Guideline for the diagnosis and management of cow's milk protein allergy (CMPA) in Hong Kong

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On behalf of Hong Kong Institute of Allergy

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DECLARATIONS OF INTEREST

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1.1.3 Older children and adults with milk allergies are less likely to become tolerant.

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1.1.5 CMPA can present with a time of onset of a symptom complex that can vary from minutes to days and occasionally even weeks.

1.1.6 Symptoms include skin rashes, eczema, angioedema, gastrointestinal symptoms, oral allergy syndrome, enteropathies, eosinophilic oesophagitis/enteritis, rhinitis, asthma and laryngeal oedema.

1.1.7 Certain danger signals should alert clinicians to make an urgent referral to an Allergist or Paediatrician, including failure to thrive due to chronic diarrhoea and/or refusal to feed and/or vomiting; iron deficiency anemia due to occult or macroscopic blood loss; hypoalbuminemia; endoscopically confirmed enteropathy or severe colitis; erythrodermic or exfoliative dermatitis; severe atopic dermatitis with hypoalbuminemia or failure to thrive or iron deficiency anemia; acute laryngeal oedema; bronchospasm.

1.1.8 History and examination are central to differentiate different forms of CMPA.

1.1.9 While skin tests and measurement of sIgE can help, the gold standard for diagnosis is oral milk challenge.

1.1.10 Guidelines published in other countries often stress the importance of food challenge early in the diagnostic process. In Hong Kong the numbers of specialists are few and the facilities for food challenges are very limited so children are usually pre-screened using sIgE measurements for milk before being subjected to milk oral challenge. It helps to reduce significantly the need for oral challenge.

1.1.11 To determine tolerance or natural remission, periodic re-challenge is the cornerstone of management.

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1.2.9 Partially hydrolyzed formula and goat's milk are not suitable for management of CMPA at any age. Non-dairy milk drinks such as rice milk and oat milk should not be used for management of CMPA in infants, but may be used in children over 12 months and adults.

1.2.10 While oral immunotherapy has shown promising results in treating CMPA, it is not recommended for routine clinical practice, due to uncertain long-term tolerance and safety data.

1.2.11 Most CMPA naturally resolves during childhood, and infants so children with CMPA should be re-evaluated 6-12 monthly for their tolerance toward cow's milk protein and readiness for milk reintroduction.

1.2.12 Milk reintroduction should be done in a systematic and graded manner according to the "milk ladder" as described Table 5. Reintroduction can be done at home for children with only mild symptoms.

2. Introduction and objective

The objective of this guideline is to provide pragmatic advice for diagnosis and management of cow's milk protein allergy (CMPA) to support mainly primary and secondary care clinicians and allied health professionals such as dietitians.

Cow's milk protein allergy (CMPA) is defined as an adverse immune responses towards cow milk proteins or as a form of adverse reaction to food associated with a hypersensitive immune response to cow milk protein. Cow's milk contains several Class 1 food allergens (Caseins (a, b, k), a-lactoalbumin, b-lactoglobulin, serum albumin) which are the primary sensitizers. They are stable to acid and proteases. Some of the allergens are sensitive to heating. Sensitization may occur through the gastrointestinal tract or cutaneous route. The natural history of CMPA:

1. It usually presents in infancy.
2. There are very few cross reactions to other bovine proteins leading to beef allergy but milk from other mammalian species, e.g. goat, have a high degree of homology and cross reactivity.
3. Most of children become tolerant or seem to" outgrow" their food allergies to milk, within a few years.
4. 85% of children with milk allergy become tolerant by age of 3 years.
5. Older children and adults who persist with milk allergies are less likely to become tolerant.

Infants with cow's milk allergy have significant higher chance of hypersensitivity to unrelated food proteins.

3. Prevalence

3.1. Worldwide

Cow's milk allergy can be regarded as an integrated model of food allergy as cow's milk entailing a wide spectrum of clinical manifestations and is usually one of the first food proteins that infants are exposed to in the Western Hemisphere [1, 2]. Prevalence studies from Sweden [3] Denmark [4] and the Netherlands [5] demonstrated a prevalence of CMPA 1.9-2.8%. Prevalence figures from Australia were similar[6]. In China, the newly assumed second largest economy of the world, an increase in CMPA has been associated with rapid urbanization, with a latest estimation of CMPA of 2.3% in a major city [7]. Allergy to milk was suspected in 6.7% and

confirmed in 2.2%. Of confirmed cases children, about slightly more than a half had IgE-mediated allergy, and the remaining were classified as non-IgE mediated [8].

3.2. Hong Kong

According a recent a cross-sectional population-based questionnaire survey over 7300 children targeted at children aged 0-14 years old [9], 352 reported having adverse reaction to foods and the estimated prevalence was 4.8% (95% CI 4.3-5.3%). In terms of relative frequency, shellfish is the top allergen and accounted for more than a third of all reactions. It was seconded by hen's egg (14.5%), third by cow's milk and dairy products (10.8%) and co-fourth by peanut and combined fruits (8.5%). Out of 352 subjects reported adverse reactions, 127 (36.1%) had urticaria and or angioedema and 79 (22.4%) had eczema exacerbations. Combined gastrointestinal symptoms accounted for 20.8 % (diarrhoea 12.8%; vomiting 5.4%; abdominal pain 2.6%). Fifty-five (15.6%) had anaphylaxis, and 7 (2%) had respiratory difficulties. Another study of similar design recruited over 3800 Hong Kong children aged 2-7 years through nurseries and kindergartens had their parents answered a self-administered questionnaire found cow's milk was one of the common causes of parent-reported adverse food reactions [10].

Table 1. Comparisons of self-reported symptoms at all ages between pooled international data and Hong Kong data

	Pooled international data [8]	Hong Kong Data [9] (95% C.I.)
Peanut	0.6%	0.4% (0.3% - 0.6%)
Cow's Milk	3% #	0.5% (0.4% - 0.7%)
Hen's Egg	1%	0.7% (0.5% - 0.9%)
Fish	0.6%	0.2% (0.1% - 0.3%)
Crustacean shellfish	1.2%	1.8% (1.5% - 2.1%)
Fruits	0.02-8.5%	0.4% (0.3% - 0.6%)
Tree nuts	0-4.1%	0.08% (0.04% - 0.18%)
Wheat	0.2-1.3%	0.03% (0.01% - 0.1%)
Soy	0-0.6%	0.4% (0.3% - 0.5%)

Greater prevalence in children than adults, not specifically estimated but it appears to be about 6 - 7% in children and 1 - 2% in adults.

Hong Kong is in many ways similar to reported pooled international data except cow's milk. The reason for the lower cow's milk allergy in Hong Kong is not entirely clear and may be due to the under-recognition of the non-IgE mediated CMPA.

4. Clinical features and pathogenesis

CMPA presents to clinicians with a symptom complex which develops after ingestion of cow's milk, with a time of onset ranging from minutes to days and occasionally weeks, as in the case of atopic dermatitis (Tables 2 and 3).

The threshold for developing food allergic reactions can be lowered when there are co-factors. This includes exercise (as in food dependent exercise induced anaphylaxis), alcohol, food additives and non-steroidal anti-inflammatory drugs. It is unknown to what extent co-factors play a role in children with CMPA.

