


**2023 ESPGHAN POSITION PAPER ON COW MILK ALLERGY (CMA)**

YVAN VANDENPLAS MD, PhD



1

---

---

---

---

---

---

---

---

**Disclosures**

- Y Vandenplas has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for:
  - Abbott Nutrition, Alba Health, Arla, Ausnutria, Biogaia, By Heart, CHR Hansen, Danone, ELSE Nutrition, Friesland Campina, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson Nutrition, Pileje, United Pharmaceuticals (Novalac)
  - **None pose any conflict of interest for this presentation**

*The opinions reflected in this presentation are those of the speaker and independent of Nutricia North America*



2

---

---

---

---

---


---

---

---

**Learning Objectives**

- Following this presentation, participants will be able to:
  - Summarize the updated ESPGHAN recommendations for diagnosing and managing of CMA
  - Describe the role of hydrolyzed, amino acid, rice, and soy formulas for the management of CMA
  - Detail the benefits of lactose for formula fed infants



3

---

---

---

---

---

---


---


---

**An ESPGHAN position paper on the diagnosis, management and prevention of cow's milk allergy.**

*Vandenplas Y, Broekaert I, Domellöf M, Indrio F, Lapillonne A, Pienar C, Ribes-Koninckx C, Shamir R, Szajewska H, Thapar N, Thomassen RA, Verduci E, West C.*

*J Pediatr Gastroenterol Nutr.* 2024;78(2):386-413  
doi: 10.1097/MPG.0000000000003897.

Scan here to access the article → 



4

---

---

---

---

---


---

---

---

**What's New?**

- Available evidence on the role of dietary practice in the prevention, diagnosis, and management of CMA
- The impact of CMA on nutrition, growth, cost, and QoL
- The roles of hydrolyzed rice formula, soy and vegetable infant feeds in the diagnostic and therapeutic approaches to CMA.



5

---

---

---


---

---

---

---

---



**ESPGHAN POSITION STATEMENTS ON DIAGNOSIS AND MANAGEMENT OF COW MILK ALLERGY**

**DIAGNOSIS**  
MANAGEMENT

6

---

---

---

---

---

---

---

---




**The Cow's Milk-Related Symptom Score (CoMISS™): A Useful Awareness Tool<sup>1</sup>** Diagnosis

CoMISS™ cannot be considered as a stand-alone CMA diagnostic tool, but as a useful awareness tool for CMPA as well as for monitoring symptom improvement.

- CoMISS™ was developed as a clinical tool aimed at increasing health care professionals awareness of the presence and intensity of clinical manifestations possibly related to CM intake.
- Infants exhibiting symptoms possibly related to CM, present with a higher median CoMISS™ score than healthy infants - 6 to 13 (from 16 studies) versus 3 to 4 (from 5 studies) respectively.
- In those with CMA, 11 studies found a CoMISS™ score of  $\geq 12$  & predicted a favorable response to a CM-free diet; however, sensitivity and specificity varied.
- **A decrease of CoMISS™ score during a CM elimination diet was also predictive of seeing a reaction to the oral food challenge.**

1. Bajzerova K, et al. Nutrients. 2022 May 14;14(10):2059.




---

---

---

---

---

---

---

---

---

---

10


**Interpretation of the final score** Diagnosis

**INTERPRETATION OF THE TOTAL SCORE**

**Total score  $\geq 10$ :** May be suggestive of cows milk-related symptoms and could potentially be CMA.

**Total score  $< 6$ :** Symptoms are not likely to be related to CMA. Look for other causes.

The CoMISS® scoring form is not intended to be used as a diagnostic tool and should not replace an oral food challenge. CMA diagnosis should be confirmed by a 2 to 4 week elimination diet followed by an oral food challenge.




