

Cows' Milk Protein Allergy Diagnosis in Infants

A clinical conundrum?



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Over the years non-immunoglobulin-E (non-IgE) cows' milk allergy (CMA) diagnosis in infants has remained topical. Those familiar with the area will be aware of the criticisms of some early guidelines and their association with infant formula companies. However, the lack of home challenge in practice has been identified as a central issue.¹ The reality of management shines a light on a range of expectations; from symptom control to avoiding delayed or improper diagnosis, minimising costs, and unnecessary formula use. Due to time- and resource-poor clinical teams, these can be tricky to juggle.

Non-IgE CMA is a phenomenon of recent decades and what is known today has moved forward significantly, owing to the availability of more evidence. Whilst much is understood, this article looks at recent evidence and if there is consensus toward a more precise diagnosis.

Prevalence of CMA symptoms in infants

Difficulties in the diagnosis of non-IgE CMA stem from the non-specific associated symptoms in infants. The Enquiring About Tolerance (EAT) cohort recently published a secondary data analysis on the frequency of symptoms associated with non-IgE CMA in infants (n=1303) exclusively breastfed until 6 months age.²

Symptoms were defined by the international Milk Allergy in Primary Care (iMAP) guideline (see **Table 1**).³ An average of 25.3% of infants had ≥ 2 mild-moderate symptoms of non-IgE CMA between 3-12 months age which peaked at 3 months (37.6%). Unfortunately, infants with symptoms prior to 3 months age were excluded, which fundamentally excluded a big group.²

On average per month, blood in stools was the least commonly reported symptom (0.2%). Whereas reflux was the most common (45.8%), which staggeringly peaked around infants 3 months age (78.1%). Colic (or persistent irritability) was reportedly highest at 3 months age (27.8%) and appeared to reduce thereafter. Severe symptoms were less commonly reported.²

Table 1: Summary of International Milk Allergy in Primary Care guidelines – diagnosis of non-IgE cows' milk allergy³

	Mild-moderate	Severe
Criteria	Symptoms are mostly 2-72 hours after ingestion of cows' milk protein. Usually in formula fed infants at onset of formula feeding. Rarely in exclusively breastfed infants. Usually several of the following symptoms will be present. Symptoms persisting despite first-line measures are more likely to be allergy-related (e.g. atopic dermatitis or reflux).	Symptoms are mostly 2-72 hours after ingestion of cows' milk protein. Usually in formula fed infants at onset of mixed feeding. Rarely in exclusively breastfed infants. One but usually more of these severe, persisting & treatment resistant symptoms.
Gastro-intestinal (GI)	Persistent irritability – colic Vomiting – reflux – gastro-oesophageal reflux disease Food refusal or aversion Diarrhoea-like stools – abnormally loose +/- more frequent Constipation – especially soft stools, with excess straining Abdominal discomfort, painful flatus Blood and/or mucus in stools in otherwise well infant	Diarrhoea Vomiting Abdominal pain Food refusal or aversion Significant blood and/or mucus in stools Irregular or uncomfortable stools +/- faltering growth
Skin	Pruritus (itching), erythema (flushing) Non-specific rashes Moderate persistent atopic dermatitis	Severe atopic dermatitis +/- faltering growth

Milk-related symptoms were reported in 2.2% (per month) in infants 4-12 months age, but these were not differentiated by severity or type of symptoms. Overall, 33 infants were prescribed an extensively hydrolysed or amino-acid formula. However, the use of non-cows' milk formula was managed outside of the EAT research team.² Furthermore, the need for specialised formula was not refuted by double-blind placebo-controlled food challenge.

Interpretations of this data are limited to the EAT cohort as mixed-fed or infants <3 months were not included, which does not reflect the general infant population in the UK. However, it demonstrates an imperative case that guidelines such as iMAP may construe common symptoms as CMA.

