

Latest updates on infants with allergies: The gut microbiota and DRACMA guidelines

2024 Nutricia Pediatric Nutrition Masterclass



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Objectives

- Explore the role of environmental and dietary factors associated with development of gut microbiota in infants born during the pandemic.
- Discuss the importance of *Bifidobacterium* on the outcome of allergic phenotypes
- Review the DRACMA guideline updates on the nutritional management of CMA
- Review recommendations of plant-based beverages for children < 1 year of age with CMA.

What is Cow Milk Allergy?



keungchopan via iStock Photo/Getty Images

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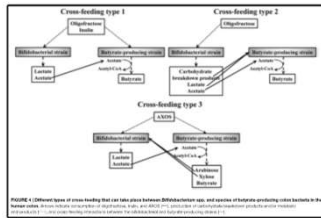


FIGURE 4. Different types of cross-feeding that can take place between Bifidobacterium spp. and species of butyrate-producing enterobacteria in the human colon. Adapted from [10] and [11].

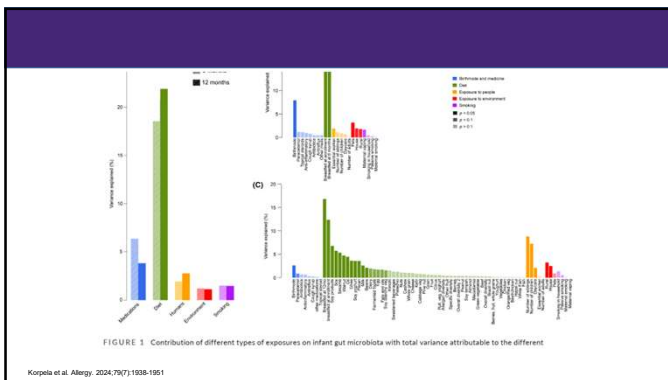
Two important butyrate producing bacteria
Bifidobacteria "assist" with butyrate production
Firmicutes phylum e.g. Lactobacillus, and in particular Clostridial clusters IV and XIVa. (not present in first 6 months)

Riviere et al. Front Microbiol. 2016;7:979.
Sasaki et al. Allergy 2024 Jul;79(7):1789-1811.

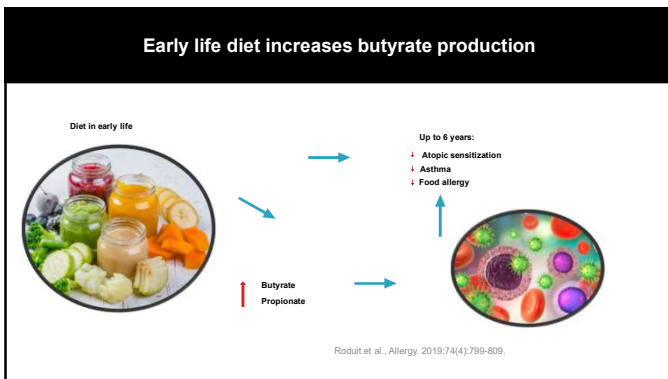
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Food allergen introduction and the infant microbiome

Gut microbiota show associations with allergic dermatitis and mode of delivery in early life, and matures towards adult phenotype as allergenic solids are introduced

In the per-protocol analysis, the prevalence of any food allergy was significantly lower in the early-introduction group than in the standard-introduction group (2.4% vs. 7.3%, $P=0.01$), as was the prevalence of peanut allergy (0% vs. 2.5%, $P=0.003$) and egg allergy (1.4% vs. 5.5%, $P=0.009$).

Marrs et al. JACI 2021 <https://doi.org/10.1016/j.jaci.2020.09.042>

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Discuss the importance of *Bifidobacterium* on the outcome of allergic phenotypes

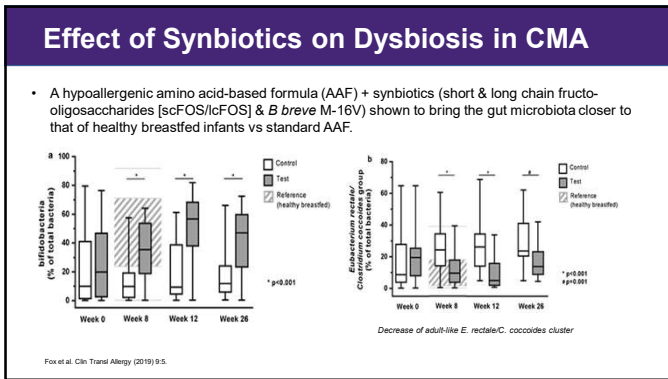
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Gut microbiota in CMA