---

---

---

---

---

---

---

---

---

---

11

**CoMiss (Cow's Milk-related Symptom Score) Awareness tool for CMA**

Statement	Mean/median	Votes
The baseline Cow's Milk related Symptom Score (CoMISS) and its reduction during an elimination diet may be indicative for CMA, but is not diagnostic.	8.4/9	6; 7; 8 (2x); 9 (9x)

While CoMISS might increase awareness and thus favor over-diagnosis, it might as well decrease over-diagnosis since symptoms in at least two organ systems are needed

---

---

---

---

---

---

---

---

---

---

12

### Diagnosis of CMA – Cow’s Milk Elimination Diet

Diagnosis: Elimination Diet

**Diagnostic Cow’s Milk Elimination Diet**

- Allergy-focused clinical history – feeding history and personal and familial history of allergic disease.
- Physical exam


**Non-IgE-mediated CMA**

- Elimination diet typically requires 2-4 weeks before reintroduction
- Short term diagnostic elimination diet followed by reintroduction/OFC before embarking on a long-term elimination diet

**IgE-mediated CMA**

- Elimination diet typically requires 1-2 weeks before reintroduction

Statement	Mean/median	votes
In <b>IgE mediated allergy</b> , the response to the diagnostic elimination diet is to be expected within 1 to 2 weeks.	8.8/9	8 (2x); 9 (11x)
In <b>non-IgE mediated allergy</b> , the response to the diagnostic elimination diet is to be expected within 2 to 4 weeks.	8.7/9	7; 8; 9 (11x)



13

---

---

---

---

---

---

---

---

---


---

### Diagnostic Elimination Diet in Breastfed Infants

Diagnosis: Elimination Diet

In the exclusively breastfed infant, CMA is **rare**.

Statement	Mean/median	Votes
In rare cases when CMA is suspected in an exclusively breastfed infant, diagnostic maternal CM free diet for 2-4 weeks whilst continuing to breastfeed may be considered. In order to confirm the diagnosis, CM should then be reintroduced in the maternal diet with monitoring of symptoms.	8.8/9	8 (3x); 9 (10x)



14

---

---

---

---

---

---

---

---


---

---

### Formulas and the Elimination Diet

Diagnosis: Elimination Diet

- eHF
- AAF
- Rice
- Soy



15

---

---

---

---

---

---

---

---

---


---

### Diagnostic Elimination Diet in Non-Breastfed Infants

Diagnosis: Elimination Diet

- EHF is the first choice for CMA management.
- Preferable to use CM based eHFs

Statement	Mean/median	Votes
In formula fed infants, a CM derived extensively hydrolysed formula (eHF) is the first choice for a diagnostic elimination diet.	7.2/9	0 (2x); 7; 8 (3x); 9 (7)
Only CM derived eHFs tested in randomized clinical trials should be used.	8.6/9	7 (2x); 8; 9 (10x)
There are insufficient comparative trials to make a recommendation whether to use whey versus casein hydrolysates.	8.8 / 9	8 (3x); 9 (10x)



16

---

---

---

---

---

---

---

---

---

---


### Diagnostic Elimination Diet in Non-Breastfed Infants

Diagnosis: Elimination Diet

Subset of children where AAF may be indicated:

- Anaphylaxis
- Faltering Growth
- Multiple and Severe Complex GI Food Allergies
  - Acute and chronic severe FPIEs
- EoE not responding to exclusion diet
- Symptom persistence on eHF

Statement	Mean/Median	Votes
In formula fed infants, amino acid-based formula (AAF) for a diagnostic elimination diet should be reserved for severe cases or patients with severe malnutrition.	8.5 / 9	7; 8 (4x); 9 (8x)



17

---

---

---

---

---

---

---

---

---

---

### AAF as first-line has gradually become an international trend

Diagnosis: Elimination Diet

2009

Australia  
AAF Save medicare resources

2016

Brazil<sup>7</sup>  
AAF as First-line for diagnosis

2019

Turkish<sup>3</sup>  
AAF as First-line diagnosis

2017 2019

China  
AAF as First-line for diagnosis

1. Flooch A, et al. World Allergy Organ J. 2018;11(1):2.  
 2. Vanderplas Y, et al. Arch Dis Child. 2007;92(10):900-8.  
 3. Guer N, et al. Allergol Immunopathol (Madr). 2020;48(2):202-10.  
 4. Guent JF, et al. Curr Med Res Opin. 2009;25(2):339-49.  
 5. Morais MBd, et al. Journal of Medical Economics. 2016;1:21.