Table 2 – The spectrum of food allergy of different immunopathophysiology

IgE mediated		Non-IgE mediated cellular
Immediate type (onset times to 30min up to 2hrs)	Mixed type	Delay type (onset few hours to days)
Urticaria/angioedema Rhinitis/Asthma	Atopic dermatitis	FPIES
Oral allergic syndrome Vomiting & diarrhoea	AEE(EoE)/AGE GERD	Coeliac disease/dermatitis herpetiformis contact dermatitis

(AEE(EoE)/AGE = Allergic eosinophilic esophagitis (Eosinophilic esophagitis)/allergic eosinophilic gastroenteritis, GERD = gastro-esophageal reflux disease, FPIES=food protein induced enterocolitis syndrome

Table 3: Clinical features of food protein allergy / intolerance in children

Cutaneous reactions	
IgE mediated	• Atopic dermatitis • Urticaria • Angioedema
Non-IgE mediated	• Contact rash • Atopic dermatitis (some forms)
Gastrointestinal reactions	
IgE mediated	• Immediate gastrointestinal hypersensitivity (e.g. nausea, vomiting, diarrhea) • Oral allergy syndrome • Abdominal colic
Non-IgE mediated	• Allergic eosinophilic oesophagitis, gastritis, or gastroenteritis • Dietary protein colitis, enteropathy
Respiratory reactions	
IgE mediated	• Rhinoconjunctivitis • Asthma • Laryngeal edema • Food-dependent exercise-induced asthma
Non-IgE mediated	• Pulmonary hemosiderosis (Heiner's syndrome [rare])
Systemic anaphylaxis	

4.1. IgE mediated CMPA

Type I hypersensitivity reactions occur when patients develop IgE antibodies against cow's milk proteins or peptides that penetrate into the body through skin, gut or respiratory lining. The antigen is then processed by an antigen presenting cell which presents the antigen in a MHC restricted manner to T cells. Activation of the T cell receptor leads to cross talk between T and B cells leading to the production of specific IgE antibodies. The IgE antibodies circulate and bind to the IgE receptors on the surfaces of mast cells and basophils (Figures 1 and 2). Upon re-exposure of allergen, a much quicker and stronger response ensues, leading to the degranulation of effectors cells and the release of pre-formed granular mediators such as histamine, chemokines and tryptase and newly synthesized membrane derived lipid mediators including prostaglandins and leukotrienes. These mediators have the ability to induce vasodilatation, mucous secretion, smooth muscle contraction and influx of other inflammatory cells, all characteristics of a classical inflammatory response.

Figure 1 – A schematic diagram illustrating the hypothetical gastrointestinal and immune interface. The digestive processes and absorption of food are dependent on gastric acidity, enzymatic digestion, and tight junctions. This is followed by antigen processing via local mucosal lymphoid (Peyer's patch) involvement, which then leads to IgE, non-IgE or mixed type mediated food hypersensitivities. There is a continuous interplay of cellular and humoral molecular factors and signaling pathways. Abbreviations: APC = antigen presenting cells; TNF-α = tumour necrosis factor alpha; IL-5 = interleukin 5 [11]

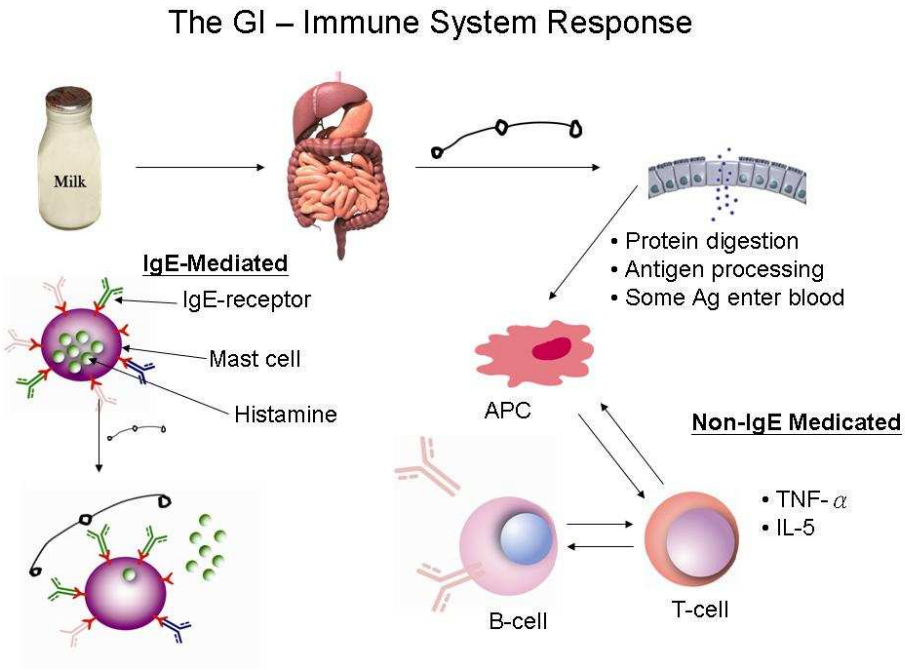
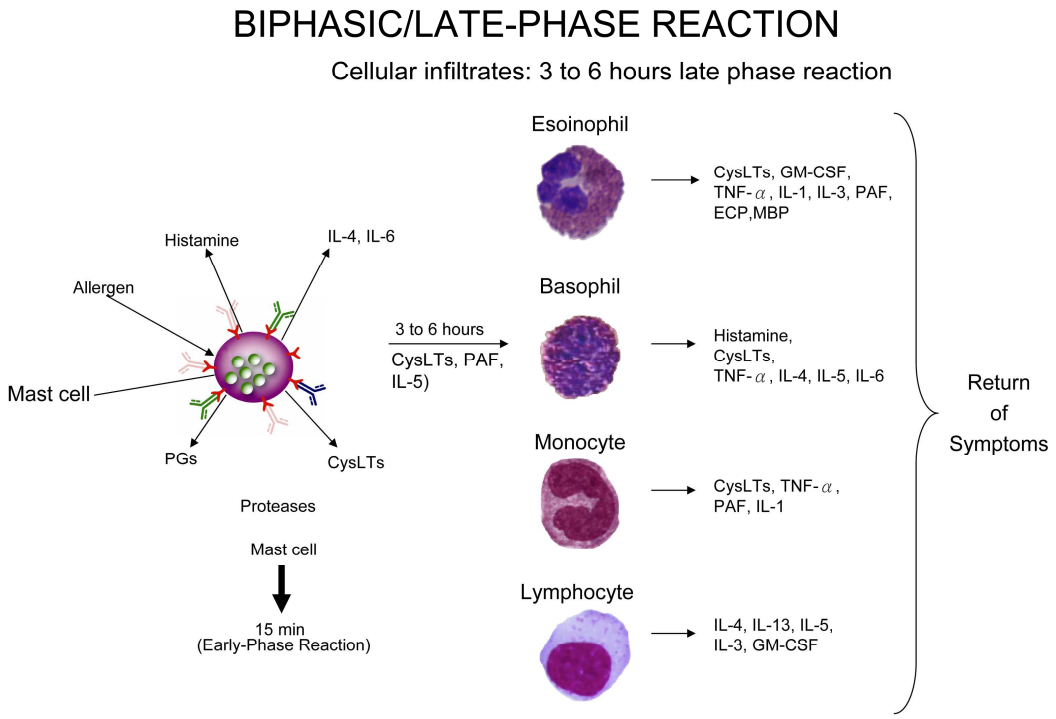


Figure 2 – A schematic diagram illustrating the time sequence and key factors precipitating the early and late phase reactions of food allergy or anaphylaxis (Biphasic Reactions). Abbreviations: CysLT = cysteinyl leukotriene; ECP = eosinophilic cationic protein; GM-CSF = granulocyte macrophage colony stimulating factor; IL = interleukin; MBP = major basic protein; PAF = platelet activating factor; TNF-α = tumour necrosis factor alpha. [11]



The classical symptoms of IgE-mediated reactions are rapid in onset and can result in multi-system or systemic manifestations. In general, IgE-mediated are considered to be acute reactions, the cutaneous manifestations, including urticaria and angioedema, are the most prevalent symptoms. Patient may develop chronic symptoms through the late phase reaction and recurrent exposures associated with influx of inflammatory cells.

