

COW'S MILK PROTEIN ALLERGY "CMPA"-FROM A TO Z

Christina West MD, PhD

**Associate Professor and Senior Consultant
in Pediatrics, Pediatric allergist**

Clinical Sciences, Pediatrics, Umeå University



UMEÅ UNIVERSITY

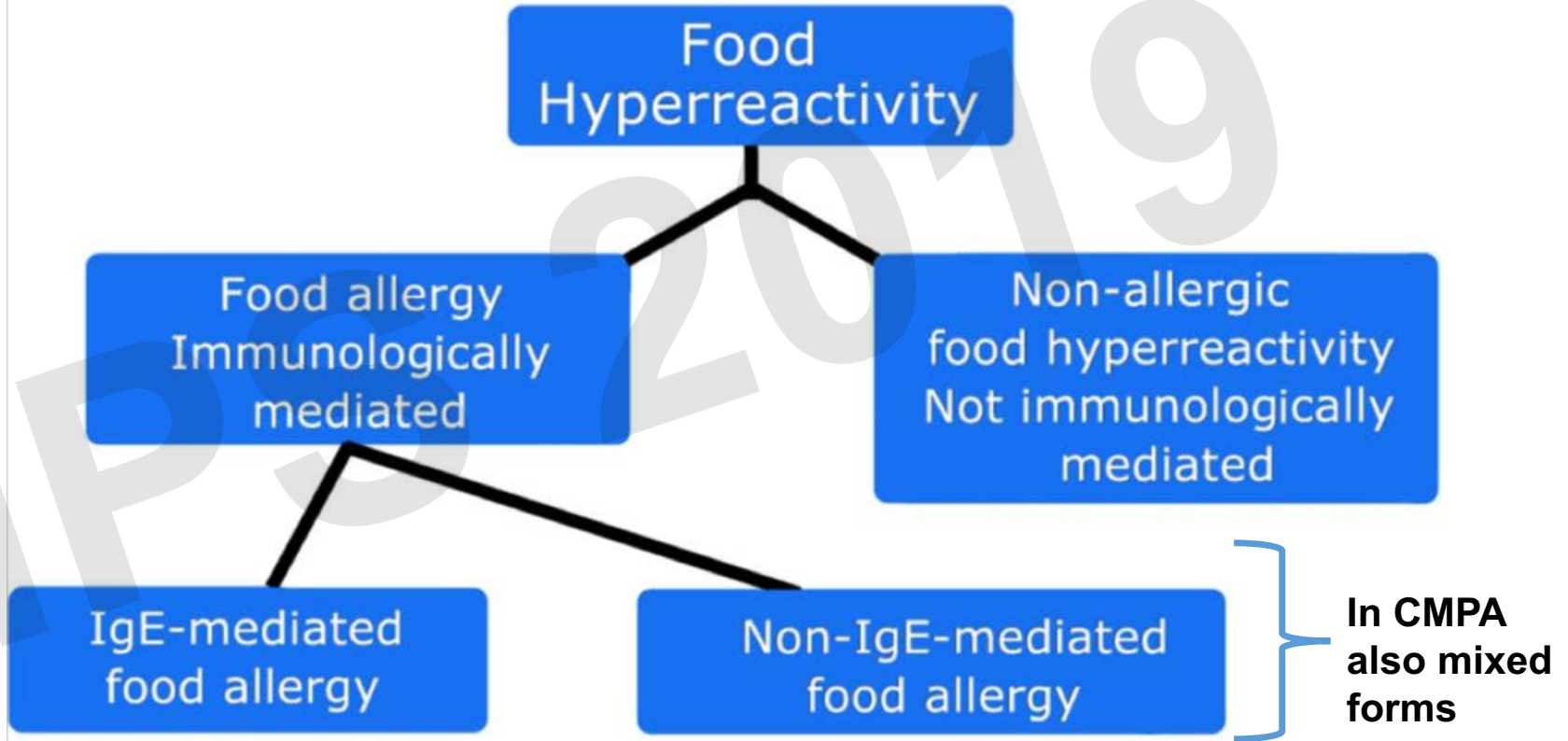
OUTLINE

- **Definitions of cow's milk protein allergy**
- **Epidemiology**
- **Clinical presentations**
- **Clinical guidelines for diagnosis and treatment**



UMEÅ UNIVERSITY

DEFINITIONS:



PREVALENCE OF FOOD ALLERGIES

Children 6-8%

- ✓ Cow's milk 2.5%
- ✓ Egg 1.3%
- ✓ Peanut 1-2%
- ✓ Soybean
- ✓ Wheat
- ✓ Tree nuts
- ✓ Fish
- ✓ Shellfish

