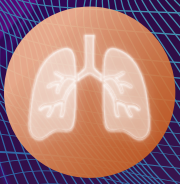
GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF COW'S MILK PROTEIN ALLERGY (CMPA) IN CHILDREN

2024 (2ND EDITION)



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TARGET READER

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

FORMAT

This guideline consists of easy-to-read information with appropriate tables and flow charts. As far as possible, all information is evidence-based. Where evidence is not currently available, a consensus from the combined opinions of the committee members were used.

AVAILABILITY

The e-version of this guideline may be obtained from the following websites:

Malaysian Paediatric Association (MPA):
https://mpaeds.my/

Malaysian Society of Paediatric Gastroenterology, Hepatology and Nutrition (MySPGHAN):
https://www.myspghan.my

Malaysian Society of Allergy and Immunology (MSAI):
http://www.allergymsai.org

Novamil Malaysia:
https://novamil.com.my/

CONTENT

The committee members hold the exclusive sole right to shape the guideline's content, ensuring its independent development devoid of any sponsor influence.

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No conflict of interest is declared by any of the committee members.

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TERMS OF REFERENCE

DISCLAIMER

The content and recommendations made in this guideline are 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 may have on the recommendations made within this guideline. Healthcare providers are encouraged to exercise their discretion when utilising the information contained within this guideline in their clinical practice.

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ABBREVIATIONS

AAF	Amino acid formula
CMF	Cow's milk formula
CMP	Cow's milk protein
CMPA	Cow's milk protein allergy
DBPCFC	Double-blind, placebo-controlled food challenge
eHF	Extensively hydrolysed formula
eHCF	Extensively hydrolysed casein formula
eHRF	Extensively hydrolysed rice formula
EoE	Eosinophilic oesophagitis
FC	Faecal calprotectin
FPIES	Food protein-induced enterocolitis syndrome
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HRF	Hydrolysed rice formula
IgE	Immunoglobulin E
LGG	*Lactobacillus rhamnosus Gorbach Goldin*
OFC	Oral food challenge
OIT	Oral immunotherapy
pHF	Partially hydrolysed formula
SBF	Soy-based formula
sIgE	Specific immunoglobulin E
SPT	Skin prick test

1 INTRODUCTION

CMPA is one of the most common forms of food allergies in infants. Currently, there is a lack of epidemiological data on the incidence and prevalence of CMPA in Malaysia. It is likely that cow's milk is one of the most common food allergens in Malaysia as well as in Asia.[1] In developed countries, the incidence of CMPA among infants is estimated to be ~2-3%.[2] However, this is likely to be an underestimation of the true incidence since there is a wide variability between self-reported and challenge-confirmed CMPA. In addition, intolerance to the lactose component of cow's milk may also be confused with CMPA. This discrepancy underlines the importance of accurate diagnosis to minimise inappropriate dietary restriction, which may be detrimental to nutritional adequacy, as well as unnecessary prescription of costly alternative diets. Since the manifestation of CMPA is protean and the management of CMPA is evolving, a local guideline as an easy reference for the diagnosis and management of CMPA remains highly relevant.

2 EPIDEMIOLOGY

The prevalence of CMPA among infants up to 24 months in Asia ranges from 0.1-3.0%.[3-5] Since there is a lack of clinical and epidemiological data on CMPA in Malaysia, the prevalence of CMPA in Malaysian children is unknown. However, it is likely that CMPA is one of the most common food allergies in infants and young children in this country. In Singapore, the estimated prevalence of CMPA among infants 12-24 months ranges between 0.1-0.44%,[3] and is the second most common food allergy in this age group of children.

3 CLINICAL FEATURES

CMPA has a diverse mode of presentation. Generally, children with CMPA present with the following organ systems involvement:[6]

- GI 32 – 60%
- Skin 5 – 90%
- Respiratory 15 – 30%
- Systemic – anaphylaxis 0.8 – 9%

3.1 CLINICAL HISTORY

A diagnosis of CMPA should be suspected when one or more of the following symptoms involving different organ systems appear after a recent introduction of cow's milk or CMP-containing food (Table 3.1).[7]

Characteristic features of CMPA are:

- GI tract involvement is the most common manifestation of CMPA in any age group;
- Involvement of ≥2 systems increases the probability of a diagnosis of CMPA;
- Certain symptoms, e.g., angioedema and atopic eczema, are more commonly observed in children with a positive CMP-sIgE;
- Significant overlap exists in GI symptoms between IgE- and non-IgE-mediated CMPA. Hence, GI symptoms alone should not be used to differentiate between these two conditions.[8]

3. CLINICAL FEATURES

Table 3.1: Common symptoms of CMPA

ORGAN	SYMPTOMS
Gastrointestinal tract	Recurrent regurgitations Vomiting Diarrhoea Constipation Blood in stool
Skin	Atopic dermatitis Swelling of lips or eyelids (angio-oedema) Urticaria unrelated to infections, drugs, or other causes
Respiratory tract (Unrelated to respiratory infection)	Runny nose or otitis media Chronic cough Wheeze
General	Persistent distress or colic (wailing/ irritable for ≥3 h per day) for at least 3 days a week over a period of 1 week Iron deficiency anaemia

Note: It should be noted that when CMPA presents with GI tract involvement alone, other diagnoses, e.g., GI infections, should be excluded in the first instance. Other differential diagnoses should also be considered depending on the predominant symptoms. GERD should be excluded in children with recurrent regurgitations whilst functional constipation is the most common cause of constipation in children instead of CMPA. However, as stated above, the involvement of 2 or more systems in a person increases the possibility of CMPA as the cause of the symptoms.

Table 3.2 History taking in a child suspected of CMPA

COMPONENTS	QUESTIONS
1. Is this CMPA?	Which system(s) is/are involved? ▪ GI, respiratory, skin, or generalised.

COMPONENTS	QUESTIONS
2. Previous exposure to CMP?	Timing of reaction post exposure ▪ IgE-mediated reactions usually occur within minutes to 2 hours following the ingestion of or exposure to cow's milk. ▪ Non-IgE-mediated reactions usually are more delayed in onset (up to 48 hours to weeks after ingesting CMP). ▪ A minority of exclusively breastfed infants may acquire CMP through mother's milk. Maternal dietary history is necessary.[2]
3. Consider other differential diagnoses and other food protein-induced allergies.	
4. Any family history of allergies?	A positive atopic family history is common in children with food allergy, including CMPA.[9]
5. Any concomitant atopic conditions?	▪ Children with CMPA often have other atopic manifestations, including atopic eczema, allergic rhinitis, and asthma.[10] ▪ These children often also have other food allergies, such as, egg and/or peanut allergies.[6]

3.2 CLASSIFICATION OF PRESENTATIONS OF CMPA

- Generally, *IgE-mediated CMPA* manifests within minutes to 2 hours after exposure (Table 3.3). On the other hand, symptoms of *non-IgE-mediated CMPA* are commonly delayed after exposure (Table 3.4).
- *Mixed IgE* and *non-IgE-mediated CMPA* are commonly delayed and may occur in the same patient (Table 3.5).

Table 3.3. Conditions associated with IgE-mediated reactions[6]

IgE-mediated systemic reactions (anaphylaxis)	▪ Most severe manifestation, potentially fatal. ▪ Involves the skin and mucosa, respiratory (dyspnoea, bronchospasm, stridor, hypoxaemia), hypotension, organ dysfunctions, GI symptoms (colic and vomiting), and shock.[6] ▪ Anaphylaxis can be: → Immediate onset: within minutes of ingestion. → Late-onset: at 1 hour to several days after ingestion.
IgE-mediated GI reactions	▪ Oral allergy syndrome is less common in children and may manifest as lip swelling.[11] ▪ In immediate GI allergy, symptoms include vomiting and diarrhoea.[6]
IgE-mediated respiratory reactions	▪ Severe clinical manifestations include anaphylaxis, asthma attack and rhinitis.[12-17]
IgE-mediated cutaneous reactions	▪ Immediate-onset; acute urticaria, angioedema, contact urticaria. ▪ Late-onset: atopic dermatitis.