Respiratory symptoms together with ocular symptoms can occur in isolation or more commonly with other systemic reactions. Asthma, by itself, is an uncommon manifestation of CMPA.

Gastrointestinal symptoms such as throat discomfort, mouth and tongue itchiness, nausea, vomiting, abdominal cramps, and diarrhea may be clinical manifestations in patients with IgE-mediated CMPA. The onset can range from minutes to two hours for upper gastrointestinal symptoms or occasionally over two hours for lower gastrointestinal symptoms.

Cardiovascular symptoms are the most severe manifestation of a systemic reaction and may include hypotension, vascular collapse, arrhythmia, etc. Cardiovascular symptoms seldom occur alone without the involvement of other organ systems.

4.2. Non-IgE mediated / mixed IgE mediated CMPA

Clinical symptoms are subacute or chronic in nature and usually present with isolated gastrointestinal symptoms. CMPA induced enterocolitis, proctitis, proctocolitis, and pulmonary hemosiderosis are forms of non-IgE mediated reactions [12].

Food protein-induced enterocolitis syndrome (FPIES)

Food protein-induced enterocolitis syndrome (FPIES) is an under-recognized and frequently misdiagnosed non-IgE-mediated food hypersensitivity disorder. It occurs in infants prior to 8-12 months of age, but may be delayed in breast-fed babies. Cow's milk or soy protein-based formulas are implicated [13, 14]. Symptoms may include irritability, protracted vomiting 1- 3 hours after feeding, bloody diarrhoea, dehydration, anaemia, abdominal distension, and failure to thrive. Longitudinal follow up found 50% resolved at 18 months and about 90% at 3 years of age.

Food protein-induced enteropathy can present between 0 and 24 months of age, but usually within the first few months of life. The common presentation is diarrhoea and about 80% are associated with mild to moderate steatorrhea [13, 14]. Failure to thrive is also common. Foods implicated include milk, cereals, egg, and fish. Definitive diagnosis requires a mucosal biopsy, which would show patchy villous atrophy with a prominent mononuclear round cell infiltrate but with few eosinophils. Patients typically respond well to an exclusion diet and quickly relapse upon re-introduction or re-challenge. A significant proportion resolve by 2-3 years of age.

Food protein-induced proctocolitis is thought to be due to food proteins passed to the infant in maternal breast milk, cow's milk based formula or soy-based formula. Rectal bleeding is common [13, 14]. Infants usually have a good response to extensively hydrolyzed formulas. If breast feeding, the mother should avoid consumption of dairy products. Food protein-induced

protocolitis carries very good prognosis with the majority having resolution by 12 months of life [15, 16]. Table 4 shows a clinical comparison of the 3 entities: enteritis, enteropathy and protocolitis.

Table 4 – A clinical comparison of different presentations of CMPA induced enteropathy syndrome (FPIES)

Clinical comparison of different presentation of FPIES			
Non-IgE mediated: FPIES (Non-IgE mediated) Protein Induced syndromes			
	Enterocolitis	Enteropathy	Proctocolitis
Age of onset	Infant	Infant/Toddler	Newborn
Times from onset to remission	12-24 months	12 - 24 months	< 12 months
Clinical features	Failure to thrive; shock; lethargy; chronic diarrhoea	Malabsorption syndrome; villous atrophy on biopsy; chronic diarrhoea	Bloody stools; usually well baby; eosinophils in peripheral blood

Heiner's Syndrome

Heiner's Syndrome is a rare form of infantile pulmonary hemosiderosis resulted in anemia and failure to thrive. It is widely believed to be cow's milk-associated and infants may develop precipitating antibodies to cow's milk protein.

Atopic dermatitis

Atopic dermatitis generally begins in early infancy. It is characterized by a typical distribution, extreme pruritus, and a chronically relapsing course. Food allergy plays a pathogenic role in about 35% of moderate-to-severe childhood atopic dermatitis [17-19].

Eosinophilic oesophagitis and eosinophilic gastroenteritis

CMPA can lead to eosinophilic oesophagitis and eosinophilic gastroenteritis. Studies have demonstrated food sensitivity in some of the patients and food elimination can both be helpful

in diagnosis and therapeutic in eosinophilic oesophagitis [20, 21]. Endoscopy and biopsy are often needed for definitive diagnosis.

Onset of clinical symptoms

The Melbourne Milk Allergy Study (MMAS) described a diverse group of clinical symptoms and syndromes that could be demonstrated by dietary challenge [2]. These ranged from anaphylaxis and urticaria occurring within minutes of challenge, to distress, vomiting and diarrhoea within hours. Exacerbations of atopic dermatitis (AD) as well as gastrointestinal or respiratory symptoms occurring after 24 hours of ingesting cow's milk were also manifestations during challenge. Analysis of these data identified three clinical groups with different immunological profiles.

The first group, the immediate reactors, developed acute skin rashes, including peri-oral erythema, facial angioedema, urticaria and pruritus at eczematous sites, with or without signs of anaphylaxis. Patients in this group typically had high levels of cow's milk-specific IgE antibodies, detected either *in vitro* by radioallergosorbent test (RAST), or *in vivo* by skin prick testing (SPT). The second, intermediate group, had reactions occurring from one to 24 hours after ingestion of milk; they had predominantly gastrointestinal symptoms, including vomiting and diarrhea. As a group, these patients did not exhibit features of IgE sensitization. The third, late-reacting group, developed symptoms from 24 hours to five days after the commencement of the challenge procedures; these patients presented with exacerbations of AD, cough, wheeze, and/or diarrhoea. Varying degrees of IgE sensitization were seen in those with AD. Subsequent studies have demonstrated that this group had greater levels of T-cell sensitization to milk than the immediate or intermediate reactors or control children [22].

Carrocio et al [23] described a group of children presenting with very delayed reactions after challenge with cow's milk protein. Symptoms included constipation, persistent wheeze or AD exacerbations [23]. In addition, Caffarelli and Petrocciou [24] reported on a small group of children with CMA who had apparent " false-negative" immediate food challenges to cow milk; however, on subsequent exposure on the day following their initial challenge they developed symptoms of immediate anaphylactic hypersensitivity.

Resolution of CMPA

Despite the occurrence of CMPA in infancy, children usually grow out of it [25]. However Kokkonen et al. described a group of school-aged children with CMPA in infancy in whom non-characteristic gastrointestinal symptoms persisted to 10 years of age, suggestive of residual cow's milk-sensitive enteropathy (CMSE) [26]. These patients may be able to tolerate small amounts of cow's milk protein but often limit their intake of dairy products. There was evidence of mucosa T-cell activation on small bowel biopsy [27, 28].

A couple of factors seem to affect the rate of resolution. It was found that non-IgE mediated allergy appeared to be a transient condition and children outgrew it faster than IgE mediated allergy [25]. Development of allergy to other foods, and progression of the atopic march towards respiratory allergy later in childhood also delayed the rate of resolution [4]. The rate of decline of IgE concentrations also seems to predict the likelihood of development of tolerance. Patients who develop tolerance were more likely to have a faster rate in decline of IgE level on sequential testing [5]. The mechanisms leading to persistent non-IgE CMPA hypersensitivity are poorly understood. Järvein et al [29] have hypothesized that sensitization to specific epitopes of several cow's milk proteins may be associated with long-term persistence of CMPA [29, 30].

