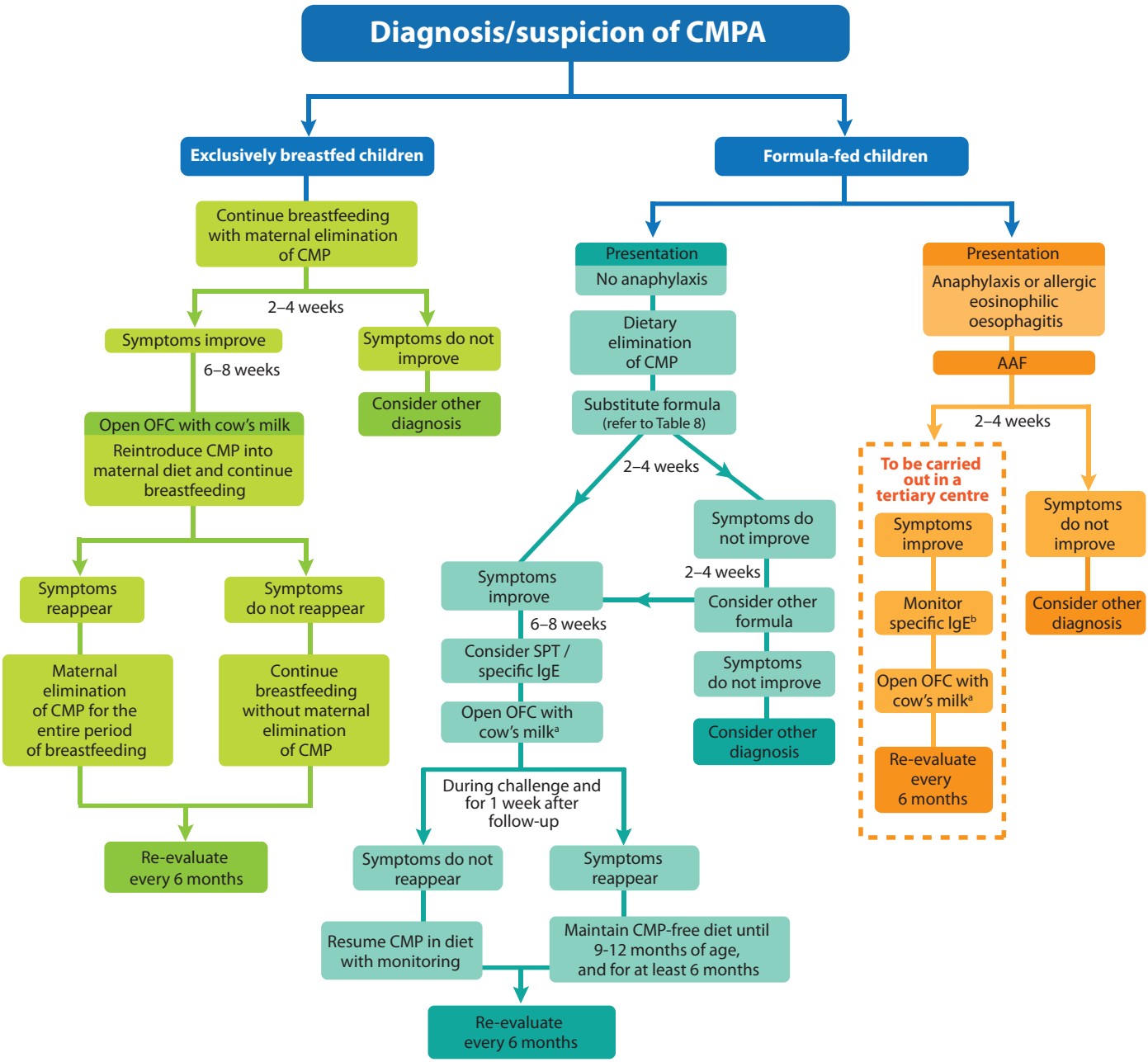
7.4 Algorithm for the management of cow's milk protein allergy



[a] Under clinical observation.
[b] For children ≥ 1 year of age.
AAF = amino acid formula; CMP = cow's milk protein; CMPA = cow's milk protein allergy; IgE = immunoglobulin E; OFC = oral food challenge; SPT = skin prick test.

Figure 3. Algorithm for the management of CMPA

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7.5 Special considerations

7.5.1 Management of anaphylaxis

Anaphylaxis is defined as a severe, life-threatening systemic or generalised hypersensitivity reaction.[14] The first-line treatment of anaphylaxis is adrenaline. Aqueous adrenaline auto-injector (1:1,000) should be administered intramuscularly into the anterior-lateral thigh at a dose of 0.15 mg for patients who weigh between 15–30 kg and 0.30 mg for patients who weigh over 30 kg (based on EpiPen®) and should be repeated at intervals of 5–15 minutes. Adjunctive treatment to adrenaline is listed in Table 9.