A CMA symptom awareness tool

Developed in 2015, and funded by Nestlé Health Sciences, *CoMiSS* (Cow's Milk-related Symptoms Score) is an awareness tool used to identify probable symptoms of CMA in infants up to 6 months age.⁴ As many guidelines lack detail on the symptoms suggestive of CMA, the tool differs. Explicit descriptions of symptoms are rated by severity and a *CoMiSS* of ≥ 12 is suggestive of likely CMA (range 0-33).⁴ *CoMiSS* alone does not replace oral food challenge (OFC) or diagnose CMA.⁵ Criteria for scoring include crying frequency, regurgitation episodes, stool consistency, skin and respiratory severity (see **Table 2**).⁶

An expert panel recently published data pooled from existing studies on *CoMiSS* in healthy and allergic infants under 6 months age.⁷ *CoMiSS* of ≥ 12 ranged from 0-4.9%, in healthy infants (median *CoMiSS* was 3-4). Age demonstrated an inverse relationship with *CoMiSS* (prominently for scores on crying and regurgitation). This strikes similarities to observations from the EAT cohort, although these infants were included from birth to <6 months age and findings are from few studies (n=5) with small numbers.⁷

In allergic infants (n=22 studies) comparison was difficult due to differences in design and inclusion criteria. Where reported, sensitivity and specificity for CMA diagnosis were between 20-77% and 54-92% respectively. Observed reductions in *CoMiSS* were larger in those with a positive OFC, and a *CoMiSS* reduction by <6 was seen with the elimination of cow's milk. However, not all studies performed OFC to confirm the clinical response to cows' milk elimination.⁷

The score threshold has been updated and lowered to ≥ 10 .⁶ The authors point out that its use should be supervised by a healthcare professional, and that caution is necessary to avoid misdiagnosis of other potentially severe disorders. Long-term studies that follow the clinical course of patients identified through *CoMiSS* are required to understand its practical use as part of the diagnosis of CMA.

Table 2: Cows' Milk-related Symptoms Score Tool – detection of probable cows' milk allergy⁶

Symptom		Score	
Crying* Assessed by parents & without any obvious cause ≥ 1 week duration	≤ 1 hr/day	0	
	1-1.5 hr/day	1	
	1.5-2 hr/day	2	
	2-3 hr/day	3	
	3-4 hr/day	4	
	4-5 hr/day	5	
	≥ 5 hr/day	6	
Regurgitation* ≥ 1 week duration	0-2 episodes/day	0	
	≥ 3 - ≤ 5 x of volume <5 mL	1	
	>5 episodes of >5 mL	2	
	>5 episodes of \pm half of the feed in < half of the feeds	3	
	Continuous regurgitations of small volumes >30 min after each feed	4	
	Regurgitation of half to complete volume of a feed in at least half of the feeds	5	
Regurgitation of the complete feed after each feeding	6		
Stools* Brussels Infant and Toddlers Stool Scale (BITSS) ≥ 1 week duration	Hard stools	4	
	Formed stools	0	
	Loose stools	4	
	Watery stools	6	
Skin symptoms	Atopic eczema ≥ 1 week duration	0-6	
		Head-neck-trunk	Arms-hands-legs-feet
	Absent	0	0
	Mild	1	1
	Moderate	2	2
	Severe	3	3
Acute urticaria* and/or angioedema* (no 0/yes 6)		0-6	
Respiratory symptoms* ≥ 1 week duration	No respiratory symptoms	0	
	Slight symptoms	1	
	Mild symptoms	2	
	Severe symptoms	3	

* In the absence of infectious disease

Source: This table has been adapted from *Vandenplas Y, et al. (2022). The Cow's Milk Related Symptom Score: The 2022 Update. Nutrients, 14(13): 2682*. This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license: <https://creativecommons.org/licenses/by/4.0>.

Quality of existing CMA guidelines

As previously mentioned, guidelines for CMA have been under scrutiny due to their associations with infant formula companies. The World Allergy Organization (WAO), Diagnosis & Rationale Against Cow's Milk Allergy (DRACMA) group performed a quality appraisal of guidelines published within the last 10 years (up to 2020).⁸ The following domains in each guideline were appraised: (I) *scope and purpose*; (II) *stakeholder involvement*; (III) *rigour of development*; (IV) *clarity of presentation*; (V) *applicability*; (VI) *editorial independence*.