4.3. Special considerations in infants

4.3.1 Multiple food allergy of infancy (MFA)

It refers to infants allergic to cow's milk, soy and extensively hydrolyzed formula, as well as several other major food allergens including egg, wheat, peanut and fish. These infants need to be distinguished from those with "oligo-food hypersensitivity" who are intolerant to only a few common food, such as milk, egg, peanut, and nuts, but who tolerate soy or extensively hydrolyzed formulae.

The remission of symptoms occurs at two weeks of commencing an amino acid-based formula (AAF) [31, 32]. Two studies [33, 34] have reported similar data for infants with this disorder. These MFA infants were frequently identified with lymphocytic or eosinophilic esophagitis and subtle enteropathy on endoscopy, as well as a consistent pattern of delayed immune maturation with low IgA, IgG2, IgG4, Cd8+ and natural killer cells [35].

A prominent feature of MFA infants was their frequent onset of symptoms while being exclusively breast-fed, their intolerance to soy and extensively hydrolyzed formulae and a good response to AAF [36].

4.3.2 Infantile colic

Infantile colic refers to a syndrome of paroxysmal fussiness characterized by inconsolable, agonized crying. It generally develops in the first 2 to 4 weeks of life and persists through the third to fourth months of age, affecting between 15 and 40% of infants. The role of dietary factors on colic is controversial [13]. A maternal elimination diet may be cautiously introduced if the baby is on breast milk. If the baby is being formula fed, the clinical diagnosis can be established by implementation of several brief trials of hypoallergenic milk formula to assess whether there is symptom improvement, and whether there is symptom relapse on re-introduction of normal milk formula.

4.3.3 Gastro-esophageal reflux and oesophagitis in infants

Gastroesophageal reflux disease (GERD) is common during infancy and is considered pathological if it causes esophagitis, failure to thrive or respiratory symptoms. Several studies suggest a causal relationship between CMPA and GERD in infancy [37-40]. Infants with GERD and esophagitis associated with CMPA may improve symptomatically on changing to extensively hydrolyzed formula.[38] Electrophysiological studies have reported a gastric motility disturbance following ingestion of cow's milk, [39] making an association of food allergies and GERD plausible.

5. Diagnostic evaluation

There are certain "danger signals" that should alert clinicians to refer children with possible CMPA to a specialist (Table 5).

History and clinical examination are of paramount importance in clinical practice to differentiate the different forms of CMPA. Despite the improvement in diagnostic methodology using wheal size diameters in allergen skin testing or levels of food specific IgE in serum, a conclusive diagnosis is still dependent on elimination and challenge testing (Fig 3). To demonstrate the tolerance, natural resolution or the persistence of food allergy, periodic re-challenge remains the cornerstone of practice. Monitoring for the development of tolerance by clinical history

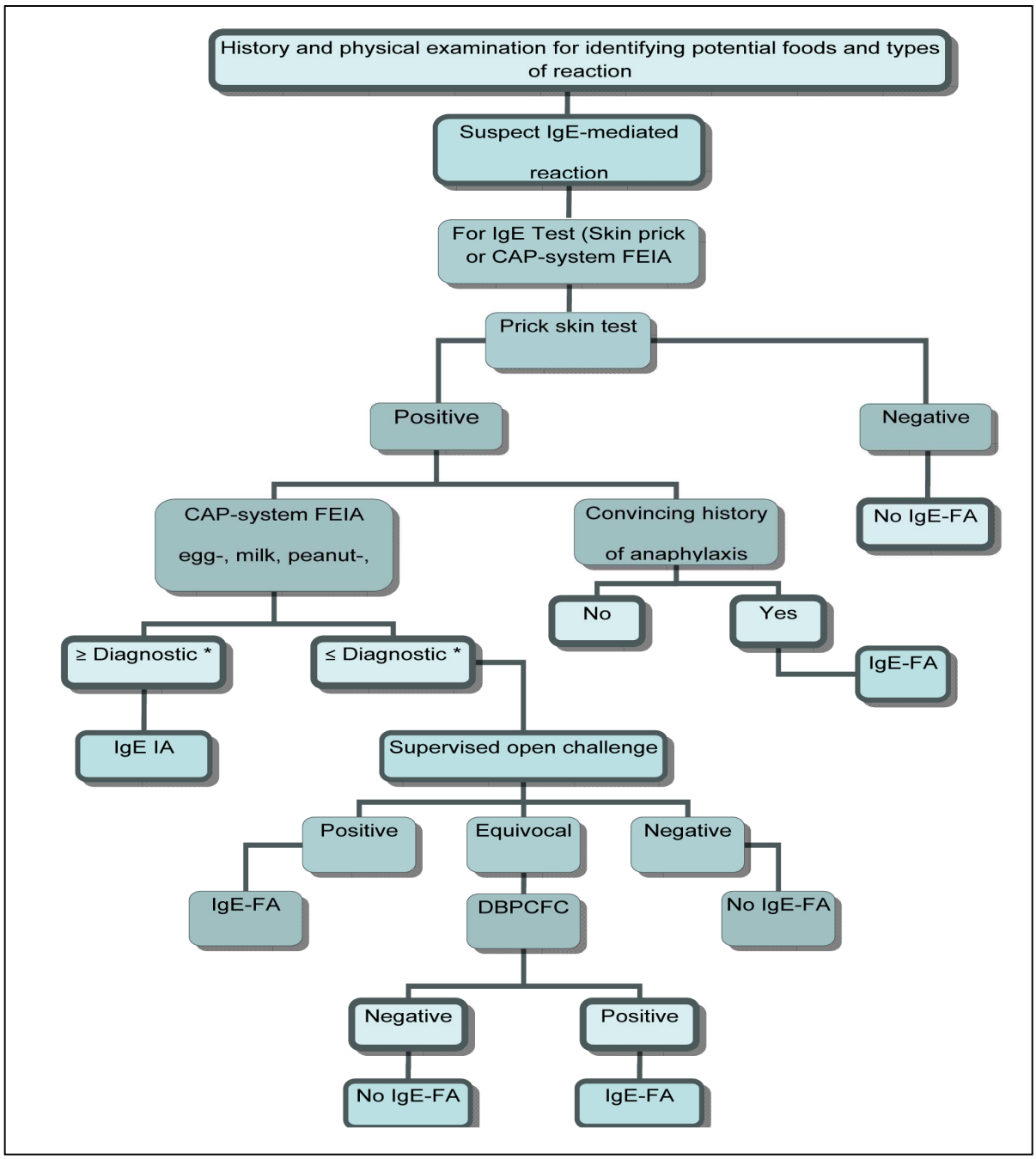
upon inadvertent exposure, in vivo skin testing, and the level of food specific-IgE may also provide useful information regarding a time to conduct a food challenge.

Recent advances in food allergy in early childhood have highlighted increasing recognition of a spectrum of delayed onset , non-IgE-mediated manifestations of food allergy. Common presentations in infancy including atopic eczema, infantile colic and gastroesophageal reflux are associated with food hypersensitivity and often respond to dietary elimination.

Table 5. Alarming symptoms/signs of possible severe CMPA (can be found alone or in combination). Patient should be referred early for specialist consultation

Organ involvement (Mechanism)	Symptoms and Signs
Gastrointestinal tract (Non-IgE)	Failure to thrive due to chronic diarrhoea and/or refusal to feed and/or vomiting
	Iron deficiency anaemia due to occult or macroscopic blood loss
	Hypoalbuminaemia
	Endoscopic/histologically confirmed enteropathy or severe colitis
Skin (Non- IgE)	Erythrodermic/ exfoliative changes
	Exudative or severe atopic dermatitis with hypoalbuminaemia or failure to thrive or iron deficiency anaemia
Respiratory tract (IgE)	Acute laryngoedema or bronchial obstruction with difficulty breathing (non-infectious)
General Anaphylaxis (IgE)	

Fig 3 Diagnostic algorithm for IgE mediated food allergy including CMPA (legend: CAP-system FEIA= fluorenzymeimmunoassay; FA= food allergy, DBPCFC=double blind placebo controlled food challenge)



For diagnosis/management of non IgE cow's milk allergy see Figure 4.