- In allergic infants, several studies show the presence of altered gut microbiota, or 'dysbiosis' (a breakdown in the balance of intestinal bacteria)
 - *Bifidobacteria* are the first colonisers of healthy infant gut
 - Children with CMA have lower gut microbiota diversity
 - Infants with IgE-mediated allergy typically have low levels of *Bifidobacteria*
 - Children with non-IgE mediated allergy have dysbiosis driven by *Bacteroides* and *Alistipes*
 - Systematic review 2023: suggest that the gut microbiome, characterized by an enrichment of the Clostridia class and reductions in the Lactobacillales order and *Bifidobacterium* genus, is associated with CMA in early life
 - Infants who outgrew CMA were reported to have enriched Clostridia class at 3–6 months

Savo et al. Pediatr Allergy Immunol. 2024;35:e14984.
Thompson-Chagoyan CC, et al. Int Arch Allergy Immunol 2011; 156: 325-332. Kirjavainen PV, et al. Gut 2002; 51: 51-55. Sobh A, et al. J Pediatr Gastroenterol Nutr. 2014 Jul 19(1): 78-88. Casati et al. Sci Rep. 2019 Aug 21;9(1):2020. Baryshevich et al. J Allergy Clin Immunol. 2016;138(1):102-110. Peterson et al. Cell Rep. Med. 2:100200. Yang et al. Front Microbiol 2021;12:716667. Moriké et al. Nutrients 2022; 14, 4037

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Effect of Synbiotics on Medication Use

Table 2 Concomitant medication use (number of subjects taken medication) in All subjects treated (AST)

	Test (N=35)	Control (N=35)	P-value (Fisher's exact test)
Concomitant medication (N (%))			
Overall			0.394
Any concomitant medication	25 (71.4%)	29 (82.9%)	
Subcategory*			
Dermatologicals	6 (17.1%)	16 (45.7%)	0.019
Antibiotics and chemotherapeutics	1 (2.9%)	2 (5.7%)	1.00
Antifungals	0 (0%)	3 (8.6%)	0.504
Antiparasitics	0 (0%)	2 (5.7%)	0.493
Antibiotics and disinfectants	1 (2.9%)	4 (11.4%)	0.356
Antiepileptics	0 (0%)	2 (5.7%)	0.661
Antidepressants/antipsychotics	0 (0%)	1 (2.9%)	0.603


Source: Fox et al. Clin Transl Allergy (2019) 9:5.

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- ### DRACMA Guidelines - What the update covers
- Diagnosis of cow's milk allergy (CMA)
 - Formula choice if formula is required
 - Oral Immunotherapy
 - And so much more!
- DRACMA = World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy

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Fiocchi et al. *World Allergy Organization Journal* (2022) 15:100609
<http://doi.org/10.1016/j.waojou.2021.100609>



WORLD ALLERGY ORGANIZATION JOURNAL
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World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - I - Plan and definitions

Alessandro Fiocchi, MD^{*,}, Antonio Bognanni, MD^{*,}, Jan Brożek, MD, PhD^{*,}, Motohiro Ebisawa, MD, PhD^{*,} and Holger Schünemann, MD^{*,}, On behalf of the WAO DRACMA guideline group¹

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Summary of papers




Oksana Kuzmina via Shutterstock

	Topic	Method of publication
General		
1	Overview and definitions	This paper
2	CMA epidemiology and natural history	Narrative review
3	CM allergens and immunologic mechanisms	Narrative review
4	Clinical presentations: IgE-mediated	Narrative review
5	Clinical presentations: non IgE-mediated	Narrative review
6	Comparison among different guidelines	Systematic review
7	DRACMA methodology	Synthesis of methods
CMA diagnosis		
8	Diagnosis of CMA	Systematic review
9	Recommendations on CMA diagnosis	Guideline
Treatment options		
10	Breastfeeding a baby with CMA	Narrative review
11	Substituted formulae	Systematic review
12	Recommendations on substitutive treatment	Guideline
13	Oral immunotherapy for CMA	Systematic review
14	Recommendations on CMA OIT	Guideline
15	Other milks (goat's, mare's, donkey's, camel's, and substitutes from non animal sources)	Narrative review
16	Nutritional considerations in CMA infants	Narrative review
Conclusions		
17	Which is the 1st choice formula case by case?	Synthesis of recommendations
18	Unmet needs, Recommendations for research, Recommendations for the implementation of the DRACMA Evidence-Based Guidelines (EBG) and DRACMA	Synthesis of recommendations