Of the 12 guidelines included, the median of all domains was 60%. The lowest scoring domains were: *rigour of development* (median 30%), where there was little discussion of the strengths and limitations of evidence; *stakeholder involvement* (median 63%), where there was a lack of involvement of the target population; *applicability* (median 68%), where there was a lack of practical application or barriers described.⁸ Interestingly, iMAP guidance scored 50% overall, where the rigour of development was the lowest domain (28%). Only 3 guidelines achieved 100% in ≥3 domains: the National Institute for Health and Care (NICE) (2019) (which achieved 100% across all domains), the British Society of Allergy and Clinical Immunology (BSACI) (2014) and WAO (2010).⁹⁻¹¹

What is interesting is the comparison of diagnosis recommendations for non-IgE CMA across the guidelines (see summary in **Table 3**). Clinical history and physical examination were predominant diagnostic recommendations for non-IgE CMA across the majority of guidelines including iMAP,³ BSACI,¹⁰ NICE⁹ and the European Society of Gastroenterology, Hepatology and Nutrition (ESPGHAN).¹² However, variations in the guidelines exist in the components of clinical history and physical examination, or they are not explicitly described, and what constitutes probable symptoms of CMA. Differences also become apparent for the duration of elimination of cows' milk, including for the types of symptoms or severity, in some guidelines.

Although guideline quality was reasonable across the board, this clearly demonstrates variation in the practice of non-IgE CMA diagnosis. This may reflect the changes in knowledge and evidence available at the time each guideline was published. Guideline updates are expected, at least by the WAO, which are eagerly anticipated.

Table 3: Summary of infant non-IgE cow's milk allergy guidelines⁸

	Clinical history and physical examination	Elimination-reintroduction	Duration of elimination and setting
WAO 2010	No official recommendation	No official recommendation	No official recommendation
ESPGHAN 2012	Recommended	Recommendation for use of CMF diet and, in case of resolution of symptoms, confirmation with standardised OFC (not if clear immediate type reaction or anaphylaxis)	1-2 weeks if early and late reactions (i.e. vomiting, atopic eczema) 2-4 weeks if gastrointestinal symptoms (i.e. diarrhoea, constipation) If the history suggests an immediate reaction, only 3 to 6 days If delayed reactions are suspected (e.g. allergic proctocolitis), then up to 14 days Under medical supervision
BSACI 2014	Recommended (including severity evaluation)	Recommendation for use of CMF diet and, in case of resolution of symptoms, confirmation with OFC	At least 6 weeks in infants with eczema Reactions to baked milk are less likely to be severe, and tolerance to baked milk is developed earlier than to fresh milk (home baked CM reintroduction) In hospital protocol provided
iMAP 2019	Recommended (specifically allergy-focused)	Mild to moderate non-IgE CMA: Re-introduction of CM at home. CMA is confirmed only if symptom improves after return to elimination diet after home re-introduction Severe non-IgE CMA: Referral to local paediatric allergy service (also if no improvement despite elimination diet and CMA still suspected) and dietitian	2-4 weeks Mild to moderate non-IgE CMA: home reintroduction with CM
NICE 2019	Recommended (specifically allergy-focused and including: nutritional status and growth, any signs of a clinical reaction, or comorbid conditions such as atopic eczema, asthma, and/or allergic rhinitis, or suggesting an alternative diagnosis)	Recommendation for use of CMF diet and, in case of resolution of symptoms, confirmation with OFC (home reintroduction) CMA confirmed only if symptom improves after return to elimination diet after OFC If CMA still suspected despite a lack of response to diet, referral to specialist for advice to eliminate other foods	2-4 weeks Home reintroduction with CM (return to regular maternal or infant's diet, or standard CM formula)

Key: BSACI: British society of allergy and clinic immunology; CM: cow's milk; CMA: cow's milk allergy; CMF: cow's milk free; ESPGHAN: European society of gastroenterology, hepatology and nutrition; iMAP: International milk allergy in primary care; NICE: National institute for health and care; non-IgE: non-immunoglobulin-E; OFC: oral food challenge; WAO: World allergy organization.
Source: This table has been created/adapted from Strö yk A, et al. (2022). *World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - IV - A quality appraisal with the AGREE II instrument. World Allergy Organ J.*; 15(2): 100613. This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license: <https://creativecommons.org/licenses/by/4.0>.