18

---

---

---

---

---

---

---

---

---


---

### Plant-Based Formulas and Liquid Feedings for Infants and Toddlers.

Vandenplas Y, et al. *Nutrients*. 2021 Nov 11;13(11):4026

Diagnosis: Elimination Diet

- Worldwide, rice is the most cultivated crop.
- Health care providers and parents are familiar with hydrolyzed rice-based infant formula for the treatment of CMA.
- Hydrolyzed rice infant formulas are present in many European countries since more than 30 years, and occupy a significant market share
  - (2018 in France : 5% of all formulas for children aged 0–3 years)



19

---

---

---

---

---

---

---

---

---

---


### Comparison of Rice Drink to Hydrolyzed Rice Formula (HRF)

Diagnosis: Elimination Diet

Per 100 kcal	Rice drink	HRF 1	HRF 2	HRF 3	Codex (Min-Max)
Calories (kcal/100 ml)	46	66	68	63	60-70
Protein (g)	0.9	2.7	2.5	2.2	1.8-3.0
Fat (g)	2.3	5.0	4.7	4.4	4.4-6.0
Carbohydrates (g)	18.2	11.0	11.9	12.2	9.0-14.0
Sugar (g)	11.8	1.4	0.8	1.0	-

Rice drink has lower calories, protein content and fat content than HRF.

**Rice drink is not adapted to infants and should NOT be used instead of rice hydrolysate formula.**



20

---

---

---

---

---

---

---

---

---

---

### Efficacy of HRF During CMA

Diagnosis: Elimination Diet

Author	Number	Groups	Results
Fiocchi et al.	18 infants : CMA and soy allergy	HRF	100% tolerance
Fiocchi et al.	100 children: CMA	Provocation test with HRF	All challenges negative
Reche et al.	92 infants: CMA	2 groups : 46 HRF 46 eHF	100% tolerance with HRF and 1 allergy to eHF
Vandenplas et al.	36 CMA	HRF	100% tolerance

Fiocchi A, et al. Clin Exp Allergy. 2003 Nov;33(11):1576-80. Fiocchi A, et al. Clin Exp Allergy. 2006 Mar;36(3):311-6. Reche M, et al. Pediatr Allergy Immunol. 2010 Jun;21(4 Pt 1):577-85. Vandenplas Y, et al. Eur J Pediatr. 2014 Sept;196(3):329-36.

21

---

---

---

---

---

---

---

---

---

---

### Considerations of Arsenic in Rice Formula

Diagnosis: Elimination Diet

- Infants fed with cows' milk formulas ingest approximately 0.11mg/kg per day of inorganic arsenic, >3 times higher than the estimated intake from breast milk.
- For Reche et al., arsenic content in a HRF (Blemil Arroz) 6.4 x lower than levels found in "rice milk" (drink) in the UK by Meharg et al.
- Meyer et al. studied HRFs in Europe (assessing the powder) for content on total/inorganic arsenic:
  - For any HRF consumed at normal volume (600 ml) intake, exposure would be 0.16- 0.23 µg/kg body weight.
  - Well below average exposure in EFSA data by for infants [0.24- 0.43 µg/kg] and toddlers [0.32- 0.45 µg/kg per]
  - Also > 10 fold less than WHO guidelines

**Arsenic levels in an average daily volume of HRF are 10-fold less than the WHO limits<sup>1</sup>**

Summary of rice formulas equating to an 8kg infant taking 600-800 ml per day.

Reche Pediatr Allergy Immunol 2010;21:577-85.  
[View at J Pediatr Allergy Immunol 2010](#)

22

---

---

---

---

---

---

---

---

---

---

### Soy

Diagnosis: Elimination Diet

- Soy infant formulas contain enzymatically hydrolyzed soy protein isolate
- ESPGHAN Committee on Nutrition & AAP
  - Recommended against the use of soy infant formula especially below the age of 6 months because of the risk of co-allergy
  - Age limit is no longer considered in 2024 ESPGHAN position paper

Agostoni C, et al. J Pediatr Gastroenterol Nutr 2009;49:112-25.  
[View at J Pediatr Gastroenterol Nutr 2009](#)