Fiocchi et al. *World Allergy Organ J*. 2022 Feb 1;15(1):100609 (From the DRACMA group)

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Meyer et al. *World Allergy Organization Journal* (2023) 16:100785
<http://doi.org/10.1016/j.waojou.2023.100785>



WORLD ALLERGY ORGANIZATION JOURNAL
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World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guideline update - VII - Milk elimination and reintroduction in the diagnostic process of cow's milk allergy

Rosan Meyer, RD, PhD^{a,1}, Carina Venter, RD, PhD^{b,1}, Antonio Bognanni, MD, PhD(s)^{c,d}, Hania Szajewska, MD, PhD^e, Raanan Shamir, MD, PhD^f, Anna Nowak-Węgrzyn, MD, PhD^g, Alessandro Fiocchi, MD, PhD^h and Yvan Vandenplas, MD, PhDⁱ, On behalf of the WAO DRACMA Guideline Group

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Cow's milk allergy is complex

- The diagnosis is challenging: Many of the symptoms are similar to other diagnoses. 2. Clinical pearls
- Over- and under diagnosis occur.
- Misdiagnosis carries allergic, nutritional and financial risks: including acute reactions, growth faltering, micronutrient deficiencies and a diminished quality of life.

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Diagnosing IgE mediated CMA

	Milk ladder	Liquid milk
Setting	<ul style="list-style-type: none"> • Usually under physician supervision in a medical setting • Selected cases might be considered for home reintroduction <ul style="list-style-type: none"> - younger than 3 years without previous history of anaphylaxis or wheezing - skin prick test wheal diameter less than 8 mm for cow's milk 	<ul style="list-style-type: none"> • Usually under physician supervision in a medical setting • At the physician discretion, home introduction might be considered for children who are known to tolerate milk in baked products and had mild symptoms to large amounts of liquid milk in the past
Pros	<ul style="list-style-type: none"> • Up to 70% of children who react to liquid milk, tolerate milk in a form of a baked product • High chance of success • Minimizes unnecessary milk elimination when access to food challenges is limited 	<ul style="list-style-type: none"> • Straightforward • Short period • Easy to find products
Cons	<ul style="list-style-type: none"> • Prolonged process, more labor intense • Some forms of baked foods may not be appropriate for young infants • Children who react to baked milk tend to have more severe symptoms and higher risk of anaphylaxis 	<ul style="list-style-type: none"> • More allergenic form of milk might induce uncomfortable symptoms • Children with feeding difficulties might refuse to try a new food in a medical setting under time constraint

Meyer R, et al. World Allergy Organ J. 2023 Jul 24;16(7):100795.

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Diagnosing Non-IgE mediated CMA: FPIAP, FPE

	Milk ladder	Liquid milk
Setting	<ul style="list-style-type: none"> • Usually done at home • Helpful when caregiver apprehensive / worried about reintroduction 	<ul style="list-style-type: none"> • Can be done at home as symptoms are usually delayed, e/g., appear after few days • Typically lower GI tract involved: bloody stool, diarrhea, discomfort
Pros	<ul style="list-style-type: none"> • Starting from less allergenic forms of foods at lower doses • Milder symptoms 	<ul style="list-style-type: none"> • Straightforward • Short period • Easy to find products
Cons	<ul style="list-style-type: none"> • Prolonged process • More labour intense • Some forms of baked foods may not be appropriate for infants and young children 	<ul style="list-style-type: none"> • More allergenic form of milk might induce uncomfortable symptoms

Meyer R, et al. World Allergy Organ J. 2023 Jul 24;16(7):100795.