Note: After the first exposure/intake of CMP, symptoms of CMPA only appear in ≤60% of cases, indicating that in some patients, symptoms may only present after repeated exposure to CMP.[18]

Table 3.4. Conditions associated with non-IgE-mediated reactions[6]

Non-IgE-mediated GI reactions	▪ GERD → In infants, it may be difficult to differentiate between CMPA and GERD based on history and physical examination alone.[19] Clinically, however, CMPA is an uncommon cause of GERD; other causes of GERD should be excluded in the first instance. → Mechanism: cow's milk can induce gastric dysrhythmia and delayed gastric emptying.[20] ▪ Cricopharyngeal spasm ▪ Pyloric stenosis[21,22]

Non-IgE-mediated GI reactions (cont'd)	▪ Food protein-induced allergic proctocolitis (FPIAP): → Symptoms usually present by the second month.[23] It can also occur in the early neonatal period, sometimes mimicking Hirschsprung's disease.[24,25] → Affected infants may have relatively normal stools or mild diarrhoea and low-grade rectal bleeding but are otherwise typically well and thriving.[26] → May be observed in exclusively breastfed infants. ▪ Food protein-induced enterocolitis syndrome (FPIES): → Usually presents 1-3 hours following ingestion of CMP.[27] → Symptoms: repeated projectile vomiting, hypotonia, pallor and diarrhoea. → In severe cases, may progress to dehydration and shock.[27] → May be caused by other food proteins; has been reported in exclusively breastfed infants.[28,29] ▪ CMP-induced enteropathy: → A chronic form of FPIES; may cause diarrhoea (with or without blood), growth faltering, vomiting, hypoproteinaemia, and anaemia.[27] → Clinical signs of secondary lactose intolerance may coexist.[30] → Soy milk and maternal dietary proteins transferred through breast milk have also been implicated.[29] ▪ Severe irritability (colic): → In most cases, the cause of colic is unknown, although multiple factors, including gastroesophageal reflux and oesophagitis, have been suggested.[31] Sensitivity to CMP has also been suggested.

Non-IgE-mediated GI reactions (cont'd)	▪ Constipation: → Association between constipation and non-IgE CMPA is controversial.[32] → Some authors have observed that a CMP-free diet can benefit some children with chronic constipation.[32]
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, rattling sounds upon auscultation, growth faltering, and family history of CMPA.[33] ▪ Should be considered in infants with unexplained chronic pulmonary infiltrates.

Table 3.5. Conditions associated with mixed IgE and non-IgE-mediated CMPA

Atopic dermatitis	▪ Atopic dermatitis related to CMP allergy may be early- and/or late-onset. ▪ An early-onset and a more severe form of eczema is frequently associated with a higher serum level CMP-sIgE antibody.[34]
Mixed IgE and non-IgE-mediated GI reactions	*Examples of mixed IgE and non-IgE-mediated GI reactions:* ▪ Eosinophilic GI disorders: → Characterised by swallowing difficulty, food impaction, food refusal/aversion, feeding difficulty in infants, poor weight gain and poor response to standard anti-reflux treatment.[35] → In the first year of life, EoE can present with regurgitation, vomiting, rumination, lack of appetite, burning and pain, and crying immediately or after feeding, as well as Sandifer syndrome. This condition does not respond to proton pump inhibitors. Dysphagia and food impaction occur at older age.[36]

Mixed IgE and non-IgE-mediated GI reactions (cont'd)	▪ Allergic eosinophilic gastroenteritis (AEG) affects both adults and children but is rarely observed in the first year of life. It causes abdominal pain, irritability, easy satiety, vomiting, diarrhoea, weight loss, anaemia and hypoalbuminaemia due to protein-losing enteropathy. The hallmark sign of AEG is the marked eosinophilic infiltration of the gastric or duodenal mucosa.[36] ▪ Eosinophilic colitis (EC), with diarrhoea predominantly, is less common and seems to be associated with inflammatory bowel disease and coeliac disease. Association between EC and food allergy remains unclear. Diagnosis is suggested with increased eosinophilic infiltration in the colonic mucosa in symptomatic patients.[36]
Mixed IgE and non-IgE-mediated respiratory reactions	▪ Acute respiratory manifestations of food allergy include rhinitis, laryngeal oedema, bronchospasm, and cough. ▪ In children with asthma, the rate of acute asthma provoked by OFC tests are 2-9%.[37] ▪ Children with food allergy have a higher prevalence of asthma and develop asthma at an earlier age.[38]

3.3 SEVERITY OF CMPA

The severity of CMPA can be classified into mild-to-moderate and severe. It is important to identify severe manifestations of CMPA as the management approach is different from mild-to-moderate manifestation (Table 3.6).[7]

Table 3.6 Manifestations of severe CMPA

Severe CMPA[7]	In exclusively breastfed infants, the presence of one or more of the following symptoms indicates a severe manifestation. ▪ GI: → Growth faltering due to diarrhoea or frequent regurgitation/vomiting. → Persistent feed refusal. → Moderate-to-large amounts of blood in stools with iron deficiency anaemia. → Protein-losing enteropathy (hypoalbuminaemia). ▪ Dermatological: growth faltering associated with severe atopic dermatitis.
	In formula-fed infants: The presence of one or more of the following symptoms: ▪ GI: → Failure to thrive due to chronic diarrhoea and/or regurgitation/vomiting and/or refusal to feed. → Iron deficiency anaemia due to occult or macroscopic blood loss. → Protein-losing enteropathy (hypoalbuminaemia). → Endoscopic/histologically confirmed enteropathy or severe CMP-induced proctocolitis. ▪ Dermatological: → Exudative or severe atopic dermatitis with hypoalbuminaemia-anaemia or growth faltering or iron deficiency anaemia. ▪ Systemic reactions (anaphylactic shock).

4 INVESTIGATION AND DIAGNOSTIC TESTS IN CMPA

A detailed medical history is essential and sufficient to diagnose CMPA in most instances. Extensive and potentially expensive diagnostic tests are often unnecessary. When indicated, however, the choice of test should depend on the phenotype of the suspected CMPA (see Tables 3.3 – 3.5).

4.1 COW'S MILK PROTEIN ELIMINATION AND CHALLENGE TEST

Cow's milk elimination diet is recommended following a detailed medical history and physical examination suggestive of CMPA. Diagnosis of CMPA is highly suggestive if symptoms and signs attributed to CMPA resolve following cow's milk elimination (Table 4.1).

Table 4.1. Duration of symptom resolution after cow's milk elimination[39]

IgE-mediated CMPA	Symptoms typically resolve after 1-2 weeks
Non-IgE-mediated CMPA	Symptoms usually resolve after 2-4 weeks
Severe atopic dermatitis	May take up to 8 weeks to resolve

Oral food challenge (OFC)

Even though a diagnosis of CMPA is likely when clinical symptoms resolve after cow's milk elimination, an OFC is recommended to confirm the diagnosis.[40-42]

Indications

- Confirmation: Diagnostic OFC can be considered when the diagnosis of CMPA is uncertain, i.e., non-specific symptoms or delayed onset of symptoms and/or signs, e.g., diarrhoea/rash/colic with an onset of >2 hours from ingestion of CMP.
- Evaluation: An OFC can be used to evaluate the development of tolerance to CMP. [43]

4. INVESTIGATION AND DIAGNOSTIC TESTS IN CMPA

When to perform an OFC

- Diagnostic OFC: Though there is no clear evidence on the optimal timing of a diagnostic OFC, most authors recommend performing an OFC 2 weeks after the resolution of symptoms following the elimination of CMP.[41,42] We recommend performing diagnostic OFC 6-8 weeks after symptoms resolution (Figure 6-1).
- An OFC may be delayed in patients with chronic atopic eczema or asthma, until after the disease is stable and controlled.