5.1. Skin Prick Test and serum sIgE measurements

Guidelines published in other countries often stress the importance of food challenge early in the diagnostic process. In Hong Kong the numbers of specialists are few and the facilities for food challenges are very limited so children are usually pre-screened using sIgE measurements for milk before being subjected to milk oral challenge. It helps to reduce significantly the need for oral challenge.

The diagnostic serum sIgE level defines the cut-off value that has greater than 95% positive predictive value when compared to the gold standard of oral challenge (Table 6). This is age dependent. For patient younger than age of 2 years old, a different cut off value has been defined. The re-challenge value is defined as the one which predicts that > 50% of allergic children can pass the oral challenge. It has been defined as such because most parents would be more willing to accept a challenge (which may cause potential discomfort or risk) when the chance of success is greater than 50%.

Table 6 Diagnostic Food-Specific IgE Values (CAP-system Fluorenzyme Immunoassay) of Greater than 95% Positive Predictive Value for a positive oral challenge [40,41]

Food	Serum sIgE value (KUa/L)	Re-challenge sIgE value (KUa/L)
Milk		
>= 2yr old	>=15	<=7.0
<= 2 yr old	>=5.0	

5.2. Food challenge

The gold standard for assessment of food allergy including milk allergy is the oral challenge. A food allergen challenge is a procedure where small and incremental amounts of a particular food are fed to a person while under medical supervision, and monitored to determine if the food being tested causes an allergic reaction in the person. Most challenges involve a time period of about 2 to 3 hours to eat the required doses of food, followed by 2 hours of observation. Occasionally the food is given in one serving for rare types of food allergy such as Food Protein Induced Enterocolitis Syndrome (FPIES). If an allergic reaction occurs, the procedure is usually stopped and if necessary, treatment for the allergic reaction is given. It is usually called 'positive' and the person is diagnosed as allergic to the food. If the challenge is completed without an allergic reaction; it is called 'negative'. The person will then be asked to regularly include the food in their diet.

5.3. Indications for Cow's milk challenges

- Person has outgrown an existing CMPA.
- Suspected CMPA is an actual allergy, when the history or allergy tests are unclear.
- Positive cow's milk allergy test in a person who has never before reacted to that cow's milk, to ascertain whether a real CMPA exists.
- Person with confirmed CMPA can safely eat alternative foods. For example, a soy challenge may be used to determine if a person with cow's milk allergy with a positive skin prick test to soy, is also allergic to soy.

The protocol used at Queen Mary Hospital (QMH) is shown in Table 7. This should only be carried out by experienced specialists and in a safe environment where resuscitation facilities are immediately available.

Table 7: The Cow's Milk Challenge Protocol Currently Used in Queen Mary Hospital is adapted from Australian Society of Clinical Immunology (ASCIA)

PRE-CHALLENGE ASSESSMENT /PREPARATION:
The person being challenged must be well on the day of the challenge with no fever and if asthma is present, it must be stable with no recent wheezing. The person should have not taken any antihistamine 3 days (short acting antihistamine) or 5 days (long-acting antihistamine). If the person being challenged has a prescribed adrenaline autoinjector this should be brought to the food allergen challenge. If a severe allergic reaction occurs, it may be an opportunity for the person (if old enough and well enough) or parent to administer the adrenaline autoinjector in a controlled setting. Staff will always have a supply of adrenaline available even if the patient has an adrenaline autoinjector with him/her.

CHALLENGE SUBSTANCES
1. Less than 12 months old – cow's milk based infant formula
2. More than 12 months old – full cream cow's milk

CHALLENGE PROTOCOL
Day 1

TIME	ml milk
0	Drop inside lip (not to touch outside lip)
20 min	1 ml
40 min	5 ml
60 min	15 ml
80 min	40 ml
100 min	100 ml
Daily total	~160ml

OBSERVATION POST-CHALLENGE
Generally for 2 hours

HOME CONTINUATION
Day 2
160ml
Day 3-14
Increase amount as tolerated until all bottles in an infant (<12 month of age) are cow's milk based formula or daily amount is 200-300 ml (>12 months of age).
Note: Completely or partly hydrolysed (HA) formula should NOT be used for milk challenges.

6. Treatment of cow's milk protein allergy

The following recommendations on treatments of CMPA are a summary of current national and international guidelines[8, 41-47]. Relevant studies related to CMPA dietary treatment have been included.

6.1. Dietary Avoidance

Strict dietary avoidance of cow's milk protein is key to the management of cow's milk protein allergy (CMPA), but inhalation and skin contact should also be prevented [41]. Regular cow's milk and milk formula are not suitable for patients with CMPA. Since milk is the main source of calcium in every stage of life, children avoiding milk will need to have a substitute in order to fulfill their nutritional requirements. Nutrition counseling and growth monitoring should be performed in all children with food allergies [8]. It is preferable that all children diagnosed with CMPA be assessed by a dietitian to educate about dietary avoidance, nutritional adequacy, milk substitution and reintroduction [8, 45].

6.2. Milk substitution

As cow's milk is the major source of calcium in infants' and children's diets, recommendation on milk substitution should be provided. While children on milk avoidance are more at risk for consuming less dietary calcium than recommended for their age- and gender [8], children with food allergies who received nutrition counseling have lower risk for inadequate intake of calcium and vitamin D [8]. Thus a dietitian should assess calcium intake and advise on dietary calcium intake and calcium supplementation as appropriate. In children under 2 years old, replacement with a substitute milk is mandatory to reduce these risks, while replacement may not be necessary for children older than 2 years old or in exclusively breast fed children. The best choice of milk substitute will be based on the age of the patient, severity of CMPA, and the presence of other food allergies. See Table 8 for a list of suitable cow's milk substitutes available in Hong Kong for infants with CMPA.

6.2.1.Breast milk

Although beta-lacto-globulin can be detected in the breast milk of most lactating women[45], most CMPA infants can tolerate breast milk. Studies indicated that only 0.4-0.5% exclusively breastfed infants will have symptoms [45, 48]. Therefore, milk avoidance in maternal diet is not required unless the infant has symptoms while being breast-fed [45, 49]. In breast fed infants with CMPA symptoms, their mothers should be instructed on avoidance of all milk-containing foods and drinks and assessed for their own calcium and vitamin D adequacy. Infants 6 months or older receiving breast milk as their main feed should be given vitamin D supplementation in the form of vitamin drops [45].

6.2.2.Extensively hydrolyzed Formula

Milk allergenicity can be reduced by hydrolysis [12, 13]. Therefore, extensively hydrolyzed formulas have been developed that meet the defined criterion of 90% clinical tolerance (with 95% confidence limits) in infants with proven CMPA [41, 43, 45]. Milk formulas with a higher degree of hydrolysis are generally less allergenic and more tolerable [45]. However hydrolysis also results in a bitter taste making them less palatable. Therefore, clinicians must balance between taste and tolerability when selecting the most suitable formula for their patients. In children with atopic eczema, extensively hydrolyzed whey formula had similar impact on the severity of eczema and growth compared with amino acid formula [41]. In IgE-mediated CMPA children under 6 months with low risk of anaphylactic reactions, extensively hydrolyzed formulas are the first treatment choice [8, 43-45]. As hypoallergenic formulas contain small amount of beta-lactoglobulin, infants reacting to breast milk may not be able to tolerate hypo-allergenic formulas including an extensively hydrolyzed whey or an extensively hydrolyzed casein formula[45]. See Table 9 for dietary treatment options per clinical presentations of CMPA.