23

---

---

---

---

---

---

---

---

---

---

### Rice and Soy Statements

Diagnosis: Elimination Diet

Statement	Mean/median	Votes
Although less studied than CM based eHFs, rice hydrolyzed rice formulas can be considered as an alternative for a diagnostic elimination diet.	7.4/8	1; 5; 6; 7(2x); 8 (2x); 9 (6x)
Soy infant formula should not be used as the first choice for the diagnostic elimination diet but can be considered in some cases for economic, cultural, and palatability reasons.	7.6/9	0; 6; 7(2x); 8 (2x); 9 (7x)

Agostoni C, et al. J Pediatr Gastroenterol Nutr 2009;49:112-25.  
[View at J Pediatr Gastroenterol Nutr 2009](#)

24

---

---

---

---

---

---

---

---

---

---





25

---

---

---

---

---

---

---

---

Diagnosis: OFC		
Statement	Mean/median	Votes
In clinical practice the open OFC is clinically more feasible and practical than DBPCFC and is sufficient to confirm the diagnosis of CMA and the development of oral tolerance.	8.7/9	7:8 (2x); 9 (10x)
In IgE-mediated CMA, the OFC test should be supervised by trained medical health care professionals	8.8/9	7: 8 (1x); 9 (11x)

26

---

---

---

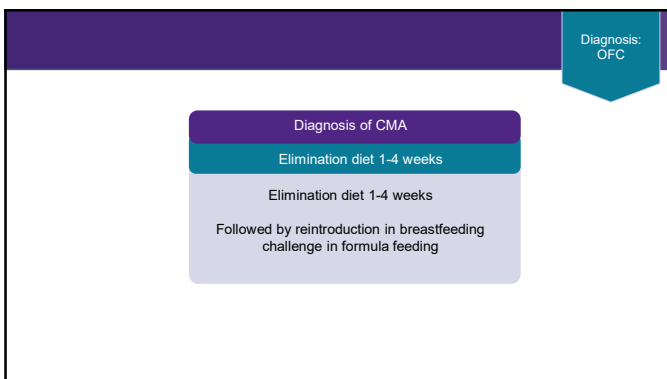
---

---

---

---

---



27

---

---

---

---

---

---

---

---

Diagnosis: OFC

Diagnosis of CMA

Elimination diet 1-4 weeks

Elimination of milk proteins for 4-6 weeks

followed by a challenge. Reduction in breastfeeding  
and increase in formula feeding

*But many caregivers refuse the OFC*

28

---

---

---

---

---

---

---

---

WHAT IS NEW TO THE GUIDELINES?

DIAGNOSIS  
MANAGEMENT

29

---

---

---

---

---

---

---

---

Management of Cow's Milk Allergy

Management

What is NOT an option?

University of Colorado Boulder | Children's Hospital Colorado | MJB

30

---

---

---

---

---

---

---

---

### Specialized Formulas for the Management of CMA

Management

- Various types of specialized formula exist to manage CMA
- **Hypoallergenic formulas** are cow's milk protein-based formulas in which the protein has been hydrolysed. These can be either partially hydrolysed formulas (pHF) or extensively hydrolysed formulas (eHF) depending on the level of hydrolysis and thus allergenicity. **eHF provide effective management for 90% of infants with CMPA. pHF are not intended for the dietary management of diagnosed CMPA.**
- **Non-allergenic or amino acid formulas (AAF)** are free amino acid-based, and are thus the least allergic option, commonly recommended for infants reacting to eHF i.e. 10% of infants with CMPA.

Kolekci S et al. J Pediatr Gastroenterol Nutr. 2012;55(2):221-6  
Lombard NJ et al. Allergy Pract. 2012;5(8):199-201  
Muraro A et al. Allergy. 2014;69(8):1009-23  
Dupont C et al. British J Nutr. 2012; 107(2):235-338

Standard Infant formulas    pHF    eHF    AAF

University of Leuven    Ghent Health Centre    VUB

31

---

---

---

---

---

---

---

---

---

---

### Current Guidelines and Future Strategies for the Management of Cow's Milk Allergy.

Management

*Vandenplas Y, Brough HA, Fioocchi A, Miqdady M, Munasir Z, Salvatore S, Thapar N, Verter C, Vieira MC, Meyer R. J Asthma Allergy. 2021 Oct 21;14:1243-1256*

CM-based partial hydrolysates cannot be recommended in the management of CMA because of insufficient efficacy and possible reactions, since only about half of the infants with CMA will tolerate a partial hydrolysate.