Contraindications

- An OFC is contraindicated if there is a history of a severe systemic reaction or anaphylaxis.
- An OFC may not be necessary if during the elimination phase, there are reactions following inadvertent exposure to CMP.

Types of OFC (Table 4.2):

- Double-blind, placebo-controlled food challenge (DBPCFC). This is considered the gold standard for diagnosing food allergies.
- Single blind OFC.
- Open OFC.

Table 4.2 Types of OFC

DBPCFC	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, DBPCFC is seldom practiced clinically.
Single-blind challenge	Single-blind challenge poses similar difficulties for blinding foods as DBPCFC and introduces subjective bias by the observer.
Open OFC	CMP is administered without blinding. In clinical practice, an open OFC can be used as a first approach, when indicated, i.e., a diagnostic OFC or assessment of tolerance to CMP (see section on *When to perform an OFC*).

Double-blind challenge may be associated with considerable anxiety in parents and is seldom used clinically. For practical reasons, an open OFC is sufficient in most clinical circumstances.

How to perform a cow's milk open OFC

Please refer to Appendix 1.

Interpretation of a cow's milk OFC[44]

- A positive OFC with objective reactions: diagnosis of CMPA can be confirmed.
- A negative OFC: CMPA can be excluded.

RECOMMENDATION STATEMENT 1

- **In most clinical situations, CMP elimination and an OFC are recommended for the diagnosis of CMPA.**

4.2 SKIN TESTING

4.2.1 Skin prick test (SPT)

SPT is useful in children suspected of IgE-mediated CMPA.

- A positive SPT does not necessarily mean the presence of an allergy; it merely suggests the presence of previous sensitisation.[45]
- A positive SPT should be interpreted in conjunction with clinical features suggestive of IgE-mediated CMPA.
- A wheal diameter cut-off of ≥6 mm (infants <2 years old) and ≥8 mm (>2 years old) is >95% predictive of reactivity for IgE-mediated CMPA.[46]
- Negative predictive accuracies of SPT are generally >90% and may be used to exclude IgE-mediated CMPA.[47]

Precautions

- Stop H_1-antihistamines 7 days before performing SPT, as its concurrent use may result in a false negative test.[45]
- Severe anaphylaxis may rarely occur while performing SPT.[48,49] SPT should only be performed in the presence of trained healthcare personnel proficient in managing anaphylaxis.

RECOMMENDATION STATEMENTS 2 – 4

- **SPT should be considered in the workup of IgE-mediated CMPA, particularly when it is impractical or unsafe to perform an OFC.**
- **The results of an SPT should be interpreted within the context of the clinical presentation.**
- **Generally, a wheal diameter cut-off of ≥6 mm (≤2 years old) and ≥8 mm (>2 years old) is highly suggestive of CMPA.**

4.2.2 Other skin tests

- An atopy patch test is used to evaluate delayed type, cell-mediated, hypersensitivity reactions.[45] It has a much lower sensitivity (53%) compared to SPT and sIgE (~88% for both).[50] There is also a lack of a standard guideline for performing the test. Routine use of atopy patch tests for diagnosing CMPA requires more evidence.[51]
- An intradermal test is used to evaluate both delayed and immediate-type IgE-mediated hypersensitivity reactions.[45]
- Currently, both tests are not recommended for the evaluation of CMPA.

RECOMMENDATION STATEMENT 5

- **Atopy patch tests and intradermal skin tests are not recommended for the diagnosis of CMPA.**

4.3 SERUM IgE

Serum total IgE is non-specific and does not provide specific information. It is often elevated in severe atopic dermatitis. A very high total serum IgE can be associated with multiple positive SPTs and sIgE, which make its interpretation challenging.[52]

4.3.1 Evaluation of serum sIgE

Serum cow's milk sIgE measurement is being used to evaluate patients with IgE-mediated CMPA.

- A value of sIgE to CMP >0.35 kU_A/L is considered a positive test.
- Similar to SPT, a positive sIgE result alone without a suggestive clinical history indicates previous sensitisation and not allergy.

Serum sIgE to cow's milk allergen components is currently available. Major allergens are casein (Bos d 8) and beta-lactoglobulin (Bos d 5). Due to the limited data, the optimal diagnostic cut-off of sIgE for both components have yet to be determined.[53]

4.4 THE USE OF sIgE AND SPT IN CMPA

- sIgE and SPT have a good sensitivity for CMPA, 87% (95% CI 75%, 94%) and 88% (95% CI 76%, 95%), respectively, but low specificity, 48% (95% CI 36%, 88%) and 68% (95% CI 56%, 77%), respectively.[50]
- sIgE and SPT have a high negative predictive value (>90%) for IgE-mediated CMPA.

Clinical applications

- In severe IgE-mediated CMPA presenting with a history of anaphylaxis (when an OFC is contraindicated) a positive sIgE or SPT is sufficient to confirm the diagnosis.
- In patients with severe atopic dermatitis and dermatographism, where SPT is not feasible, sIgE can be used alone to confirm the diagnosis IgE-mediated CMPA.

4. INVESTIGATION AND DIAGNOSTIC TESTS IN CMPA

RECOMMENDATION STATEMENTS 6 – 10

- **sIgE or SPT can be considered in the diagnosis of IgE-mediated CMPA, particularly when it is impractical or unsafe to perform an OFC.**
- **Results of cow's milk sIgE and SPT should be interpreted within the context of clinical presentation.**
- **In the presence of clinical history suggestive of CMPA, elevated sIgE or a positive SPT to CMP is a supportive diagnostic test.**
- **A negative SPT or undetected sIgE toward CMP excludes the diagnosis of IgE-mediated CMPA.**

4.5 BASOPHIL ACTIVATION TEST (BAT)

BAT is an *ex-vivo* flow cytometry test that measures the expression of activation markers, namely CD203c and/or CD63 upon basophil stimulation with a specific allergen. Small cohort studies have demonstrated BAT having a good diagnostic profile for diagnosing CMPA (sensitivity 89% and specificity 83%).[54-57] Standard laboratory reference guidelines and larger cohort studies are needed to further evaluate utilising BAT as a routine diagnostic tool for managing CMPA.

4.6 FAECAL CALPROTECTIN (FC)

FC levels in children with CMPA are significantly higher compared to healthy children.[58] However, FC is not recommended as a routine diagnostic tool in CMPA as data is limited.

RECOMMENDATION STATEMENT 11

- **Currently, both BAT and FC are not recommended as routine diagnostic tools for CMPA.**

5 MANAGEMENT OF CMPA

5.1 PRINCIPLES OF MANAGEMENT

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 in children older than 2 years of age.
- Replacing cow's milk with a substitute formula is recommended for children <2 years old as well as in non-breastfed infants.

5.2 ELIMINATION AND AVOIDANCE OF CMP

CMP avoidance is not limited to exposure via the oral route only.

- CMPs may also be encountered in inhalant or contact forms, e.g., aerosolization of CMP when cooking with cow's milk. Specific history should be asked if allergic reactions continue despite complete avoidance of oral CMP.[59-61]
- Avoiding other bovine proteins should be evaluated on a case-by-case basis; while all children allergic to beef are allergic to cow's milk,[62] the reverse is not true.[63]

A nutritionally safe and balanced diet should be prescribed. Compliance with dietetic advice should be verified throughout the elimination period, paying attention to adequate calcium and vitamin D intake. The natural history of CMPA in many children is that most may outgrow the condition as they grow older (Table 5.1). Periodical re-evaluation of tolerance to cow's milk every 6 months or longer with an open OFC is recommended until tolerance develops.

Table 5.1. Natural history of tolerance to CMP in children with CMPA[64]

AGE (YEARS) AT TOLERANCE	TOTAL TOLERANCE RATE
1	45% – 56%
2	60% – 77%
3	84% – 87%
5	90% – 95%
10	92% – 95%
15	98%

Adapted from Host A, et al. 2002.[64]

5.3 FORMULA SUBSTITUTION

Different types of formulas are available in Malaysia to replace cow's milk (Table 5.2). When choosing a substitute formula, the following factors should be taken into consideration:

- Age
- Clinical condition: e.g., severity, dietary requirements, presence of growth faltering.
- Allergenicity: e.g., concurrent allergies to soy, rice, etc.
- Child's preference: e.g., palatability.
- Individual circumstances: e.g., religious requirement (halal issue).
- Cost and availability.