6.2.3.Amino Acid Formula

Amino acid formulas are the most suitable formulas for CMPA but often reserved due to their high cost and poor palatability. Children who are highly sensitized to cow's milk may react to residual cow's milk protein in extensively hydrolyzed formulas, and amino acid formulas will be warranted [43-45]. In children with IgE-mediated CMPA at high risk of anaphylaxis, severe non-IgE mediated CMPA including allergic eosinophilic oesophagitis, enteropathies, food protein-induced enterocolitis syndrome(FPIES), or in exclusively breast fed infants with allergic symptoms, an amino acid formula is recommended over extensively hydrolyzed milk formula[8, 41-45]. If CMPA is not resolved then use of extensively hydrolyzed formulas should be combined with amino acid formula. See Table 9 for dietary treatment options per clinical presentations of CMPA.

6.2.4.Soy formula

Soy based infant formulas are nutritionally complete substitutes to cow's milk formulas [45] but may not be suitable for treatment of CMPA for various reasons. While most infants with CMPA can tolerate soy based formulas, about 10-14% of CMPA infants are sensitized to soy especially in infants less than 6 months old [43] . In addition, there have been concerns about the effect of soy formulas on infant's sexual development due to its high phytoestrogen content. Therefore, most guidelines do not recommended using soy formula as a milk substitutes in infants less than 6 months old [41, 43-45] , although other guidelines do not have this recommendation [8, 42]. Soy formula can be considered when extensively hydrolyzed formulas are not tolerated in infants older than 6 months and without soy allergy. See Table 9 for dietary treatment options per clinical presentations of CMPA.

Table 8. Cow's Milk Formula Substitution Available in Hong Kong for CMPA Infants

Brands	Protein Source	Carbohydrate and Fat Sources	Contents (per 100ml)
Extensively Hydrolyzed Casein Formula			
Nutramigen Lipil (Mead Johnson)	Hydrolyzed casein	Palm, coconut, soya and high oleic sunflower oil. Glucose syrup, modified corn starch, fructose. Lactose free.	Energy 68 Kcal Protein 1.9 g Calcium 77 mg Iron 1.22 mg
Extensively Hydrolyzed Whey Formula			
Alfare (Nestle)	Hydrolyzed Whey	Vegetable Oil, 40% MCT. Corn Maltodextrin, Potato Starch. Lactose Free	Energy 70 Kcal Protein 2.1 g Calcium 54 mg Iron 0.7 mg
Nutrifant Pepti (Danone Nutricia)	Hydrolyzed Whey	Vegetable Oil, Maltodextrin, GOS	Energy 67 Kcal Protein 1.6 g Calcium 47 mg Iron 0.53 mg
Pepti-Junior (Cow and Gate)	Hydrolyzed Whey	Vegetable oil and fish oil; 50% MCT. Glucose syrup. Lactose content insignificant.	Energy 66 Kcal Protein 1.8 g Calcium 50 mg Iron 0.8 mg
Amino Acid Formula			
Neocate LCP (Nutricia SHS)	Amino Acids	Coconut, canola and sunflower oil. Glucose syrup. Lactose free.	Energy 67 Kcal Protein 1.8 g Calcium 65.6 mg Iron 1.0 mg
Neocate Advance (Nutricia SHS)	Amino Acids	Coconut, high oleic sunflower oil and canola oil Glucose syrup. Lactose free.	Energy 100 kcal Protein 2.5 g Calcium 50 mg Iron 0.62 mg
Soya Formula*			
Nursoy (Wyeth)	Soy protein isolate	Vegetable oils, soy lecithin Corn Syrup Solids Lactose Free	Energy 67 Kcal Protein 1.8 g Calcium 67 mg Iron 0.8 mg
Isomil 1 (Abbott)	Soy protein isolate	High oleic sunflower oil, coconut oil, soy oil Hydrolyzed corn starch, sucrose Lactose Free	Energy 68 Kcal Protein 1.7 g Calcium 71 mg Iron 1.0 mg
Isomil 2 (Abbott)	Soy protein isolate	High oleic sunflower oil, coconut oil, soy oil Hydrolyzed corn starch, sucrose Lactose Free	Energy 68 Kcal Protein 1.7 g Calcium 77 mg Iron 1.0 mg

***Soy formulas should not be used in infants <6 months old or in suspected soy allergy.**

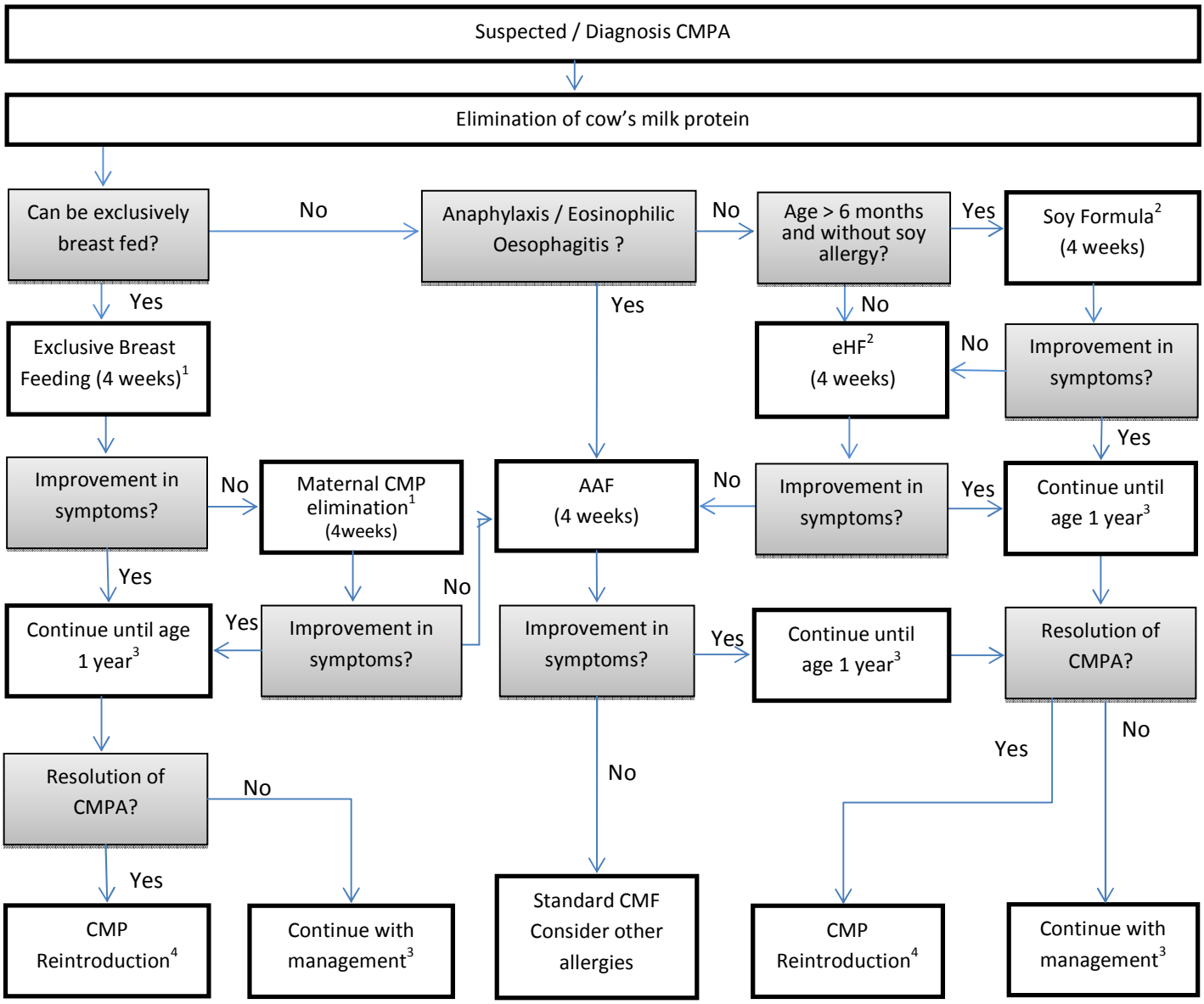
Table 9 Dietary Treatment Options for CMPA based on Clinical Presentations			
Clinical Presentation	Treatment options		
	First choice	Second Choice	Third Choice
IgE-Mediated			
Anaphylaxis	AAF	EHF	SF
Acute urticaria or angioedema	EHF or SF [1]	AAF	
Asthma	EHF or SF [1]	AAF	
Rhinitis	EHF or SF [1]	AAF	
Oral / Gastrointestinal Symptoms	EHF or SF [1]	AAF	
Non-IgE Mediated			
Allergic Eosinophilic Esophagitis (EoE)	AAF		
Atopic Dermatitis	EHF	AAF or SF [1]	
Gastroesophageal Reflux Disease (GERD)	EHF	AAF	
Cow's Milk Protein-induced Enteropathy	EHF	AAF	
Food Protein-induced Enterocolitis Syndrome (FPIES)	EHF	AAF	
Cow's Milk Protein-induced Gastroenteritis and Protocolitis	EHF	AAF	
Severe Irritability (Colic)	EHF	AAF	
Constipation	EHF	AAF	
Milk-induced Chronic Pulmonary Disease (Heiner's Syndrome)	EHF	AAF	