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Diagnosing FPIES

Milk ladder	Liquid milk
Non-IgE mediated CMA: FPIES	
Setting <ul style="list-style-type: none"> Typically under physician supervision in a medical setting Those with mild symptoms to large amounts of liquid milk might be considered for a very gradual home introduction 	<ul style="list-style-type: none"> Typically under physician supervision in a medical setting
Pros <ul style="list-style-type: none"> Some children with milk-FPIES might tolerate baked milk More gradual, starting from lower doses of baked milk Home setting usually more comfortable for infants and young children, more likely to try a new food in a familiar environment and unlimited time Might induce milder symptoms from lower GI tract compared to violent vomiting in acute FPIES 	<ul style="list-style-type: none"> Clear indication of tolerance/reactivity Short process (1 day) Easy to find foods
Cons <ul style="list-style-type: none"> Unclear what % of FPIES patients is tolerant to baked milk If tolerate baked milk, will need another trial for liquid milk Risk of FPIES symptoms at home Unclear if symptoms to baked milk would be milder than to liquid milk Prolonged process, labor intense on the part of a caregiver Some forms of baked foods may not be appropriate/well accepted by infants and young children If introduction stopped for mild, non-specific GI symptoms, it may result in unnecessary prolonged elimination of milk from diet 	<ul style="list-style-type: none"> Larger dose might induce more violent vomiting Usually intravenous access is required and can be difficult to secure Child may refuse to eat the new food in an unfamiliar setting and under time constraint

Meyer R, et al. World Allergy Organ J. 2023 Jul 24;16(7):100785.

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Comparing milk ladders

3. Clinical pearls

#	Country/Region	Protein Included	Other Ingredients	Introducing Stage	Estimated Protein Content	Nutritional Advantages	Advantages	Other Comments
1	UK	No	Small amount of highly refined CM protein	6-12 mg	No	0	For British population	Food is a single step, not a ladder or progression
2	USA	No	Microbe jump to baked cream cheese substituted (no multiple steps)	30 mg	2.2 g	No	US diet specific	Common recipe
3	USA	No	Large jump to baked cream cheese substituted (no multiple steps)	30 mg	0.3 g	No	International	Simple recipe
4	Mediterranean	No	Microbe jump to cheese	30 mg	33 g	0	Mediterranean	Calcium and increased CM protein not present in recipe
5	Indian	No	Microbe jump to cheese	30 mg	0.03 g	No	High in sugar and fat - through recipes were adjusted to reduce sugar & fat content, see also	Cultures relevant to India
6	Canada	No	Microbe jump to cheese	30 mg	0.03 g	No	Canadian	Calcium and increased CM protein not present in recipe
7	Germany	No	Microbe jump to cheese	30 mg	0.03 g	No	German	Calcium and increased CM protein not present in recipe
8	Spain	No	Microbe jump to cheese	30 mg	0.03 g	No	Spanish	Calcium and increased CM protein not present in recipe
9	Spain	No	Microbe jump to cheese	30 mg	0.03 g	No	Spanish	Calcium and increased CM protein not present in recipe

Hicks, Fleischer, Venter under review. Frontiers

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Formula milk recommendations

8. Clinical pearls

The 2023 DRACMA guidelines make the following conditional recommendations:

- Extensively hydrolyzed (milk) formula or a hydrolyzed rice formula can be used as the first option for managing infants with IgE and non-IgE-mediated CMA if breastfeeding is not possible or available.
- An amino-acid formula can be a second option.
- A soy formula would be regarded as the last option.
- Formulas without a probiotic or an extensively hydrolyzed (milk) formula containing *Lactocaseibacillus rhamnosus* (formerly *Lactobacillus rhamnosus*) GG can be used for infants with either IgE or non-IgE-mediated CMA.
- The issued recommendations are labeled as "conditional" following GRADE approach due to the very low certainty about the health effects based on the available evidence.