Table 5.2. Substitute formulas available in Malaysia for CMPA

TYPE OF FORMULA	COMMON BRANDS[a]	INDICATED AGE RANGE	PROTEIN SOURCE	COMMENTS
eHF[b]	• Nutramigen® LGG (eHCF)	<1 year	Cow's milk	Non-halal

TYPE OF FORMULA	COMMON BRANDS[a]	INDICATED AGE RANGE	PROTEIN SOURCE	COMMENTS
HRF	▪ Novarice® (eHRF)	<1 year	Rice	Halal
	▪ Similac Arize®	<1 year		
AAF	▪ Neocate®	<1 year	Amino acid	Recommended for: ▪ Severe CMPA. ▪ Persistent symptoms even with eHF. ▪ Refusal of eHF by the child. Consider cost-benefit ratio.
	▪ Neocate® Junior ▪ Comidagen Plus	>1 year		
SBF	▪ Isomil® ▪ Dupro® Soy	<1 year	Soy	Absolute indications: ▪ Galactosaemia. ▪ Hereditary lactase deficiency. ▪ Vegetarian diet. Not recommended for preterm babies. Cross-sensitisation to soy has been reported;[65,66] no advantage over cow's milk formula as supplement to breast milk. Concerns about unsuitability for use in infants <6 months due to unknown long-term effects of the high aluminium and phytoestrogen content.
	▪ Isomil® Plus ▪ Dugro® Soy 1-6 years	>1 year		

5. MANAGEMENT OF CMPA

Note: When considering the nutritional needs of young infants, the formulas listed in Table 5.2 are recognised as treatment options for CMPA.
[a] As of date of publication; [b] extensively hydrolysed casein formula (eHCF) is a specific type of eHF.

Extensively hydrolysed formula (eHF)

The introduction of eHF should always be supervised by a clinician or by a dietician with relevant experience with eHF.[67-69] eHF has residual allergenicity and may cause immediate reactions in 2-8% of children with IgE-mediated CMPA.

A recommended eHF should:

- Effectively treat at least 90% of children with CMPA.
- Support the nutritional needs for optimal growth in children.
- Socially acceptable (halal) in certain populations.

RECOMMENDATION STATEMENT 12

- **eHF is recommended as the first-line substitute formula for treating CMPA.**

Extensively hydrolysed casein formula (eHCF) with probiotics

eHCF with LGG has been found to result in accelerated tolerance acquisition, and reduces the occurrence of other allergic manifestations in children with CMPA. It also has been shown to be cost-effective.[70-72]

Hydrolysed rice formula (HRF)

HRF is suitable as a first-line alternative to eHF and amino acid formula (AAF) in treating CMPA.[73,74] HRF has shown clinical efficacy and tolerance in children with CMPA.[75,76] In addition, it has demonstrated nutritional adequacy[77,78] in maintaining growth and catch-up growth in healthy children and in children with CMPA.[75,79,80] Other potential advantages include its palatability[75,79] and lower cost compared to eHF and AAF.

The safety concern regarding the arsenic content in HRF has been addressed by the European Food Safety Authority and the World Health Organization. These organisations concluded that the arsenic content of HRF is within the stipulated safety limits.[81,82]

RECOMMENDATION STATEMENT 13

- **HRF is recommended as an alternative first-line substitute formula in infants with CMPA.**

Amino acid-based formula (AAF)

The efficacy and safety of AAF in the management of CMPA has been well researched.[67,83-85] Feeding AAF to infants with CMPA has been shown to:

- Reduce symptoms of CMPA, resulting in significant weight gain with good safety profile among infants allergic to eHF proteins.[67,84,86]
- Resolve CMPA-related GI symptoms.[85]
- Exhibit safety for long-term use in infants intolerant to eHF.[83]

RECOMMENDATION STATEMENT 14

- **AAF is recommended for severe CMPA, persistence of symptoms of CMPA or poor weight gain even with eHF.**

Soy-based formula (SBF)

SBF is not recommended in infants <6 months old due to concerns of isoflavones with a weak oestrogenic action that can lead to a high serum concentration in infants. It also contains phytate which reduces the absorption of minerals and trace elements. Consider SBF for infants >6 months old with CMPA if eHF is not tolerated, too costly or if the parents have a strong preference (e.g., strict vegans).[19,87]

RECOMMENDATION STATEMENT 15

- **SBF is not recommended as first-line treatment for CMPA and should only be considered in infants >6 months old if eHF is not tolerated or on religious preference.**

Plant-based milks

Plant-based milks are not recommended as a substitute for cow's milk in children with CMPA as they do not fulfil the United States Food and Drug Administration's defined criteria for milk[88] and do not provide comparable nutritional adequacy to standard milk and other cow's milk products.[88-91]

Goat's milk

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 hypernatremia and megaloblastic anaemia.[92]
- In addition, goat's milk may be allergenic in children with CMPA (approximately 90% cross-reactivity).[93]

RECOMMENDATION STATEMENT 16

- **Plant-based and goat's milk (goat's milk formula and fresh goat's milk) are not recommended for treating CMPA.**

6 PRACTICAL STRATEGIES FOR THE MANAGEMENT OF CMPA

For management of CMPA algorithm, see Figure 6.1.

6.1 EXCLUSIVELY BREASTFED CHILDREN

The incidence of CMPA in exclusively breastfed children is uncommon; approximately 0.5% of breastfed children have been found to have CMPA.[64]

Recommendations:

- Continue breastfeeding.
- Mothers to avoid CMP or beverages or CMP-containing food, e.g., chocolate drinks, milk teas, etc.
- Mothers should take calcium and vitamin D supplementation.

With elimination of CMP from maternal diet, it may take on average 2-4 weeks for symptoms of CMPA in affected infants to improve or disappear.[7]

- If symptoms persist after 2-4 weeks, consider an alternative diagnosis.
- If symptoms improve or disappear during maternal elimination diet, an open OFC can be considered 6 weeks later. At present, there is limited evidence to recommend a specific duration between symptom resolution and an open OFC. A 6-week duration between disappearance of symptoms and an OFC is reasonable.
- If symptoms do not reappear during an OFC, elimination of CMP in mother's diet can be discontinued.
- If symptoms reappear during an OFC, CMP should be eliminated from the mother's diet for the entire period of breastfeeding (Figure 6.1).

6.2 FORMULA-FED CHILDREN

Refer to Appendix 2 for alternatives for substitute formula based on the phenotypic presentation of CMPA.

- Avoid CMP in the diet.[7]
- In mild-to-moderate cases, eHF is recommended as a substitute to cow's milk formula. HRF is an acceptable alternative if halal requirement, cost and availability of eHF are issues.
  - → In mild-to-moderate cases, AAF is recommended if the symptoms do not improve after 2-4 weeks on eHF.
  - → If symptoms improve, continue eHF or AAF for 6-8 weeks. Consider sIgE, SPT or an open OFC under clinical observation to confirm the diagnosis of CMPA.
  - → In the absence of any symptoms suggestive of CMPA during challenge and within 1 week thereafter, a diagnosis of CMPA is unlikely and cow's milk or CMP-containing food can be resumed while monitoring is continued.
  - → AAF is recommended if the symptoms in mild-to-moderate cases do not improve on eHF after 2-4 weeks.
  - → If symptoms recur during the challenge phase, it is advised that the child continues with a CMP-free diet until they are 9 to 12 months old or for a minimum of 6 months following the recurrence. (Figure 6-1).