Table 9. Adjunctive treatment for the management of anaphylaxis in children with CMPA[70]

Drug	Comment
Salbutamol	4–8 puffs from metered-dose inhaler or 2.5–5.0 mg nebulised solution every 20 minutes or continuously as needed.
Diphenhydramine (H_1 antagonist)	Given orally or intravenously[a] at 1–2 mg/kg per dose, up to a maximum of 50 mg.
Chlorpheniramine	Given orally or intravenously at 0.1 mg/kg per dose, up to a maximum of 4 mg, every 6–8 hours.
Promethazine	Given orally or intravenously at 0.2–0.5 mg/kg per dose, up to a maximum of 25 mg, every 6–8 hours.
Hydrocortisone	Given intravenously at 2–4 mg/kg per dose, up to a maximum of 200 mg, every 6–8 hours.
Prednisolone	Given orally at 1–2 mg/kg per dose daily.
Supplemental oxygen therapy	As indicated.
Intravenous fluid	Normal saline is appropriate. Children may require up to 30 mL/kg in the first hour of management.

Adapted from Liberman DB & Teach SJ, 2008.[70]

[a] Oral liquid is most readily absorbed.

7.5.2 Immunotherapy for CMPA

While there may seem to be potentially large benefits of oral immunotherapy in the management of CMPA, frequent and serious adverse events have also been associated with its use. Until further research is done, immunotherapy is not recommended in the treatment of CMPA.

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7.6 Prevention of cow's milk protein allergy

Patients at risk of developing food allergies are defined as those with a biological parent or sibling with existing, or history of, allergic rhinitis, asthma, atopic dermatitis or food allergy. Family history is the most important determinant of allergic risk in infancy – the higher the incidence of allergy in the family, the greater the risk of developing food allergy.

An analysis of published peer-reviewed observational and interventional studies performed by en expert group set up by the Section of Pediatrics of the European Academy of Allergology and Clinical Immunology (EAACI) has found that exclusive breastfeeding for at least 4 months is associated with a lower cumulative incidence of CMPA until 18 months. Furthermore, breastfeeding combined with avoidance of solid food and cow's milk for at least 4–6 months was found to be the most preventive regimen.[71]

In the absence of breast milk, hydrolysed formulas with documented reduced allergenicity such as partially hydrolysed formula or eHF, combined with avoidance of solid foods and cow's milk, for at least 4–6 months may be considered. However, evidence for the use of hydrolysed formula is weak. SBF has no role in the prevention of CMPA as some prospective studies have shown that they are as allergenic as cow's milk-based formula.[71]

There is no conclusive evidence for a preventive effect of maternal dietary elimination of potential food allergens during pregnancy and/or breastfeeding.[72]

Recommendations:

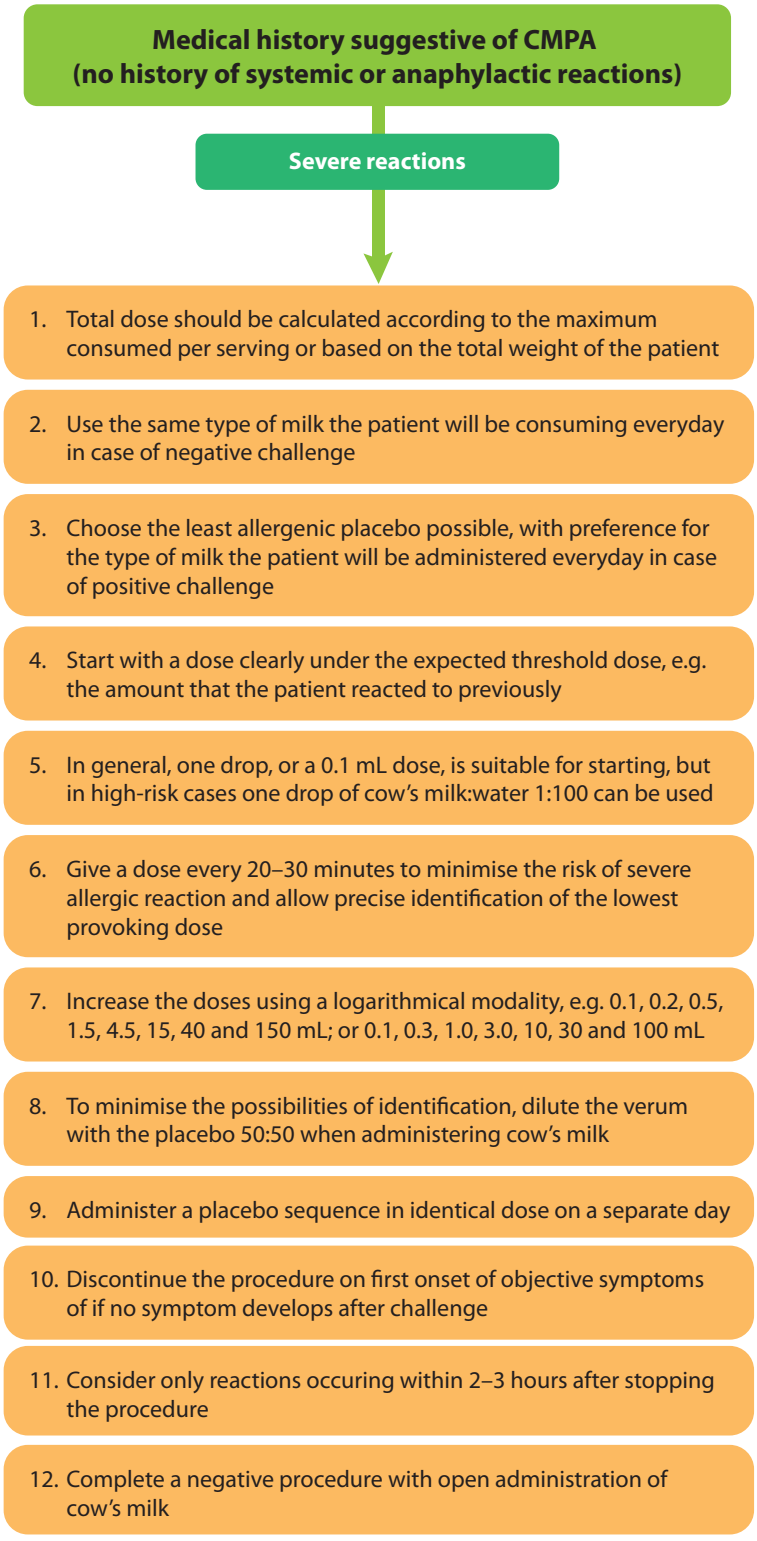
- Exclusive breastfeeding for 4–6 months
- When breastfeeding is not possible, consider a hydrolysed formula
- Avoidance of CMP during pregnancy is not necessary
- The use of SBFs to prevent CMPA is not recommended

Glossary

Term	Definition
Allergy	A hypersensitivity reaction initiated by specific immunologic mechanisms.
Anaphylaxis	A severe, life-threatening generalised or systemic hypersensitivity reaction.
Atopy	A personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins.
Cow's milk protein allergy (CMPA)	A hypersensitivity reaction to cow's milk protein initiated by specific immunologic mechanisms.
Cow's milk protein intolerance	A nonallergic hypersensitivity to cow's milk protein.
Cross-reactivity	A phenomenon that occurs when an antibody reacts not only with the original allergen, but also with other similar allergens.
Eosinophilic gastroenteritis	A condition which involves both IgE- and non-IgE-mediated reactions. It describes a constellation of symptoms that vary depending on the portion of the gastrointestinal tract involved and a pathologic infiltration of the gastrointestinal tract by eosinophils, which may be localised or wide-spread.
Eosinophilic oesophagitis (EoE)	A condition which involves localised eosinophilic inflammation of the oesophagus. Both IgE- and non-IgE-mediated mechanisms appear to be involved.
Food allergens	Specific components of food or ingredients within foot that are recognised by allergen-specific immune cells and elicit specific immunologic reactions, resulting in characteristic symptoms.
Food allergy	An adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. Also known as food hypersensitivity.
Food intolerance	A non-allergic food hypersensitivity.
Food protein-induced proctocolitis syndrome	A non-IgE-mediated disorder that usually occurs in young infants that mimics food allergies.
Hypersensitivity	Objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons.
IgE-mediated CMPA	A hypersensitivity reaction to cow's milk protein that is initiated by immunologic mechanisms involving mainly immunoglobulin E.
Immediate gastrointestinal allergy	An IgE-mediated food allergy in which upper gastrointestinal symptoms may occur within minutes and lower gastrointestinal symptoms may occur either immediately or with a delay of up to several hours.
Non-IgE-mediated CMPA	A hypersensitivity reaction to cow's milk protein that is initiated by immunologic mechanisms not involving immunoglobulin E.

Appendix A

Double-blind placebo-controlled food challenge (DBPCFC) flow chart



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The full guidelines on the management of cow's milk protein allergy may be obtained from the following websites:

- **Malaysian Paediatric Association (MPA)**
  http://www.mpaweb.org.my
- **Malaysian Society of Allergy & Immunology (MSAI)**
  http://www.allergymsai.org
- **Danone Dumex (Malaysia) Sdn Bhd**
  http://www.dumex.com.my

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Malaysian Society of
Allergy and Immunology

PERSATUAN PEDIATRIK
MALAYSIA