32

---

---

---

---

---

---

---

---

---

---

### Management of Cow's Milk Allergy

Management

What is THE BEST option?

University of Leuven    Ghent Health Centre    VUB

33

---

---

---

---

---

---

---

---

---

---

**Prevention and management of CMA in non-exclusively breastfed infants.**  
*Vandenplas Y Nutrients. 2017;9(7):731*

	Australia [29]		Dracma [10]		Espghan [3]	
	1st choice	2nd choice	1st choice	2nd choice	1st choice	2nd choice
GI syndromes	eHF soy (if >6 months)	AAF eHF	eHF	AAF	eHF	AAF
proctocolitis	eHF	AAF			eHF	AAF
Eos Eso	AAF		AAF		AAF	
Immediate FA	eHF soy (if >6 months)	AAF eHF	eHF	AAF/Soy	eHF	AAF
FPIES	eHF	AAF	eHF	AAF	eHF	AAF
Atopic eczema	eHF soy	AAF eHF	eHF	AAF/Soy	eHF	AAF
urticaria			eHF	AAF/Soy	eHF	AAF
Constipation			eHF	AAF		
Heiner syndrome			AAF	eHF		

**eHFs are the 1<sup>st</sup>-choice for most of CMA infants**

34

---

---

---

---

---

---

---

---

---

---

**Management**

Statement	Mean/median	votes
In formula fed infants, a CM derived eHF is the first choice for a therapeutic elimination diet.	7.8/9	0; 7 (2); 8 (3x); 9 (7x)

**Duration - at least > 6 months  
- up to age 9-12 months  
whatever of both is reached first**

35

---

---

---

---

---

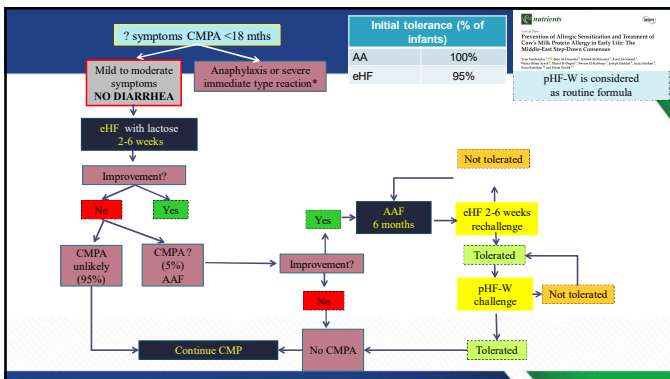
---

---

---

---

---



36

---

---

---

---

---

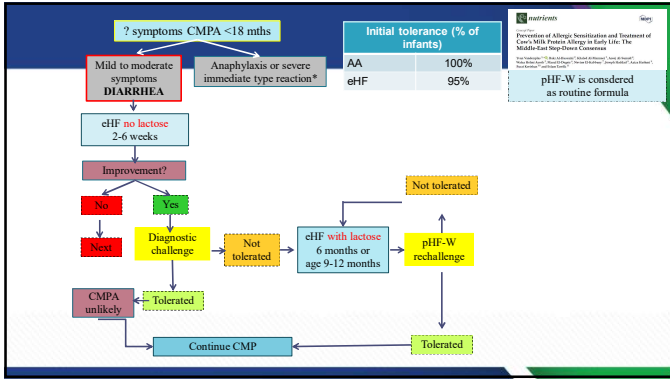
---

---

---

---

---



37

---

---

---

---

---

---

---

---

Management		
Statement	Mean/median	votes
Regarding the therapeutic elimination diet, AAF should be reserved for severe cases (faltering growth, anaphylaxis) or infants with an absent or partial response to eHF.	8.3/9	1; 8; 9 (11x)

