The Multiple Facets of Milk Allergy in Infants

Jonathan Tam, MD

Children's Hospital Los Angeles

Learning Objectives

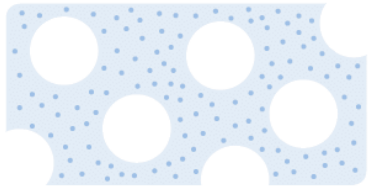
- Describe different forms of cow’s milk allergy including IgE-mediated and non-IgE mediated cow's milk allergy.
- Describe current management options and therapies for IgE-mediated and non-IgE mediated cow's milk allergy.
- Discuss impacts of cow’s milk allergy on patients

What is cow's milk?

THE CHEMISTRY OF COW'S MILK

MILK'S COMPOSITION

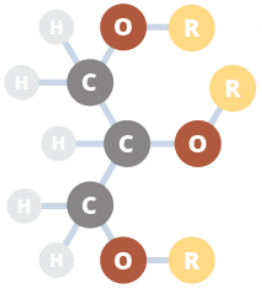
Milk is an emulsion of fat in water. It is also a colloidal suspension of proteins. Other compounds, including lactose and minerals, are fully dissolved in the solution.



WATER	87.5%
FAT	3.9%
PROTEINS	3.4%
LACTOSE & MINERALS	5.2%

FATS IN MILK

Droplets of fat in milk have an average size of 3–4 micrometres. They consist mainly of triglycerides, and also contain fat-soluble vitamins.



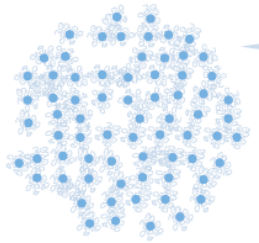
TRIGLYCERIDE

R = FATTY ACID MOLECULES

PALMITIC ACID	23.6–31.4%
OLEIC ACID	14.9–22.0%
STEARIC ACID	10.4–14.6%
MYRISTIC ACID	9.1–11.9%

WHY IS MILK WHITE?

Milk contains hundreds of types of protein, of which casein is the main type. The milk proteins form micelles. These micelles scatter light, causing milk to appear white.



CASEIN MICELLES

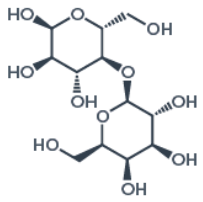
There are several models of casein micelle structure. This diagram shows the supramolecular structure.

CASEIN PROTEINS

CALCIUM PHOSPHATE CLUSTER

LACTOSE & MILK

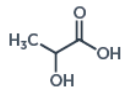
Lactose is a sugar found in milk. People who are lactose intolerant are unable to digest it. Lactose can be fermented by microorganisms to form lactic acid, causing the milk to sour.