A new Delphi consensus recommendation on CMA detection

A recent Delphi study with international multidisciplinary experts put forward consensus recommendations which aimed to minimise over- and under-diagnosis of CMA in children under 2 years.¹³ The recommendations comprise restrictive criteria to indicate the symptoms suggestive and non-suggestive of CMA (see **Table 4** for a summary).¹³

The consensus differentiates between symptoms in breastfed and formula-fed infants, which is unseen in other guidelines. Furthermore, differential diagnoses are given for various symptoms including blood in stools. CMA is not listed as probable with stool changes, respiratory

symptoms or aversive feeding unless there is a temporal relationship with milk ingestion. Faltering growth in the absence of protein-losing enteropathy is not considered in the guideline as probable for CMA.¹³ In clinical practice this may be challenging to follow as protein-losing enteropathy is characterised by low albumin, which is not readily assessed and subject to other factors.

The authors recognise further work is required to analyse the safety of the consensus recommendations.¹³ Unfortunately, certain specialists were excluded due to conflicts of interest with infant formula companies.

Take home messages

The shortcomings of non-IgE CMA diagnosis in guidelines have been highlighted here,

in terms of differences in the suggestive symptoms and diagnostic factors. Newer guidelines such as NICE⁹ and iMAP³ appear more specific, and awareness tools such as CoMiSS may find a useful place in a busy clinical practice.⁶ However, the commonality of CMA-suggestive symptoms in healthy infants and their overlap with other diagnoses are also apparent, which have recently been set out by new consensus recommendations.¹³ As such, it is unsurprising that CMA diagnosis is challenging. The need for refined, validated and coherent guidelines is paramount to support the proper implementation. It seems we are edging closer but there is a long way to go. When reached, it will enable better cost-effective care, minimise unnecessary treatment (or its delay), and enable greater patient-caregiver satisfaction.

Table 4: Delphi consensus – suggestive and non-suggestive symptoms of cows' milk allergy¹³

Symptoms suggestive of cows' milk allergy		
In exclusively breastfed	In non-exclusively breastfed	If delayed gastrointestinal or skin symptoms (within 2-48 hrs of ingesting CM)
Consider CMA if crying, vomiting, eczema, and: i) Faltering growth AND protein-losing enteropathy ii) Biopsy findings of eosinophilic gastrointestinal disorder associated with non-IgE CMA	Consider CMA if crying, vomiting, eczema, and: i) Faltering growth AND protein-losing enteropathy ii) Biopsy findings of eosinophilic gastro disorder associated with non-IgE milk allergy iii) Visible blood in stools (once daily) for at least 3 consecutive days	Consider CMA if any of the below are reproducible with CM, and CM is not tolerated in other forms: i) Skin involvement such as severe eczema ii) Gastrointestinal symptoms such as severe vomiting iii) Behavioural symptoms such as crying
Symptoms not suggestive of cow's milk allergy		
In breastfed or formula-fed without acute, delayed or chronic symptoms	If acute symptoms (erythema, urticaria, angioedema, vomiting) within 2 hrs of ingesting CM)	Other differential diagnosis
CMA does not need to be considered if any of the below alone or in combination: i) Occasional blood in stools (no daily, visible blood in stool) ii) Other colour changes in stool iii) Consistency changes in stools iv) Frequency changes in stools v) Averse feeding vi) Nasal or respiratory involvement	CMA does not need to be considered if: i) Similar symptoms without milk ingestion ii) Viral infection or reflux seems more likely iii) Symptoms not reproducible on CM ingestion	CMA is sometimes considered among the differential diagnosis of: i) Bile-stained vomiting (intestinal malrotation) ii) Faltering growth iii) Blood in stools (Infection, clotting disorders, intestinal abnormalities) iv) Eczema management involves avoiding physical triggers, emollient therapy and topical anti-inflammatory v) Colic/crying are common in healthy and if severe can be related to a range of other disorders
<p>Key: CM: cow's milk; CMA: cow's milk allergy; non-IgE: non-immunoglobulin-E This table has been created/adapted from Allen HI, et al. (2022). Detection and management of milk allergy: Delphi consensus study. <i>Clin Exp Allergy</i>; 52(7): 848-5. This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license: https://creativecommons.org/licenses/by/4.0.</p>		

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