38

---

---

---

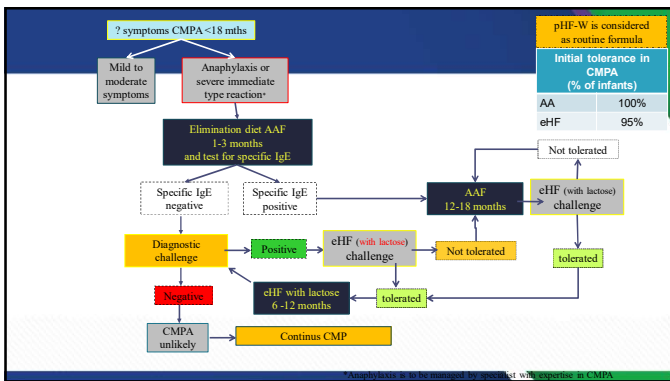
---

---

---

---

---



39

---

---

---

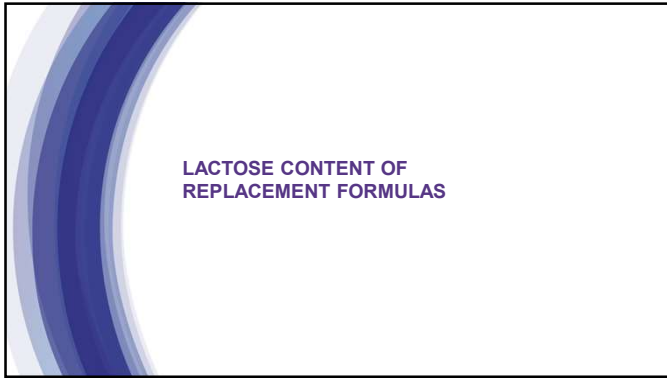
---

---

---

---

---



40

---

---

---

---

---

---

---

---

### Composition of Human Milk

- Lactose 53-61 g/l
- Fat 30-50 g/l
- Oligosaccharides (HMOs) 10-12 g/l
- Proteins 8-10 g/l

Anal Biochem 1994; 223:218-226

41

---

---

---

---

---

---

---

---

### Lactose

Lactose is the main carbohydrate found in human milk and cow milk.

#### Benefits of lactose

- 1 Undigested lactose is fermented in the colon into short chain fatty acids and may confer a prebiotic benefit, promoting the proliferation of healthy bacteria.<sup>1</sup>
- 2 Lactose can also help to increase calcium absorption.<sup>2,3</sup>

1. Naini RD, Alluase F, Bacteria P, et al. Lactose intolerance and abdominal cow's milk allergy in infants and children: current misconceptions revisited. *World Allergy Clin*. 2017;9.  
 2. Norman SB. Lactose intolerance in infants, children, and adolescents. *Pediatrics*. 2006;118:1272-80.  
 3. University of Liverpool, Liverpool Hope University, JUB

42

---

---

---

---

---

---

---

---

### Lactose Impact on Formula-fed CMA Infants

#### Microbiota in fecal samples from infants with CMPA who received an eHF with or without lactose

- Significant increase in bifidobacteria and lactic acid bacteria ( $p < 0.05$ ) reaching counts found in healthy controls
- Significant increase in Bacteroides/clostridia ( $p < 0.05$ )

Lactose increases counts of commensal bacteria.

	healthy BF controls median	eHF with lactose median	eHF without lactose median
Bifidobacteria	9.08	7.06	6.85
Lactobacillus	9.2	9.1	8.5

Lactose decreases counts of pathogenic bacteria.

	healthy BF controls median	eHF with lactose median	eHF without lactose median
Bacteroides	7.04	8.15	9.2

Francavilla R, et al. Pediatr Allergy Immunol. 2012;23:420-7.

43

---

---

---

---

---

---

---

---

---

---

### Why is lactose preferable?

- Purified lactose may further improve palatability and help promote a healthy gut microbiome and calcium absorption.

	Lactose Containing Formula	Lactose-free Formula
Calcium (n=18)		
Intake (mg/d)	507 ± 105	500 ± 91
Percentage absorption (%)	66.5 ± 11.9	56.2 ± 15.3 <sup>2</sup>
→ Total absorption (mg/d)	339 ± 88	279 ± 85 <sup>3</sup>

<sup>2,3</sup> Significantly different from lactose-containing formula (paired t test)  
<sup>2</sup>P = 0.002, <sup>3</sup>P = 0.006

Francavilla R, et al. Effect of lactose on gut microbiota and metabolism of infants with cow's milk allergy. Pediatr Allergy Immunol 2012;23:420-427.