LACTOSE

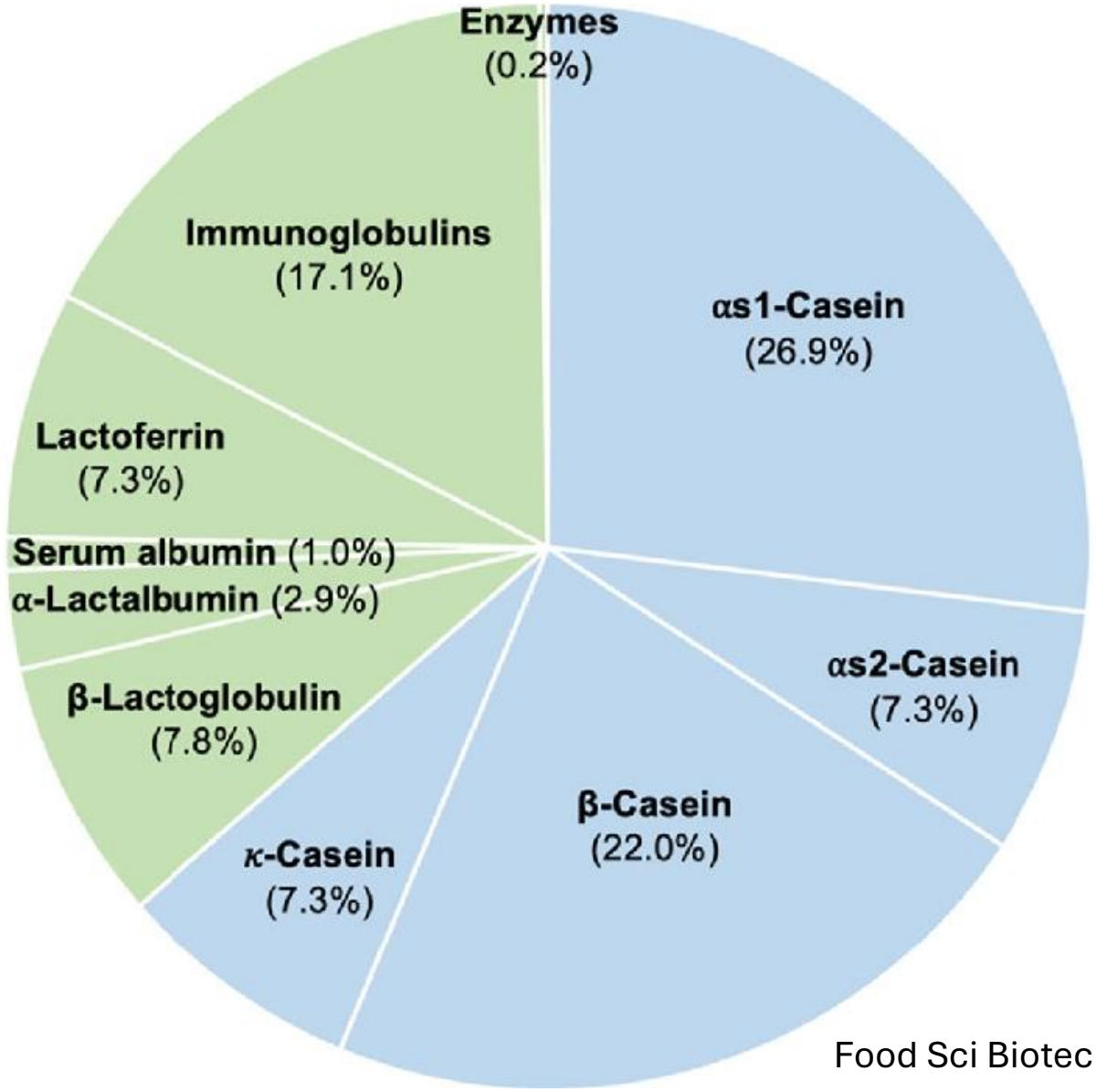
DIGESTION → GALACTOSE + GLUCOSE

FERMENTATION →



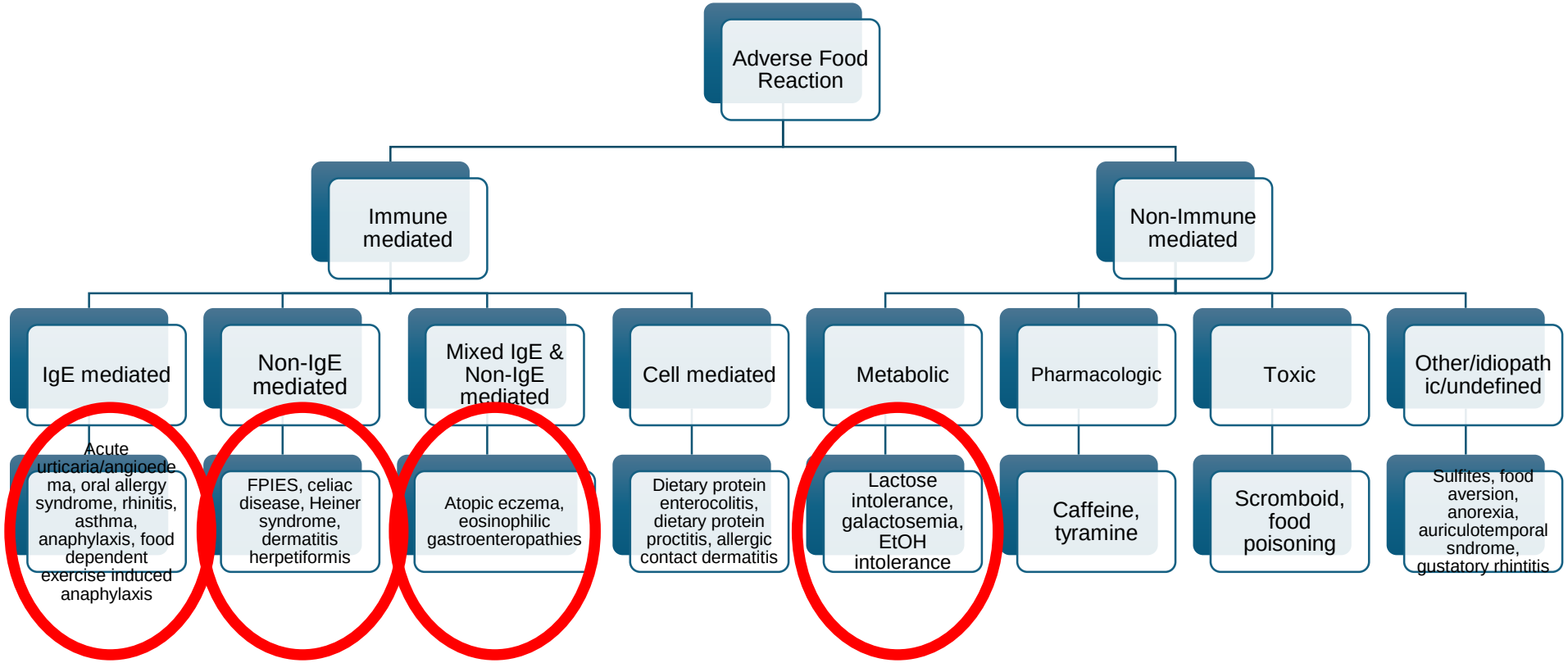
LACTIC ACID

What proteins are in milk?