EHF = Extensively Hydrolyzed Formula; AAF= Amino Acid Formula; SF = Soy Formula

1. Soy formula can be used if eHF is unavailable or unpalatable in "babies older than 6 months and without soy allergy". Partially hydrolyzed formula, lactose free milk formula, goat formula should not be used for CMPA treatment.

An algorithm for management of Cow's Milk Protein Allergy is shown in figure 4 below.

Figure 4. IgE-Mediated and Non-IgE-Mediated Cow's Milk Protein Allergy Treatment Algorithm [8, 41, 43-45]



CMP = cow's milk protein; CMPA = Cow's milk protein allergy; AAF = Amino acid formula; eHF = Extensively hydrolyzed formula; CMF = cow's milk formula;

1. Breast feeding mothers should exclude all products containing CMP from their diet and take calcium supplements if baby is symptomatic while exclusively breastfed. Infants 6 months or older receiving breast milk as their main feed should be given vitamin D supplementation.
2. Soy formula can be used if eHF is unavailable or unpalatable in babies older than 6 months and without soy allergy. Partially hydrolyzed formula, lactose free milk formula, and goat formula should not be used for CMPA treatment.
3. CMPA status should be re-evaluated every 6 to 12 months.
4. CMP shall be reintroduced systematically as CMPA spontaneously resolved.

6.2.5.Unsuitable formulas

6.2.5.1. Partially Hydrolyzed formula

Partially hydrolyzed formulas have been studied recently for their preventive role in cow's milk protein allergy and eczema. The German Infant Nutritional Intervention [50] has shown that partially hydrolyzed formulas are linked to a significantly lower risk for atopic dermatitis in infants with a hereditary risk for allergy. However, partially hydrolyzed formulas are not considered hypoallergenic and should not be used for treating CMPA [8, 41, 43-45]

6.2.5.2. Goat milk

Goat's milk formulas have been widely advertised as a cow's milk substitute for CMPA. However, since goat's milk has very similar homology and approximately a 90% cross-reactivity level to cow's milk [41, 45], approximately 95% of children with CMPA react to goat's milk [4]. Therefore, goat's milk formulas are not recommended for the management of CMPA [41, 44, 45]. Other studies have suggested that fresh goat's milk can increase risk for hypernatremia and magaloblastic anemia in children due to its high sodium and low folic acid contents [51].

6.2.5.3. Other non-dairy drinks with calcium

There is a great variety of non-dairy milk drinks available in the market. These are usually made from soy, coconut, various tree nuts such as almond or hazelnut, or various grains such as oat, rice or quinoa. While these beverages are free from cow's milk protein, they may not be nutritionally complete and suitable as a cow's milk replacement [45]. These drinks often have poor nutritional values compared to infant formulas, and thus should not be used for management of CMPA in infants. For children beyond the age of 12 months and adults, these drinks can be used as substitutes with nutritional assessment and monitoring on energy, protein and calcium intake [45].

6.3. Reading food labels for a milk free diet

In order to avoid persistent symptoms, milk avoidance must be effective and complete. Cow's milk protein is widely used in different foods, making its avoidance very difficult. It is very important for patients and family to read food labels carefully for milk or milk-related ingredients. Consultation from a dietitian is helpful in informing everyday choices for children with CMPA [41]. Milk and milk products are required to be labeled in all packaged foods by the HK Labeling Guidelines on Food Allergens, Food Additives and Date Format [52]. Cow's milk can either be consumed on its own or as different ingredients in many different foods. A list of the names for milk and milk-related ingredients are shown in Table 10. Cow's milk and related ingredients are used very frequently in many foods. See a list of possible milk-containing foods in Table 11.

Table 10. Cow's Milk and Related Food Ingredients
• **Milk / Cow's Milk / Dairy / Pasteurized Milk / UHT Milk**
• **Milk Solids / Non-Fat Milk Solids / Non-Fat Dry Milk / Milk Formula**
• **Animal milk (goat milk,**
• **Yogurt / Yogurt Drink / Greek Yogurt / Frozen Yogurt**
• **Evaporated Milk / Condensed Milk**
• **Sour Cream / Sour Milk**
• **Cheese / Cream Cheese / Cheese Powder / Curds**
• **Butter / Butter Fat / Butter Oil / Buttermilk / Butter acid / Butter esters**
• **Clarified Butter / Ghee / Margarine**
• **Cream / Artificial cream / Creamer**
• **Ice-cream / Ice Milk / Gelato**
• **Milk Protein / Hydrolyzed Milk Protein**
• **Whey / Whey Solids / Whey Powder**
• **Hydrolyzed Whey Protein / Hydrolyzed Whey Sugar**
• **Casein / Caseinate / Hydrolyzed Casein**
• **Lactalbumin / Lactoglobulin / Bovine Serum Albumin**

Table 11. Foods Often Containing Milk Ingredients	
Baked goods	• Cakes /Biscuits / Pastries / Pies / Tarts / Scones • Waffles / Eggettes / Egg Tarts • Breads / Cream Puffs /
Desserts	• Puddings / Mousse / Panna Cotta / Cheesecakes • Ice cream / Frozen yogurt / Sherbet • Chinese Desserts / Double boiled Eggs or Milk
Snacks	• Chocolates / Soft Candies • Crackers / Pretzel sticks / Sour cream or cheese flavor chips
Meat, poultry, fish	• Processed Meats / Hams / Sausages / luncheon meats • Batter-fried meats or fish
Beverages and soups	• Instant Soups / Canned soups • Espresso drinks (cappuccino, latte, mocha) • Instant 3-in-1 Drinks / Hot chocolate • Vitasoy Soy Drinks • Coffee Creamers / Coconut cream /
Condiments, sauces and Spreads	• Sauce Mix / Gravies • Vegetable Margarines

6.4. Beef

Beef protein has been known to have cross-reactive properties with cow's milk protein. While beef allergy implies CMPA in most cases, CMPA does not imply beef allergy [41]. Industrial treatment may have modified the allergenic property of beef, and thus make it tolerable to most CMPA patients [53]. Therefore, total avoidance of beef by all CMPA is not necessary. Clinicians should assess each patient's tolerance to beef and advise on avoidance as appropriate.