44

---

---

---

---

---

---

---

---

---

---

### Lactose and Taste

- Flavor, relative palatability and components of cow's milk hydrolyzed formulas and amino acid-based formula<sup>1</sup>

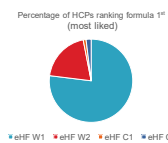
	Protein	Grams lactose
eHF W1	Whey	2.9 g/100 mL
eHF W2	Whey	3.8 g/100 mL
eHF C1	Casein	n/a
eHF C2	Casein	n/a

- The overall judgement of palatability improved with increasing levels of lactose (Spearman's coeff. corr. 0.715;  $p = 0.039$ ).

- Palatability of hypoallergenic formulas for cow's milk allergy and healthcare professional recommendation<sup>2</sup>

- The aim of this study was to assess the palatability of four different eHFs suitable for CMA with HCPs

- Overall, whey-based lactose-containing EHF were ranked better than casein-based EHF



University of Queensland, Queensland Health, and JCU Health Centre

45

---

---

---

---

---

---

---

---

---

---

### When to limit lactose?

- Adverse reactions to lactose in CMA are not supported in the literature, and complete **avoidance of lactose in CMA is no longer warranted.**
- eHFs containing purified lactose are now available and have been found **safe and effective in the management of CMA.**



46

---

---

---

---

---

---

---

---

### TAKE HOME MESSAGE

47

---

---

---

---

---

---

---

---

### Breastfeeding provides the best nutrition for babies



Breastfeeding protects against illness and infection in infants and children: a review of the evidence.

Oddy WH. Breastfeed Rev. 2001 Jul;9(2):11-8.



48

---

---

---

---

---

---


---

---

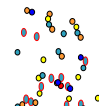


### Feeding a Child with CMA

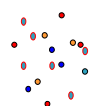
Milk intact proteins



Extensive hydrolysates with small peptides




Amino-acid or Hydrolysed Rice Formulas



- Casein and whey eHF : CM peptide remnants
- AAF and HRF: **NO** CM peptide remnants  
**but also NO lactose**

from Muraro et al. Allergy 69 (2014)



49

---

---

---

---

---

---

---

---

---

---

### Best practice for confirming CMA diagnosis upon suspicion

Feeding Regimen	Management	Compliance	Next Steps
<b>Breastfed baby</b>	Continue breastfeeding; mother should be on a CM-free diet and calcium for 2-4 weeks	Good compliance: Not CMA	Reintroduction/challenge CM
<b>Formula-fed baby (MFG to whey-based formulas)</b>	May require extensively hydrolysed formula (eHF) or hydrolysed rice formula (HRF) for 2-4 weeks	Doubtful compliance: Refer patient to dietitian or nutritionist for reassessment	No symptoms: Not CMA; Symptoms: CMA
<b>Formula-fed baby (whey-free formulas)</b>	Amino acid (based) formula (AAF) for 2-4 weeks		May not be CMA; Not CMA; Consider switching to other regimens to confirm
<b>Long-term management</b>	Eliminate all CM sources (refer to dietitian/nutritionist)		Consider breast milk or eHF/HRF/AAF (depending on tolerance) for 6 months or until 9 to 12 months of age; Monitor tolerance development

To confirm the diagnosis of CMA and avoid overdiagnosis, an oral food challenge test is recommended after a short diagnostic elimination diet

50

---

---

---

---

---

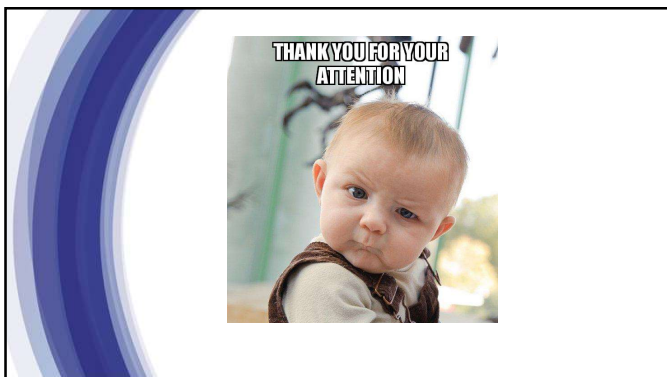
---

---

---

---

---



51

---

---

---

---

---

---

---

---

---

---