Food Sci Biotechnol . 2023 Oct 25;33(3):491-503.

Definition


Adverse Food Reaction
Immune mediated
Non-Immune mediated
IgE mediated
Non-IgE mediated
Mixed IgE & Non-IgE mediated
Cell mediated
Metabolic
Pharmacologic
Toxic
Other/idiopathic/undefined
Acute urticaria/angioedema, oral allergy syndrome, rhinitis, asthma, anaphylaxis, food dependent exercise induced anaphylaxis
FPIES, celiac disease, Heiner syndrome, dermatitis herpetiformis
Atopic eczema, eosinophilic gastroenteropathies
Dietary protein enterocolitis, dietary protein proctitis, allergic contact dermatitis
Lactose intolerance, galactosemia, EtOH intolerance
Caffeine, tyramine
Scromboid, food poisoning
Sulfites, food aversion, anorexia, auriculotemporal sndrome, gustatory rhintitis

Prevalence of Milk Allergies

- The most common food allergy among young children and infants is cow's milk allergy (CMA).
- There are immunoglobulin E (IgE)–mediated, non–IgE-mediated, and mixed mechanisms of food allergy.
- Epidemiological studies indicate that CMPA primarily occurs in infants, with a global incidence range of 2.0%–7.5%.

Prevalence: IgE mediated CMA

- Self-reported rates of CMA are considerably higher than those with oral food challenge (OFC)-verified allergy.

Allergy 2023;78:2361-417.

- In a cross-sectional US household 2015-2016 survey, 1.9% of children met criteria for convincing IgE-mediated CMA based on symptoms reported.

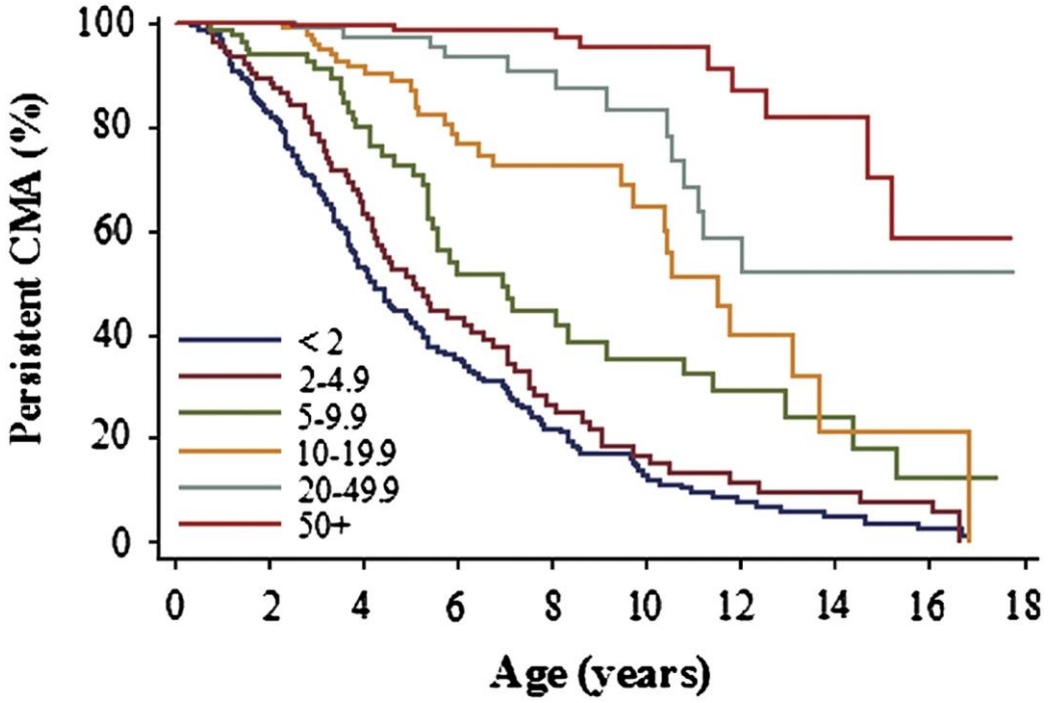
Pediatrics 2018;142:e20181235.

- In some regions of the world, CM is a more common cause of anaphylaxis than peanut.