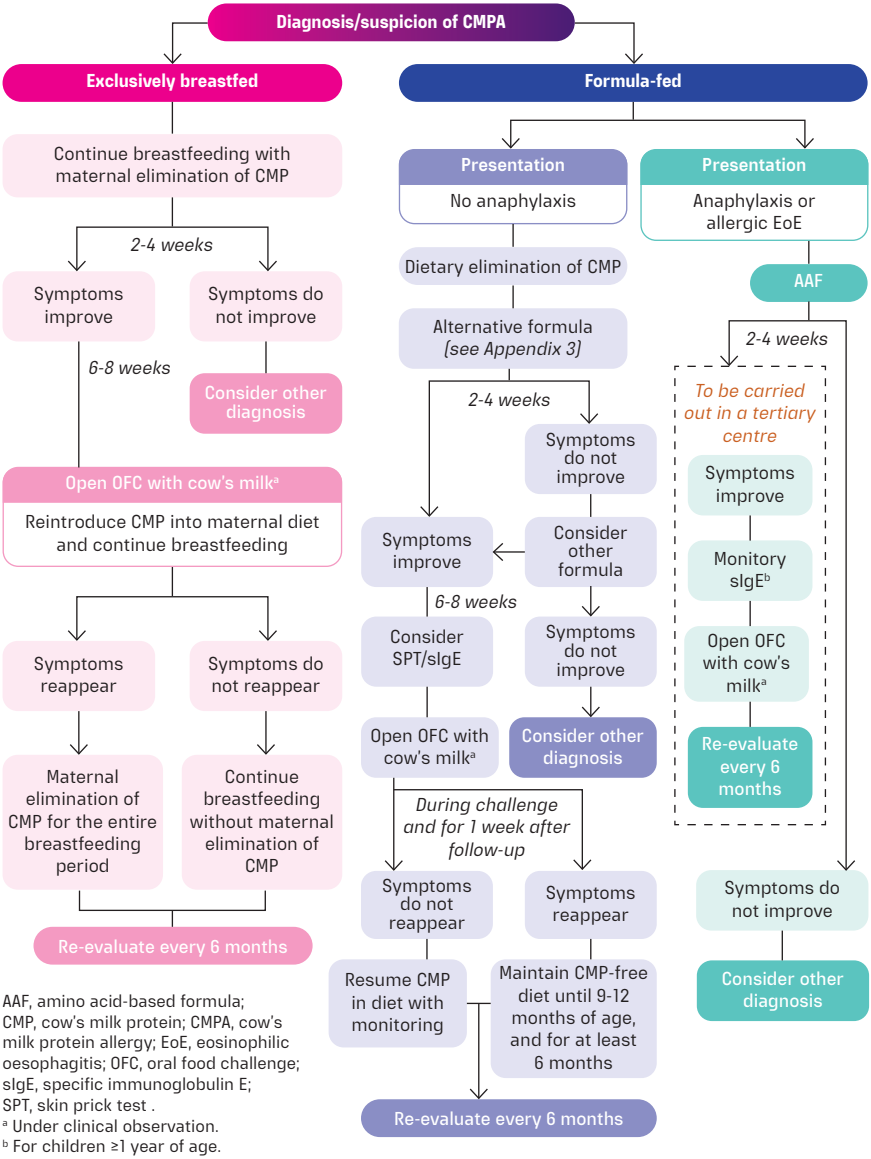
- In infants presenting with anaphylaxis or allergic EoE, AAF is recommended.
  - → If symptoms improve within 2-4 weeks, conduct an OFC with cow's milk in a tertiary centre. For children ≥1 years old, sIgE can be used for monitoring.
  - → If symptoms do not improve, consider other diagnoses.

RECOMMENDATION STATEMENT 17

- **An open OFC should be performed every 6 months to determine when a patient with CMPA has developed tolerance to cow's milk.**

6. PRACTICAL STRATEGIES FOR THE MANAGEMENT OF CMPA

Figure 6-1. Algorithm for the management of CMPA



AAF, amino acid-based formula; CMP, cow's milk protein; CMPA, cow's milk protein allergy; EoE, eosinophilic oesophagitis; OFC, oral food challenge; sIgE, specific immunoglobulin E; SPT, skin prick test .

[a] Under clinical observation.

[b] For children ≥1 year of age.

7 FOLLOW-UP MANAGEMENT OF CMPA

The prognosis of CMPA is generally good, with 60-70% of children outgrowing CMPA by 2 years of age. This increases to 84-87% by 3 years.[64] However, in IgE-mediated allergy, there is an increased risk of persistent CMPA and of developing allergy to other foods before the age of 3 years. In some patients, tolerance to CMP may only develop during adolescence.[94]

7.1 TIMING OF CMP RE-CHALLENGE

Generally, re-challenge with CMP should only be attempted at least 6 months after the diagnosis and initiation of treatment. It should be extended to 12-18 months in children presenting with severe, immediate IgE-mediated reactions.[95] Most of the current guidelines on the diagnosis and management of CMPA suggest re-evaluation of children with cow's milk allergy every 6-12 months, and reintroduction of cow's milk after a negative OFC (see section 4.2).

7.2 INDUCING TOLERANCE TO CMP

Two different approaches can be applied to induce tolerance to CMP in infants with non-IgE-mediated CMPA:

- Milk Ladder approach: progressively introduces **milk and dairy-based foods**, and is widely practiced. May cause interference from the presence of other potential food allergens present in the food.
- Step-wise approach with milk formula: introduces **formulas with different degrees of hydrolysis**.[96-98] Introducing peptides of different molecular weight may induce a more controlled tolerance. However, this is not widely practiced and requires more evidence. See Appendix 3 on how the step-wise approach can be practiced.

7. FOLLOW-UP MANAGEMENT OF CMPA

In Malaysia, it is recommended that the reintroduction of CMP among children with IgE-mediated CMPA should be performed in a hospital setting.

Milk Ladder approach

Milk Ladder, first introduced in 2013, within the Milk Allergy in Primary Care (MAP) guideline,[99] is a tool designed to guide caregivers to gradually reintroduce milk and dairy products into the diets of infants and children with **mild-to-moderate non-IgE-mediated** CMPA in a home setting.

- The Milk Ladder involves a stepwise approach of introducing milk products, beginning with foods that contain a small amount of well-cooked milk, and progressing towards uncooked dairy products and fresh milk.
- Regular introduction of tolerated forms of milk, including baked/processed forms, may help to induce accelerated tolerance, allowing for the gradual liberalisation of the diet to more allergenic forms of the food over time.[100,101]
- Caregivers using the Milk Ladder should allow children to progress as slowly as needed and tolerated. Consuming baked goods regularly (Step 1) has been shown to promote tolerance (see Figure 7-1).
- Milk ladders are contraindicated in patients with a history of life-threatening anaphylaxis or in children with poorly controlled asthma. Patients using a Milk Ladder should have regular follow-ups every 6 months.