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	DRACMA	GALEN	ESGFUEN
GMF and AA based formula	Extensively hydrolyzed (milk) formula or a hydrolyzed rice formula can be used as the first option for managing infants with IgE and non-IgE-mediated CMA if breastfeeding is not possible or available. An amino-acid formula can be a second option.	The GRADE Task Force suggests that rice formula (aged 0-1 years) is preferred over cow milk allergy with a hypersensitivity reaction as a first option. AAIF should be reserved for severe cases or infants with an absent or partial response to eHF.	In formula-fed infants, a CMA-based eHF is the first choice for a therapeutic alternative diet. AAIF should be reserved for severe cases or infants with an absent or partial response to eHF.
Hydrolyzed rice formula	See above	The GRADE Task Force makes no recommendation for or against hydrolyzed rice-based formula including rice hydrolyzates that have been available as far as managing food allergy in infancy.	HRF can be considered as an alternative to GMF-derived eHF for therapeutic substitution diet.
Partially hydrolyzed cow's milk based formula	NA	We suggest against partially hydrolyzed cow's milk formula.	Partially hydrolyzed CMA-based formula (eHF) are not recommended in the treatment of CMA.
Soy formula	A soy infant formula would be regarded as the last option.	We suggest against soy-based formula in infants under 6 months.	Soy protein-based formula is not recommended for infants <6 months, but may be used in the treatment of CMA in older children or adults and cultural reasons (and better palatability).
Preprobiotics	Formulas without a probiotic or an extensively hydrolyzed (milk) formula containing <i>Lactocaseibacillus rhamnosus</i> GG (formerly <i>Lactobacillus rhamnosus</i>) GG can be used for infants with either IgE or non-IgE-mediated CMA.	The GRADE Task Force makes no recommendation for or against any probiotic, prebiotic, or synbiotic that have been evaluated so far for managing food allergy.	There is insufficient evidence demonstrating that the addition to eHF of pre- or synbiotics should be for improve their therapeutic efficacy.

Muraro, et al. World Allergy Organiza. 2023;15(8):100687. Venet, et al. World Allergy Organ J. 2024;In press; Vanderplas et al.Pediatr Gastroenterol Nutr. 2023.

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Plant-Based Beverages

- Alternative beverages include soy, coconut, almond, rice, oat, hazelnut, cashew, walnut, pea, sesame, hemp, tigernut, quinoa
- Availability of these formulas also differ internationally but the majority can be ordered online
- It is important to be aware of the cost of alternative milks, and compare their nutrient composition against that of cow milk, particularly in terms of protein, energy, calcium, vitamin B12, Vitamin D and iodine
- Fat content is also important in children under the age of 2 years

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9. Clinical pearls

Is at least one year of age

- Eats a varied solid food diet with a variety of foods from each food group;
- Gets at least 2/3 of their energy from the varied solid food diet;
- Consumes no more than 2 servings/day (1 serving = 8 ounces/240 mls of milk substitute day or yogurt substitute);
- Eats age-appropriate textures
- Gets enough protein and fat and micronutrients in the diet from the solid foods and the available milk substitute
- Has no feeding difficulties that may reduce food variety
- Has no known micronutrient deficiencies; AND
- Has no religious/cultural dietary requirements that reduces the variety of foods consumed

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10. Clinical pearls

- The most recent DRACMA guidelines have found limited evidence of low certainty, that children with **IgE mediated CMA** who were fed **amino acid-based formula** may have an **improved growth pattern when compared to extensively hydrolyzed (milk) formula**.
- It should however be noted that the included studies are old, and the formulations of formulas have changed, and these studies did not aim to assess failure to thrive and therefore catch-up growth.
- Further research is therefore needed, to answer the question about whether certain formulas better support catch-up growth.
- Compared to soy formula, **extensively hydrolyzed (milk) formula may favor weight gain** but there is no difference on length growth.
- There was no difference when comparing extensively hydrolyzed (milk) formula to hydrolyzed rice formula or hydrolyzed rice formula to soy formula.
- In terms of **non-IgE mediated CMA**, the DRACMA guidelines suggest that compared to amino acid-based formulas, there may be **reduced length growth seen with extensively hydrolyzed (milk) formula**, however the certainty of evidence is very low and further research is required.
- No difference was found when comparing extensively hydrolyzed (milk) formula to hydrolyzed rice formula or hydrolyzed rice formula to soy formula.

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Summary

- Environmental and dietary factors affects the early life microbiome
- The early life microbiome and manipulating the early life microbiome may affect disease outcomes
- DRACMA guidelines are still being published
- We need to understand the effect of processing/heating on allergenicity better
- Oral immunotherapy should be used in suitable cases
- The verdict on pre-/probiotics is still out
- INDIVIDUALIZED avoidance of the food allergen(s) should be advised
- Use a hypoallergenic formula (not partially hydrolyzed formula)
- Avoid other mammalian milks
- Use the help of an RD when choosing plant-based milks in children (> 1 year of age)

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