J Allergy Clin Immunol 2021;148: 1515-1525.e3.

Natural History of IgE Mediated Milk Allergy

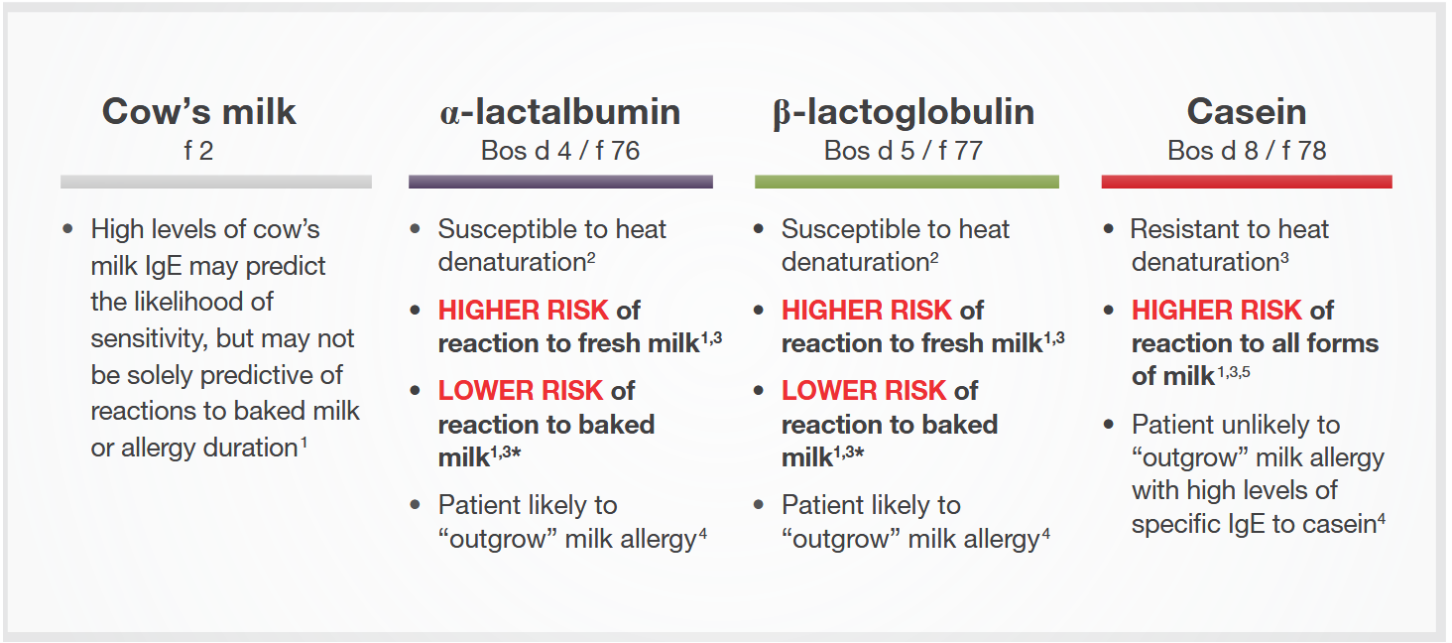
- Most children gain tolerance over time.
- 19% by age 4 years, 42% by age 8 years, 64% by age 12 years, and 79% by age 16 years.
- Concomitant asthma or allergic rhinitis is a predictor of delayed tolerance.
- Higher baseline skin prick test (SPT) size, a higher baseline specific IgE (sIgE), and moderate to severe atopic dermatitis predict delayed tolerance.
- Most children (75%) with CMA can tolerate extensively heated milk in baked goods



J Allergy Clin Immunol . 2007 Nov;120(5):1172-7.

Testing in IgE Mediated Milk Allergy

- Skin Testing
- Serum IgE Testing
- Component Testing



Cow's milk f 2	α-lactalbumin Bos d 4 / f 76	β-lactoglobulin Bos d 5 / f 77	Casein Bos d 8 / f 78
• High levels of cow's milk IgE may predict the likelihood of sensitivity, but may not be solely predictive of reactions to baked milk or allergy duration[1]	• Susceptible to heat denaturation[2] • **HIGHER RISK of reaction to fresh milk**[1,3] • **LOWER RISK of reaction to baked milk**[1,3*] • Patient likely to "outgrow" milk allergy[4]	• Susceptible to heat denaturation[2] • **HIGHER RISK of reaction to fresh milk**[1,3] • **LOWER RISK of reaction to baked milk**[1,3*] • Patient likely to "outgrow" milk allergy[4]	• Resistant to heat denaturation[3] • **HIGHER RISK of reaction to all forms of milk**[1,3,5] • Patient unlikely to "outgrow" milk allergy with high levels of specific IgE to casein[4]

SPT and sIgE are **limited** in distinguishing children who can tolerate BM and an **OFC is often required**.