7. FOLLOW-UP MANAGEMENT OF CMPA

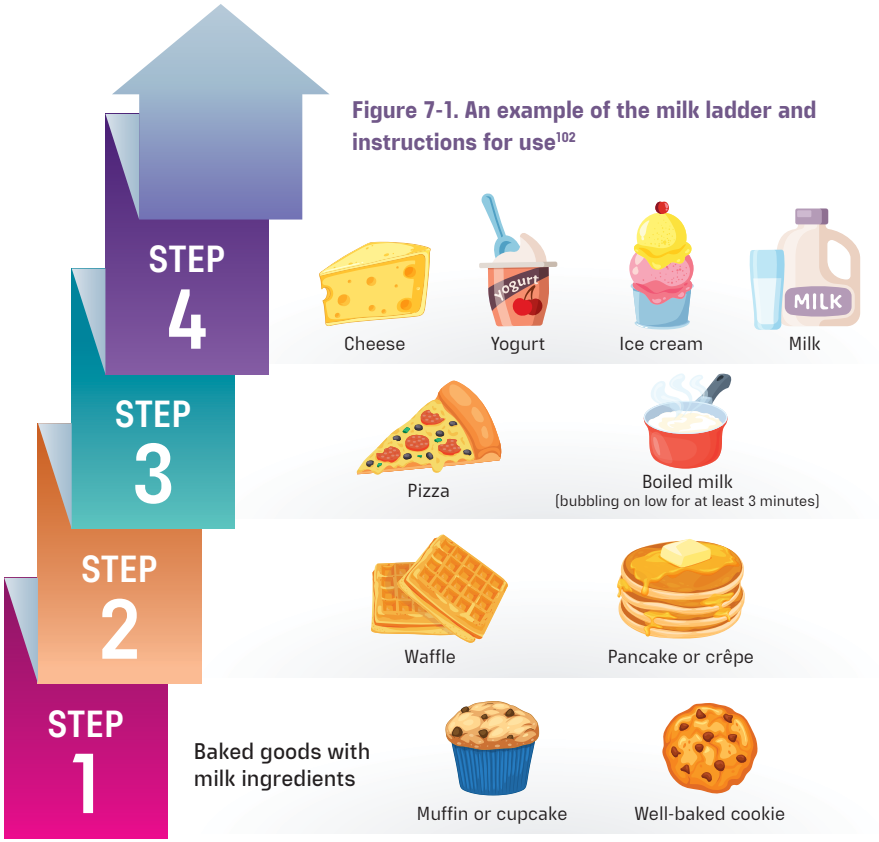


Figure 7-1. An example of the milk ladder and instructions for use[102]

The Milk Ladder (Figure 7-1) can be used or adapted for use in Malaysian children. Western food used in the Ladder are readily available in the Malaysian market. However, many Malaysian foods use coconut milk as a base instead of cow's milk, rendering them naturally dairy-free. Nevertheless, it is still important to be cautious when dining out or buying packaged foods, as some food may contain CMP or other dairy ingredients (e.g., pancakes, pizza, and cakes and cookies). Some Malaysian foods that could potentially contain CMP are:

- ***Roti canai*:** *Roti canai* is usually dairy-free, but some may have added sweetened condensed milk for additional flavour.

- **Curries:** Some Malaysian curries might contain ghee (clarified butter) or other dairy products such as butter, buttermilk, or evaporated milk.
- **Cakes and pastries:** Western-style cakes and pastries in Malaysia, especially those from bakeries and cafes, often contain butter, milk, or cream.
- **Local desserts:** Various types of *kueh* such as '*air batu campur*' (ABC), dessert jellies and doughnuts may contain dairy, especially if they have creamy fillings, gravy, or toppings.
- **Ice cream:** Many desserts, such as ice cream, may contain cow's milk. Ice cream may also be added to traditional desserts such as *cendol*.
- **Beverages such as *teh tarik*, '*Milo*' and *sirap bandung*:** These beverages are traditionally made with condensed milk.
- **Rice dishes:** Specialty rice dishes such as biryani, tomato rice (*nasi tomato*), oily rice (*nasi minyak*) and others may use yogurt or evaporated milk as one of the ingredients.

Caregivers should be aware of possible cross contamination during food preparation when a myriad of ingredients may be used. When in doubt, caregivers should find out the ingredients used in preparing the food to ensure that it's safe to consume.

Practical instructions to use the Milk Ladder:[102]

- Start at Step 1 and work the way up to Step 4.
- Give the food daily. May be taken as a meal or part of a meal.
- Start with a grain or pea-sized amount of food. Gradually increase to an age-appropriate amount over several days or weeks.
- Once an age-appropriate amount has been consumed with no allergic symptoms, consume foods in the same category for a minimum of 1-3 months before advancing to the next category.
- If allergic symptoms develop after advancing to the next category, revert back to the previous category for another month before reintroducing food in the next category.

7.3 INFANTS ABOVE 12 MONTHS NOT ACHIEVING CMP TOLERANCE

In children aged ≥12 months who have not achieved CMP tolerance, a variety of food with balanced nutrition should be encouraged as a source of nutrients. In instances where milk supplement is needed, the eHF or AAF for infants available in Malaysia could still be considered. This is because eHF and AAF formulated for children older than 1 year of age is not easily available in Malaysia.

RECOMMENDATION STATEMENTS 18-19

- **Re-challenge with CMP should only be done ≥6 months after diagnosis and initiation of treatment.**
- **A Milk Ladder approach can be considered for infants with mild-to-moderate non-IgE-mediated CMPA.**

8 SPECIAL CONSIDERATIONS

8.1 MANAGEMENT OF ANAPHYLAXIS

Anaphylaxis to CMP is a severe, life-threatening systemic hypersensitivity reaction.[103]

- The first-line treatment of anaphylaxis is adrenaline.
- Anaphylaxis should be managed immediately with aqueous adrenaline (1:1,000) administered intramuscularly into the anterior-lateral thigh at a dose of 0.15 mg for patients weighing between 15-30 kg and 0.30 mg for patients with weight ≥30 kg.
- Adjunctive treatment to adrenaline is found in Appendix 4.

8.2 MONOCLONAL ANTIBODIES FOR CMPA

Monoclonal antibodies as immunotherapy for managing CMPA is an attractive, novel strategy. Two monoclonal antibodies, omalizumab[104-106] and dupilumab[107] have been evaluated for CMPA. Omalizumab has recently been approved by the US Food and Drug Administration (USFDA) for use in IgE-mediated food allergy in certain adults and children ≥1 years old for the reduction of type I allergic reactions, including reducing the risk of anaphylaxis, which may occur with accidental exposure to one or more foods.[108]

Omalizumab treatment for 16 weeks, tested in adults and children ≥1 years old in a randomised clinical trial, effectively increased allergic reaction threshold for peanut and other common food allergens, including milk.[109] A meta-analysis[110] of 36 studies involving assessing omalizumab and placebo revealed that omalizumab monotherapy increased the tolerated dose of multiple food allergens, including milk, and reduced allergic reactions for all. Additionally, administering omalizumab before OIT had significantly improved desensitisation compared to placebo.

8. SPECIAL CONSIDERATIONS

OIT in the context of food-allergy is a management approach to alleviate anaphylactic reactions due to food allergens by continuous ingestion of small amounts of the causative food. OIT for IgE-mediated CMPA still lacks a standard protocol.[111] However, published protocols share a few essential characteristics, which include:

- Initiating the OIT programme with a build-up phase, in which the physician gradually increases the amount of cow's milk administered in a dedicated clinical setting equipped for management of anaphylaxis.
- Subsequently, daily administration of the maximum allowable dose (amount/volume) of cow's milk is performed at home. The dose of cow's milk is typically increased every week or every other week until a predefined threshold dose is achieved.

OIT with unheated cow's milk in CMPA patients has been associated with an increased probability of tolerance to cow's milk. However, it is also associated with an increased risk of serious adverse events such as increased frequency of anaphylaxis and epinephrine use, and GI symptoms.[111]

At this stage, OIT for the management of CMPA requires further standardisation and research to understand its impact on resource requirements, quality of life and cost-effectiveness.

9 PREVENTING CMPA

Preventing CMPA has been an area of active research recently. Most studies in this area focus on infants at risk of developing CMPA, i.e., those with at least one parent or biological sibling with a history of allergic disease.[112] However, more than half of all infants who have CMPA have no identifiable risk factors or a family member with atopy.[113]

Exclusive breastfeeding for 4-6 months is best for all infants irrespective of the risk of having CMPA. Exclusive breastfeeding remains the best preventive strategy for the development of CMPA in infants.[114] Exclusive breastfeeding for at least 4 months has been associated with a lower cumulative incidence of having CMPA at 18 months.

For at-risk infants, if exclusive breastfeeding is not possible, there is insufficient evidence to recommend the use of pHF or eHF to prevent allergic diseases, such as CMPA.[9,115,116] A standard cow's milk formula is recommended.[117]

SBF is not indicated in the prevention of CMPA. Some prospective studies have shown that SBF is as allergenic as cow's milk-based formula.[114]

At present, there is insufficient evidence to suggest consuming any prebiotic, probiotic or synbiotic during pregnancy, during breastfeeding (by mothers), and/or in infancy, have an effect on preventing the development of food allergy in children, including CMPA.[118]

There is no evidence to suggest that maternal dietary restrictions of CMP or CMP-containing products during pregnancy or during breastfeeding will prevent subsequent development of CMPA in their children.[119] Any restriction to the mother's diet will likely affect the mother's nutrient intake and adversely affect the health of the mother and her baby.