6.5. Medications and supplements

Some medications and supplements are manufactured with lactose as an inactive ingredient, while lactose (milk sugar) can be easily contaminated with cow's milk protein [45]. Therefore, caution is warranted when prescribing medication for patients with severe CMPA.

6.6. Immunotherapy

Although the majority of children outgrow their CMPA, some of them will remain allergic to milk. Traditionally, strict avoidance is the only treatment for these children. However, accidental exposure remains unavoidable and posts risks for allergic reactions. Therefore, research has focused on developing new treatment methods for food allergies.

Oral immunotherapy, or oral tolerance induction, has opened a treatment option for CMPA with promising results [45]. Oral immunotherapy has been studied in CMPA, and a significant percentage of the children treated can be desensitized and be fully tolerant to milk [54, 55]. A recent systematic review and meta-analysis showed that children on oral immunotherapy are 10 times more likely to achieve full tolerance (>150 ml milk) and 5 times more likely to achieve partial tolerance (5-150 ml milk) compared to strict avoidance [56, 57]. Maintenance of tolerance to cow's milk was shown to be effective with a consumption of 150-200 ml milk twice weekly [58].

Despite its effectiveness, there are risks associated with oral immunotherapy and precautions must be taken. Studies indicated that adverse reactions can happen in up to one in every 6 doses, while these reactions are mostly mild to moderate reactions [45] Nevertheless, severe reactions while rare have been reported. One study reported that epinephrine administration is needed in one in every eleven children [57]. There is great variation in milk immunotherapy protocols, which can affect risk of adverse reactions. In addition, long-term tolerance and safety has not been determined for oral immunotherapy, and most guidelines do not recommend oral immunotherapy for routine clinical practice [41, 44-46].

7. Re-evaluation and reintroduction

7.1 Re-evaluation

Most CMAP naturally resolves during childhood [8, 41, 45], but the actual timing varies greatly. Infants and children with CMPA should be re-evaluated periodically (6-12 monthly) for their tolerance toward cow's milk protein [8, 41, 45]. Children who have reduced sIgE to cow's milk with development of clinical tolerance to cow's milk are suitable for reintroduction.

7.2 Reintroduction

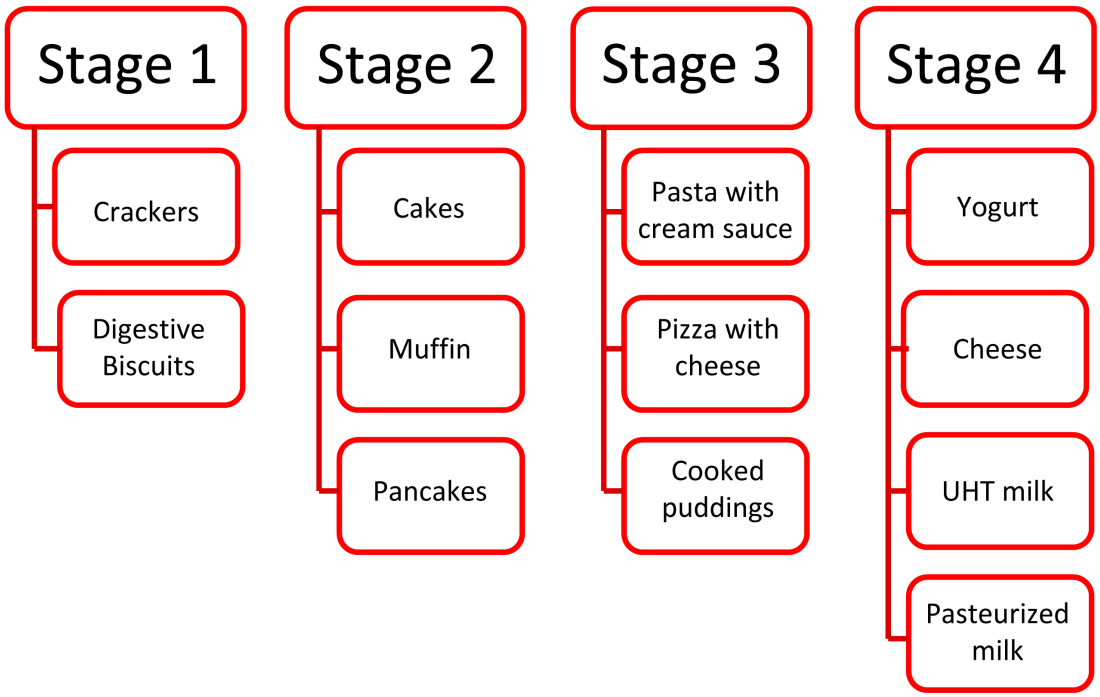
When children have spontaneous remission of cow's milk allergy, milk can be reintroduced into their diet. High heat in the cooking process such as baking can reduce the allergenicity in cow's milk protein, [12] and its allergenicity is further reduced when binding to other ingredients during food processing, such as wheat. Study has shown that 75% of children with CMPA were able to tolerate baked milk products [59]. For children with only mild symptoms, with no reaction to milk over the past 6 months, and with a significant reduction of sIgE to milk, home milk reintroduction may be attempted under clinical supervision [45]. Reintroduction should proceed as tolerated, as rapid high-dose exposure may result in severe reaction.

7.2.1 Milk ladder

When reintroducing milk, one should always start with foods containing small amount of baked milk with a wheat-milk matrix, such as crackers and biscuits [45, 59]. Patient should start with a small portion of the food, i.e. one bite of a biscuit, then proceed as tolerate to larger amount. When most foods within one stage are tolerated, the patient may try foods with higher amount of baked milk, such as cakes and pastries, then to milk less extensively cooked, such as cheese sauce or pizza, and finally to boiled and fresh milk. A dietitian can provide personalized advice on specific foods within each stage according to each patient's dietary habits. Please see Figure 5 for an example of a milk ladder. General tips on using a milk ladder for milk reintroduction:

- Always reintroduce milk from stage 1, do not proceed to the next stage if any slight reaction occurs (e.g. milk rashes, tummy ache)
- Only try a small amount the first day and then try a larger portion the following day. If tolerated, the food can be gradually increased to a normal portion appropriate for your child's age.
- Repeat this process for other foods containing milk within the same stage.
- Patient should discuss with their doctors or dietitian for advancing to the next stage if your child successfully tolerates most foods in the stage.

Figure 5: The Milk Ladder



8. Conclusions

Cow's milk protein allergy is responsible in HK for about 10% of food induced allergic reactions. It can present with cutaneous, respiratory and gastrointestinal symptoms which occur immediately or after many hours. In the worst case scenario allergic patients may suffer potentially life threatening anaphylaxis.

Diagnosis is dependent on a detailed history and examination supported by skin tests or blood tests to detect the presence of sIgE to cow's milk proteins. The gold standard for diagnosis is the oral challenge test in equivocal cases. However this should be done with care under supervision in an environment where immediate resuscitation facilities are available in case of severe reactions following challenge.

The mainstay of management is elimination of cow's milk with use of appropriate milk substitutes. A detailed description of the commonly used substitutes available in HK is provided and an algorithm has been produced to explain the treatment options for this condition. Finally advice is provided about how to reintroduce milk products after spontaneous resolution of the allergy.

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