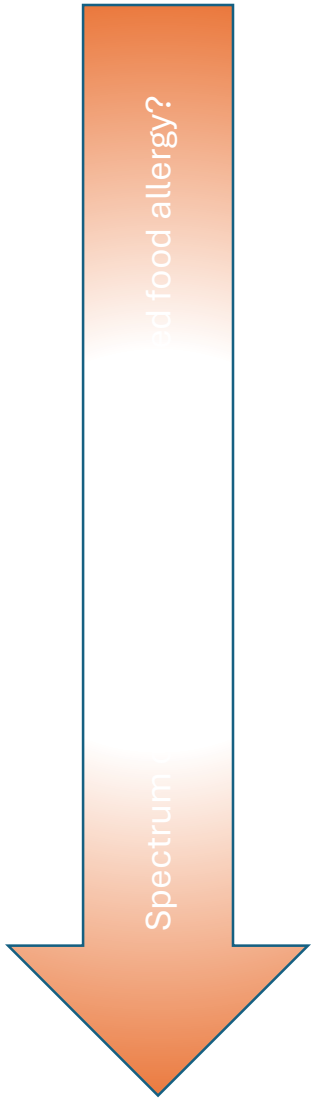
J Allergy Clin Immunol 2020;146:1434-1437.e2

Spectrum of Non-IgE Mediated Food Allergy

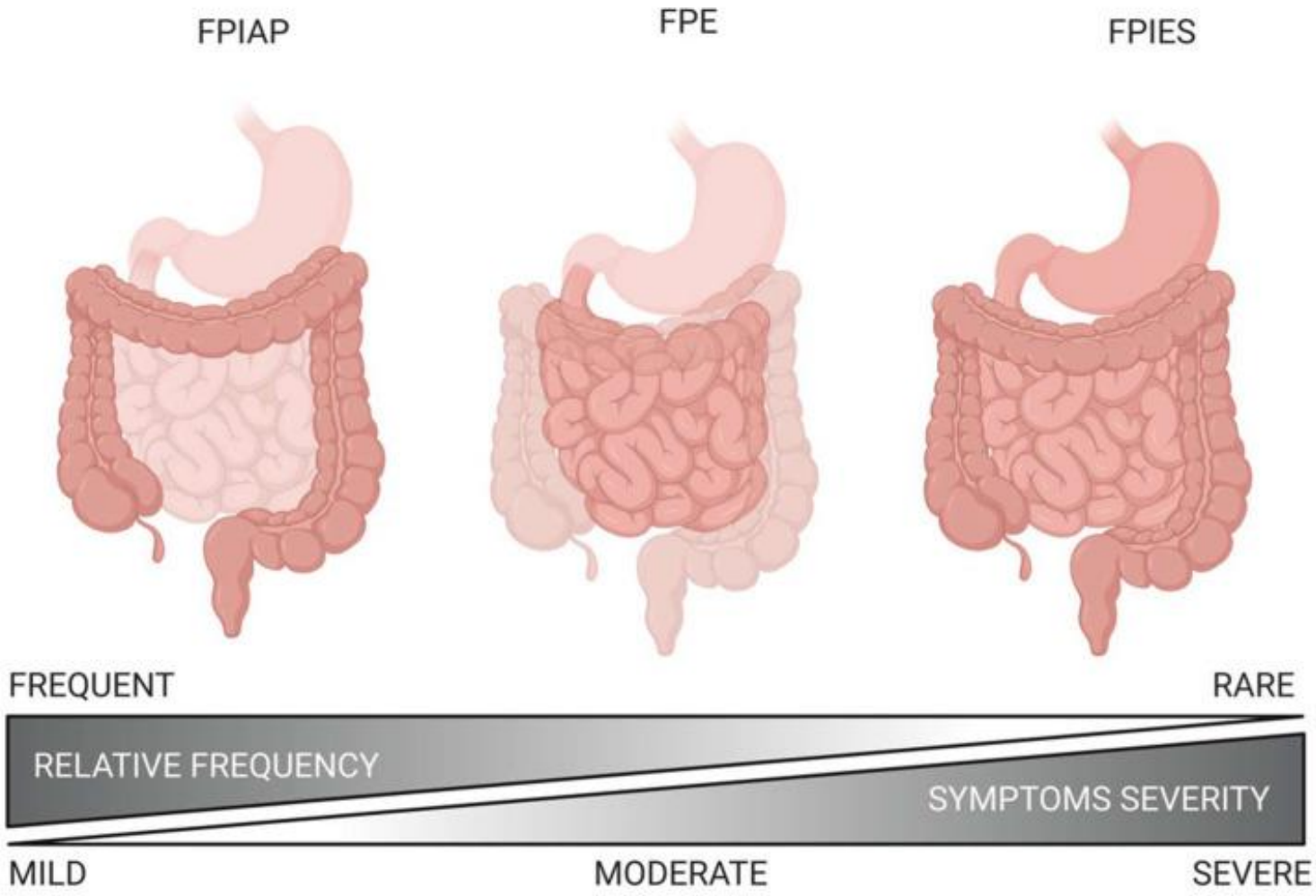
- Food Protein induced allergic proctocolitis (FPIAP)
  - AKA allergic proctocolitis
  - AKA eosinophilic proctocolitis
  - AKA milk protein allergy (please don't call it that)