9. PREVENTING CMPA

RECOMMENDATION STATEMENTS 20-24

- **Exclusive breastfeeding should be encouraged for 4-6 months for all infants due to its multiple benefits.**
- **If exclusive breastfeeding is not possible, there is insufficient evidence that the use of either pHF or eHF formula prevents CMPA. A standard infant formula is recommended.**
- **The use of SBF to prevent CMPA is not recommended.**
- **There is insufficient evidence to suggest that consuming any prebiotic, probiotic or synbiotic during pregnancy, during breastfeeding by mothers, and/or during infancy, had an effect on CMPA prevention.**
- **Avoidance of CMP during pregnancy or lactation is not recommended in CMPA prevention.**

10 HEALTH ECONOMICS OF CMPA

In addition to possible nutrient deficiencies,[120] growth faltering[121] and parental anxiety,[122] CMPA also imposes significant financial burden on families of affected children with CMPA and the healthcare system. These costs include:

- Direct healthcare costs such as consultation visits, emergency department visits, diagnostic tests, and medications.
- Out-of-pocket costs related to provision of care for CMPA are generally borne by the patient's family. This includes the cost of the special milk formulae, over-the-counter medications for allergic manifestations and transportation cost.
- Indirect costs refer to the time lost stemming from the disease, e.g., when parents of children with CMPA take time off to provide care for the children, or lost wages from visits to the healthcare providers.

Two large, retrospective studies[123,124] demonstrated the significant direct cost of managing infants with newly diagnosed CMPA. The estimated cost of managing one infant with CMPA in the first 12 months after diagnosis was approximately RM8,000-10,000 (£1,381 per patient and €2,076.90 per patient).

Strategies to improve (shorten) time to diagnosis, appropriate treatment, and resolution of symptoms of CMPA could potentially reduce the financial burden imposed on health services and parents.

Cost-effectiveness of various CMPA treatments

Comparative cost-effectiveness studies of hypoallergenic formulas in reducing allergic manifestations and promoting tolerance in infants with IgE-mediated CMPA:

- Four studies (France,[125] United Kingdom,[126] Italy[127] and Indonesia[128]) found that eHF+ *Lactobacillus rhamnosus* Gorbach Goldin (LGG) was more cost-effective compared to AAF, extensively hydrolysed whey formula or SBF.
- eHF+LGG was associated with a lower total cost and a higher proportion of children being symptom-free and acquiring immune tolerance 3 years after diagnosis.

10. HEALTH ECONOMICS OF CMPA

Compared to the conventional approach of referral for confirming the diagnosis, investigations, medications and using alternative formula (SBF and eHF), early introduction of AAF for infants suspected of CMPA was found to result in potential cost saving of 10-17%.[129]

- The study was conducted in the Gulf Countries using a specific AAF involving children <24 months **suspected of CMPA** and were prescribed AAF as first-line treatment.
- The potential cost saving was primarily due to the minimal use of SBF, reduced medication costs, and reduced examination costs (i.e., costs incurred for medical consultations: 2 during symptomatic and 1 during asymptomatic periods, medical staff costs and investigations).

Summary

Shortening the duration to diagnosis and initiation of treatment has the potential to reduce the significant financial burden imposed by this condition. At present, eHF with added LGG and the early introduction of AAF (without going through the conventional approach) have been found to be cost saving. Other alternative formulas apart from eHF+LGG, however, need further proper evaluation to ascertain their cost-effectiveness.

CONCLUSION

CMPA is one of the most common food allergies in infants globally, including Malaysia. The clinical presentation is diverse with more children presenting with GI manifestations. A thorough clinical history is the cornerstone for diagnosing CMPA while an OFC is recommended if the diagnosis is uncertain. Breastfeeding is the recommended treatment for managing CMPA. However, among infants who cannot be breastfed, alternative formulas to whole milk formulas are recommended, with eHF as the first choice while HRF and AAF can be considered as acceptable alternatives depending on phenotype of the disease, severity, availability and acceptability. Plant-based and goat's milks are not recommended for treating CMPA. Monitoring is essential to determine if tolerance to cow's milk has developed. At present, there are no effective strategies to prevent CMPA.

APPENDICES

APPENDIX 1: CHECKLIST FOR PERFORMING A COW'S MILK OPEN OFC

<table>
<tr><td>1.</td><td>Check the indications and contraindications for performing an open OFC.</td><td></td></tr>
<tr><td>2.</td><td>An OFC is preferably performed after an age-appropriate period of fasting.</td><td></td></tr>
<tr><td>3.</td><td>Consider medication use:
▪ Antihistamines should be avoided 5-7 days before the test.
▪ Prolonged high-dose steroid or drugs that control atopic disease may affect the interpretation of the OFC.
▪ Beta-blockers may reduce the effectiveness of adrenaline if required during resuscitation.</td><td></td></tr>
<tr><td>4.</td><td>In suspected IgE-mediated CMPA or severe FPIES, an OFC should be performed in clinical settings with adequate personnel and equipment to perform resuscitation.</td><td></td></tr>
<tr><td>5.</td><td>Choice of cow's milk: <1 year: Cow's milk infant formula.
▪ Introduce the cow's milk in a graduated incremental manner every 20 minutes.

<table><tr><th>TIME</th><th>VOLUME</th></tr><tr><td>0 min</td><td>1 ml</td></tr><tr><td>20 min</td><td>3 ml</td></tr><tr><td>40 min</td><td>9 ml</td></tr><tr><td>60 min</td><td>30 ml</td></tr><tr><td>80 min</td><td>90 ml</td></tr><tr><td colspan="2">2-hour observation</td></tr><tr><td>Each day</td><td>200 ml/day x 2 weeks</td></tr></table>Adapted from Keil T, et al. 2010[130]</td><td></td></tr>
</table>

6.	Identify the clinical signs and symptoms suspected to be related to CMPA before performing the test.	
7.	Monitor for the occurrence of these signs and symptoms during the OFC. ▪ At the presence of any positive signs or symptoms of CMPA, the OFC should be stopped immediately. ▪ The amount of milk ingested, and the detailed reactions should be documented.	
8.	Monitor oxygen saturation continuously during the OFC.	
9.	Monitor the vital signs (blood pressure and heart rate) every 5-10 minutes before increasing the milk volume.	
10.	Monitor the patient for signs and symptoms of CMPA, their oxygen saturation and vital signs for 2 hours after the last exposure to cow's milk.	
11.	If no reactions are observed, the patient can be discharged.	
12.	Advice to parents on patient's discharge: ▪ Monitor for signs and symptoms at home. ▪ Continue to administer at least 200 ml of cow's milk a day at home for at least 2 weeks.	

Adapted from Sampson HA, et al. 2012.[44]

APPENDIX 2: ALTERNATIVES FOR SUBSTITUTE FORMULA BASED ON THE PHENOTYPIC PRESENTATION OF CMPA

CLINICAL PRESENTATION	ALTERNATIVES		
	1ST OPTION	2ND OPTION[a]	3RD OPTION[b]
Immediate onset reactions (<1 hour)			
Anaphylaxis	AAF	eHF/HRF[d]	SBF[c]
Acute urticaria/ angioedema	eHF/HRF[d]	AAF/SBF[c]	-
Asthma/rhinitis	eHF/HRF[d]	AAF/SBF[c]	-
Immediate GI allergy including oral allergy syndrome	eHF/ HRF[d]	AAF/SBF[c]	-
Delayed onset reactions (>1 hour)			
Allergic EoE	AAF	-	-
Atopic dermatitis	eHF/HRF[d]	AAF/SBF[c]	-
GERD	eHF	AAF	-
CMP-induced enteropathy	eHF/HRF[d]	AAF	-
Food protein-induced enterocolitis syndrome	eHF	AAF	-
CMP-induced gastroenteritis and proctocolitis	eHF	AAF	-
Severe irritability (colic)	eHF	AAF	-
Constipation	eHF	AAF	-
Heiner's syndrome	eHF	AAF	SBF[c]

AAF, amino acid-based formula; eHF, extensively hydrolysed formula; EoE, eosinophilic oesophagitis; HRF, hydrolysed rice formula; SBF, soy-based formula.