- Food Protein induced enteropathy (FPE)
  - AKA allergic enteropathy
  - AKA cow's milk sensitive enteropathy
  - AKA malabsorption syndrome with milk intolerance

- Food Protein induced enterocolitis syndrome (FPIES)

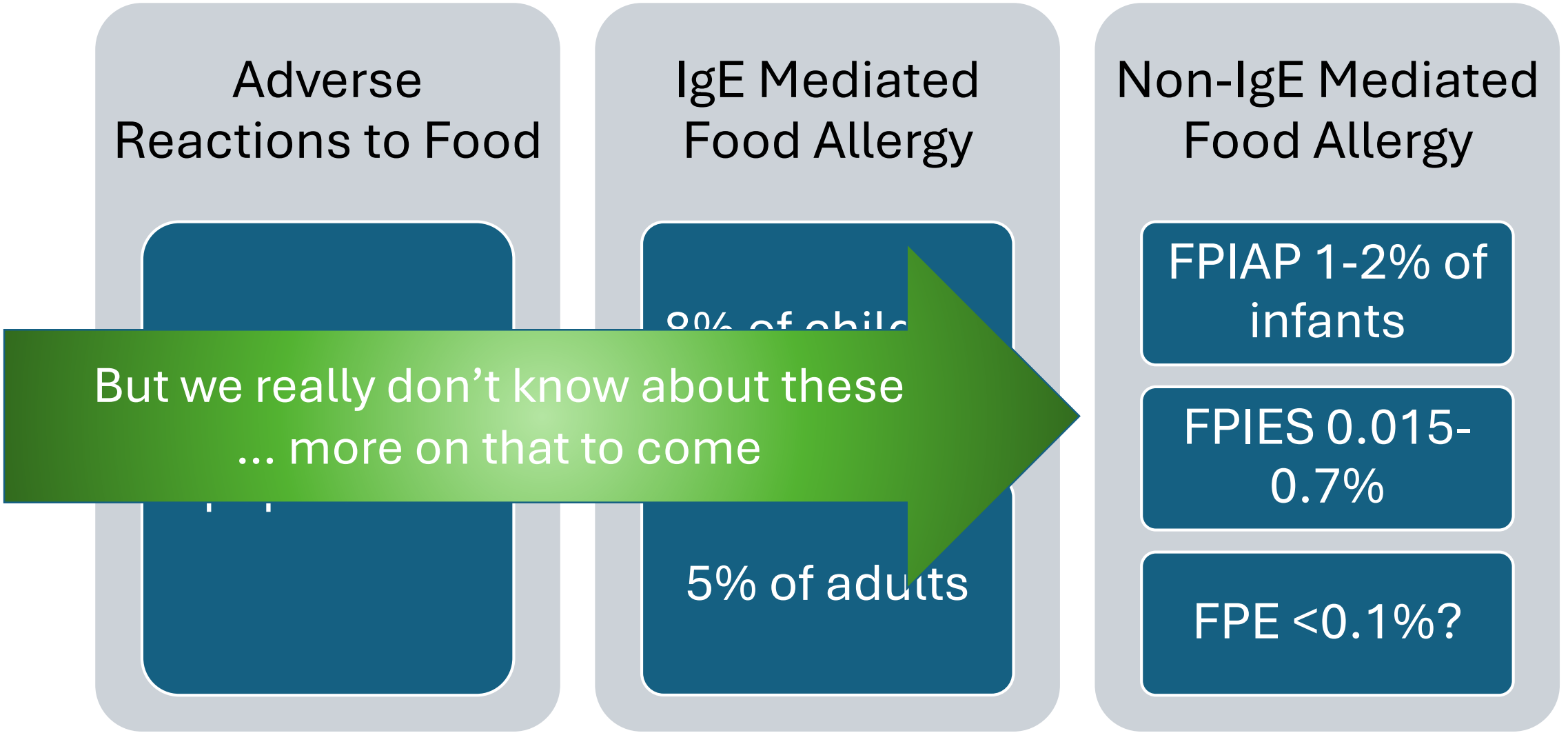


Gastrointestinal organs affected in different non-IgE mediated food allergies



Nutrients. 2020 Jul 14;12(7):2086. doi: 10.3390/nu12072086.