[a] If 1st option is not tolerated. [b] If 2nd option is not tolerated. [c] For infants above 6 months of age. [d] When available, it can be substituted for eHF.

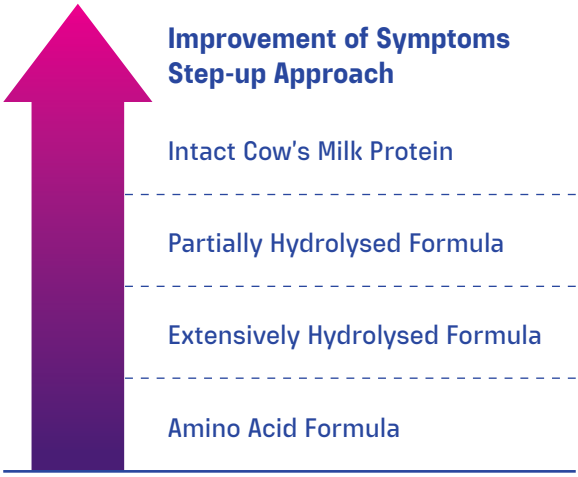
Adapted from Fiocchi A, et al. 2010; Kemp A, et al. 2008; Fiocchi A, et al. 2022.[6,74,131]

APPENDIX 3:
STEP-WISE APPROACH TO INDUCE CMP TOLERANCE

Introducing hydrolysates with different degrees of hydrolysis has been practiced recently with an aim to foster a faster oral tolerance (see Figure).[96-98]

- The step-up approach for children with CMPA using a hydrolysate milk ladder incorporates pHF as a bridge between eHF or AAF and intact cow's milk formula.
- This step-up approach should be implemented in a clinical setting with stringent medical guidance and used in selected cases such as in confirmed IgE-medicated CMPA.

Figure. Step-up approach for early tolerance in the management of IgE-mediated CMPA[97]



The step-up approach is used when there is improvement of symptoms. However, in cases where the symptoms worsen or recur, a step-down approach should be taken until the symptoms resolve.
Adapted from Vandenplas Y et al. 2019 [97]

APPENDIX 4: ADJUNCTIVE TREATMENT FOR THE MANAGEMENT OF ANAPHYLAXIS IN CHILDREN WITH CMPA

DRUG	COMMENT
Salbutamol	4-8 puffs from a metered dose inhaler or 2.5-5.0 mg nebulised solution every 20 minutes or continuously, as needed.
Diphenhydramine (H_1 antagonist)	Given orally[a] or intravenously 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.

[a] Oral liquid is most readily absorbed.
Adapted from Liberman DB & Teach SJ, 2008.[132]

GLOSSARY

TERM	DEFINITION
Allergic 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 GI tract involved and a pathologic infiltration of the GI tract by eosinophils, which may be localised or wide-spread.
Allergy	A hypersensitivity reaction initiated by specific immunologic mechanisms.
Anaphylaxis	A severe, life-threatening generalised or systemic hypersensitivity reaction
Atopic dermatitis	Also known as atopic eczema or eczema, it is the cutaneous manifestation of an allergic reaction resulting in dry, inflamed, and cracked skin.
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.
Atopy patch test	It is a procedure involving epicutaneous patch tests with the suspected allergen and the evaluation of the resulting eczematous skin lesions.
Colic	The frequent, prolonged, and intense crying or fussiness in a healthy infant that may be relieved after the infant passes gas or has a bowel movement.
Cow's milk protein allergy (CMPA)	A hypersensitivity reaction to CMP initiated by specific immunologic mechanisms.
Cross-reactivity	A phenomenon that occurs when an antibody reacts not only with the original allergen, but also with other similar allergens.

GLOSSARY

TERM	DEFINITION
Dermatographism	Also known as dermographism urticaria, or urticaria factitia, it is an urticarial eruption upon pressure or trauma to the skin. Downward pressure on the skin produces a linear wheal in the shape of the applied external force.
Double-blind, placebo-controlled food challenge (DBPCFC)	The gold-standard for diagnosing CMPA. The test aims to reproduce symptoms that are triggered during the natural exposure of the food allergen without interference from the patients, family, or physician. The food for testing and a placebo are added to a vehicle in increasing doses and at regular intervals. The test sequence (food for testing or placebo) should only be known to the person conducting the test.
Eosinophilic colitis	It is a heterogeneous entity that can present with an acute self-limited bloody diarrhoea in otherwise healthy infants secondary to eosinophilic infiltration of the colon.
Eosinophilic oesophagitis (EoE)	A condition that involves localised eosinophilic inflammation of the oesophagus. Both IgE- and non-IgE-mediated mechanisms appear to be involved.
Extensively hydrolysed casein formula (eHCF)	An eHF where the casein component of the CMP is further hydrolysed (broken down).
Extensively hydrolysed formula (eHF)	The proteins in cow's milk are broken down into small peptides by hydrolysis and other processes (e.g., ultrafiltration) to make these formulas less allergenic that whole milk formulas.

TERM	DEFINITION
Faecal calprotectin (FC)	Calprotectin is a protein that belongs to the S-100 protein family and is characterised by its ability to bind to calcium and zinc. This protein is primarily found in neutrophils and is distributed throughout the human body. The presence of calprotectin in faeces is a result of neutrophils migrating into the GI tissue due to an inflammatory process. The concentration of FC is highly correlated with intestinal inflammation, making it a useful biomarker for GI disorders.
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 protein-induced allergic proctocolitis	A non-IgE-mediated disorder that usually occurs in young infants that mimics food allergies.
Food protein-induced enterocolitis syndrome (FPIES)	FPIES generally occurs a couple of hours after ingestion of the food trigger. Typical symptoms of FPIES include severe vomiting, diarrhoea, and dehydration two hours after eating. These symptoms can lead to other complications, including changes in blood pressure and body temperature, lethargy, and failure to thrive.
Gastroesophageal reflux disease (GERD)	The repeated reflux of acid from the stomach into the oesophagus that irritates the oesophageal lining.
Hydrolysed rice formula (HRF)	Proteins from rice are extracted using various methods, e.g., physical extraction, alkaline extraction or enzymatic extraction. This improves the digestibility and bioavailability of the proteins. Extraction is followed by hydrolysis of the rice proteins to improve their solubility, and emulsifying and foaming properties.

GLOSSARY

TERM	DEFINITION
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 CMP that is initiated by immunologic mechanisms involving mainly IgE.
Mixed IgE CMPA	CMPA that involves IgE-mediated and non-IgE mediated allergic reactions.
Non-IgE-mediated CMPA	A hypersensitivity reaction to CMP that is initiated by immunologic mechanisms not involving IgE.
Oral food challenge (OFC)	Considered a highly accurate diagnostic test for food allergies where the suspected food trigger is fed in measured doses and the patient observed for a period of time for any signs of a reaction. It may also be done to determine if the patient had built tolerance to the food allergen.
Partially hydrolysed formula (pHF)	These formulas are developed to reduce protein allergenicity through heat treatment and chemical and enzymatic hydrolysis, which results in a reduced molecular weight and peptide size. However, unlike eHFs, pHFs retain a slightly larger protein size and therefore, immunogenicity to potentially induce oral tolerance to CMP with minimal sensitisation.
Skin prick test (SPT)	A simple test where the skin is pricked, and a minute amount of the suspected allergen is administered into the skin.
Specific immunoglobulin E (sIgE)	In contrast to measuring the total serum IgE released during an inflammatory process, sIgE measures how much IgE is produced in response to a single allergen.

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