Epidemiology



Aliment Pharmacol Ther . 2015 Jan;41(1):3-25.

Pathophysiology of Non IgE Mediated Milk Allergy

- Pathogenesis of non-IgE mediated food allergy poorly understood
- Several mechanisms have been suggested in the pathophysiology for the development of FPIAP including an immature immune system, altered intestinal permeability and activation of local immune function.
  - In FPE, food-specific T cell infiltration thought to lead to clinical findings
  - FPIAP characterized by eosinophilic infiltration

Are we over diagnosing FPIAP?

"Commonly estimated to affect 1 to 2 percent of infants"

- Prospective population-based study from Israel (n >13,000 children) reported the prevalence of milk-induced proctocolitis at only **0.16%**.

- Prospective observational healthy infant cohort study in suburban Massachusetts **17%** (153 of 903) were diagnosed by their pediatrician with FPIAP.

Pediatric Allergy and Immunology. 2012;23(8):765-769.

The Journal of Allergy and Clinical Immunology: In Practice. 2020. 8, 1692. e1-1699

FPIAP Management

- Diagnosis is via clinical history
- No value in testing for food allergy
  - Food prick skin tests and serum food-IgE negative

- Treatment is **protein elimination**
  - Resolution of symptoms in 48–72 h
  - Though symptoms may not fully resolve for several weeks

- Tolerance to allergen usually occurs by 1 yr of life

How should we diagnose FPIAP?

"FPIAP is diagnosed clinically, no testing is necessary"

- By strictly using milk elimination followed by subsequent challenge to make the diagnosis of FPIAP, Arvola et al were only able to confirm disease in only 18% of infants presenting with rectal bleeding.

Pediatrics. 2006;117(4):e760-e768.

- In a small cohort of 16 neonates with rectal bleeding, 10 out 16 colonic biopsies supported the diagnosis of FPIAP, but only two were confirmed to be food-induced by OFC. Those not confirmed by OFC had spontaneous resolution after an average 4 days and were diagnosed with idiopathic neonatal transient colitis.

European Journal of Pediatrics. 2012;171(12):1845-1849.

- A case-controlled study looking at the validity of FOBT for the diagnosis of FPIAP, more than a third of healthy control infants had abnormal

Revista chilena de pediatría. 2018;89:630-637.

Are we having infants avoid milk too long?

"Infants usually become tolerant by 1-3 years of age, most before 1 year"

- Up to 20% of breastfed infants may have spontaneous resolution without any changes in the maternal diet.

Journal of Allergy and Clinical Immunology. 2015;135(5):1114-1124.

- Some studies show tolerance of suspected food in a majority of infants 1-3 months after the diagnosis.

Pediatric Allergy and Immunology. 2012;23(8):765-769.

Pediatrics. 2006;117(4):e760-e768.

Journal of Pediatric Gastroenterology and Nutrition. 2000;30(1):S58-S60

Nutritional risks

- Children with CMA are at risk of inadequate nutrient intake and poor growth.
  - In an age-matched cohort study, children with CMA had consistently lower weight-for-age and height-for-age z-scores than controls.

    Int Arch Allergy Immunol 2024;185:536-44.

  - In a retrospective study of 9938 children with food allergy, those avoiding CM were significantly shorter and weighed less than a matched control group, whereas children strictly avoiding milk were shorter than those consuming BM products.

    J Pediatr 2014;165:842-8

- Children with CMA were significantly more likely to have inadequate intake of energy, vitamins A, E, B1, B6, C, and folic acid, and magnesium and iron.

  Ann Allergy Asthma Immunol 2024;132:745-751.e2.

- Children with persistent CMA have shown lower lumbar spine bone mineral density z scores.

  Pediatrics 2016;137: e20151742.

Formula choices for CMA

Guideline	1st Choice	2nd Choice	3rd Choice
WAO (Bognanni et al)	extensively hydrolyzed formula (casein or whey) Hydrolyzed rice formula	Amino acid-based formula	Soy
GA2LEN (Muraro et al)	extensively hydrolyzed formula (casein or whey)	Amino acid-based formula	Soy if >6 mo
ESPGHAN (Vandenplas et al)	extensively hydrolyzed formula (casein or whey)	Hydrolyzed rice formula—although less studied, can be considered an alternative to eHF Amino acid-based formula	Soy should not be used as first option but can be considered for economic, cultural, or palatability reasons

What do the guidelines say?

ESPGHAN (J Pediatr Gastroenterol Nutr, 78 (2024), pp. 386-413)

World Allergy Organization guideline/DRACMA guideline consortium (World Allergy Organ J, 17 (2024), Article 100888)

EAACI (Allergy, 69 (2014), pp. 1008-1025)

GA2LEN (Global Allergy and Asthma Excellence Network) (World Allergy Organ J, 15 (2022), Article 100687)

- History is key for the classification and diagnosis of CMA.
- In IgE-mediated allergy, SPT and sIgE are the recommended first-line complementary tests, while total IgE or component-resolved diagnostics are not recommended in ESPGHAN guidance. The EAACI suggest that these can be useful in specific cases, but strongly advocates **against** the use of IgG or IgG4 testing, and together with the ESPGHAN document, also discourages the use of the atopy patch test. Basophil activation test use is not supported in clinical practice.
- The role of milk ladder is discussed only in DRACMA and ESPGHAN consensus, and proposed as a way to reintroduce milk at home in certain presentations of non eIgE-mediated CMA. In the DRACMA document, risk concerns on the increasing use of milk ladder for IgE-mediated allergy are raised and a call for standardization is made.

Treatment of Milk Allergy

- Dietary management
- Baked milk
- Milk ladder
- Desensitization
- Biologics?

Milk Ladders

A

B

C

D

		Energy Value (Kcal)/100 g	Portion (g) (*)	Estimated Milk Protein (g/Portion)
1.1	Beef burger	188	~60 g baked (80 g raw)	0.07
1.2	Oat biscuit with olive oil	95	~40 g baked (50 g raw)	0.07
2.1	Sweet whole wheat muffins with berries or raisins	137	100 g baked (125 g raw)	0.875
2.2	Savory muffin with tomato and olives	139	100 g baked (125 g raw)	0.875
3.1	Med type potato puree	145	200 g cooked	1.47
3.2	Crepes with whole wheat flour	180	80 g baked	1.47
4.1	Bread with cheese, olives and tomato	160	55 g baked (80 g raw)	3.44
4.2	Lentil burger with cheese	130	60 g baked (85 g raw)	3.44
4.3	Feta cheese 16 gr milk protein/100gr	264	34.9 g	3.44
5.1	Rice pudding	134	150 g cooked	3.44
5.2	Bechamel	127	130 g cooked	3.44
6	Yogurt	140	300 g	4.2
7.1	Cocoa banana ice	35	390 g	3.44
7.2	Avocado-cocoa ice	162	375 g	3.44
7.3	milk	73	300 g	3.2

E

F

G

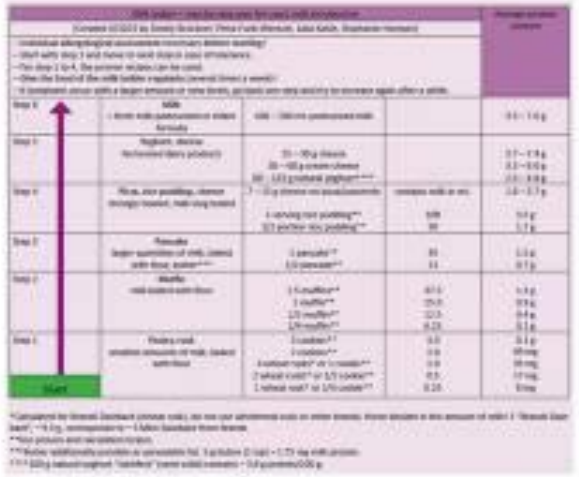


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Table. Cooking temperature and milk protein content for each recipe.

AVMI LEVEL	Meal	Cooking temperature (°C)	Protein mg	Equivalent in milk ml
1A	Cookies	180	95	3.1
1B	Muffins	180	825	26.6
2A	Sweet pancakes	>72	260	8.4
2B	Salted pancakes	>72	1900	61.3
	Croquettes	120	1900	61.3
3A	Bechamel	120	1900	61.3
	Spanish omelette	>72	1900	61.3
3B	Bechamel	100	2600	89.3
	Banana Puree	>72	2600	89.3
	Fillings for the stew	>72	2600	89.3
	French Omelette	>72	2600	89.3
	Sweet French Omelette	>72	2600	89.3
	Spanish Omelette	>72	2600	89.3
4A	1 Yogurt (125g)	N.A.	4000	129
4B	Milk	N.A.	6200	200

Front Nutr . 2024 Feb 28;11:1371772. doi: 10.3389/fnut.2024.1371772

Clinical Pearls

- FPIAP is a common cause of rectal bleeding in young infants. and is a benign disorder of healthy infants and is characterized by an inflammatory reaction to a food allergen limited to the rectum and distal sigmoid colon. It typically affects infants under 12 months of age.
- FPE causes small bowel injury, leading to malabsorption, intermittent vomiting, diarrhea, failure to thrive, and rarely, bloody stools. FPE usually presents in the first 1-2 months of life but may start as late as 9 months.
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- Food challenges or reintroducing foods if they do not appear to affect symptoms is important to optimize nutrition during this critical time for growth and development.