Adults 3-4 %



PREVALENCE OF FOOD ALLERGY

- Varies between countries from 1-2% to 10%¹⁻²
- Self-reported allergy (at least) 4x as common as confirmed food allergy
- Meta-analysis (EuroPrevall working group)³:

	Milk	Egg	Peanut	Fish	Shellfish
Self-reported 12-13%	3.5%	1%	0.75%	0.6%	1.1%
Symptomatic/sensitized 3%	0.6%	0.9%	0.75%	0.2%	0.6%
OFC-confirmed 3%	0.9%	0.3%	n/a	0.3%	n/a

¹Chafen JAMA 2010, ²Sicherer JACI 2011,

³Rona et al JACI 2007



Europe / Nordic (n=34)

UK	Czech R	Lithuania
Germany	Russia	Slovenia
Switzerland	Bulgaria	Estonia
Greece	Albania	Croatia
Poland	Ukraine	Romania
Netherlands	Moldova	Hungary
Belgium	Denmark	Serbia
France	Norway	Georgia
Austria	Iceland	Latvia
Spain	Sweden	Belarus
Portugal	Finland	
Italy	Turkey	

Asia / Oceania (n=18)

Australia	Philippines
New Zealand	Indonesia
China	Malaysia
Thailand	Burma
Taiwan	Bangladesh
Korea	Sri Lanka
Japan	Vietnam
Hong Kong	India
Singapore	Mongolia

Americas (n=15)

Canada	Chile
USA	Cuba
Colombia	Peru
Mexico	Venezuela
Panama	Ecuador
Honduras	Paraguay
Argentina	
Uruguay	
Brazil	

Africa (n=12)

Ghana #
Mosambique #
Tanzania #
South Africa
Morocco
Kenya
Congo #
Nigeria
Zimbabwe
Tunisia
Botswana #
Algeria

Middle East (n=10)

Israel
United Arab Emirates #
Lebanon
Iran
Egypt
Jordan
Kuwait
Azerbaijan
Afghanistan
Pakistan

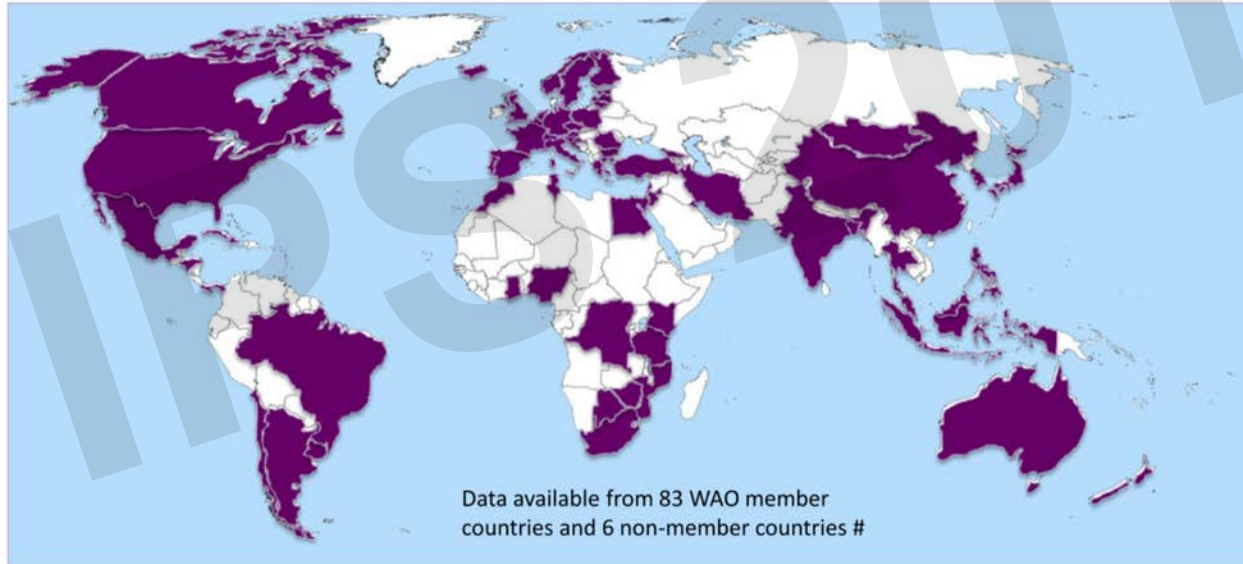


Figure 1 List and distribution of countries who participated in the survey or which had published data available on food allergy prevalence.

?



A global survey of changing patterns of food allergy burden in children. Prescott SL, et al. WAO J. 2013; (6):1:21.

Studies reporting Food Allergy Prevalence for children of all ages (e.g. 0-18 years)

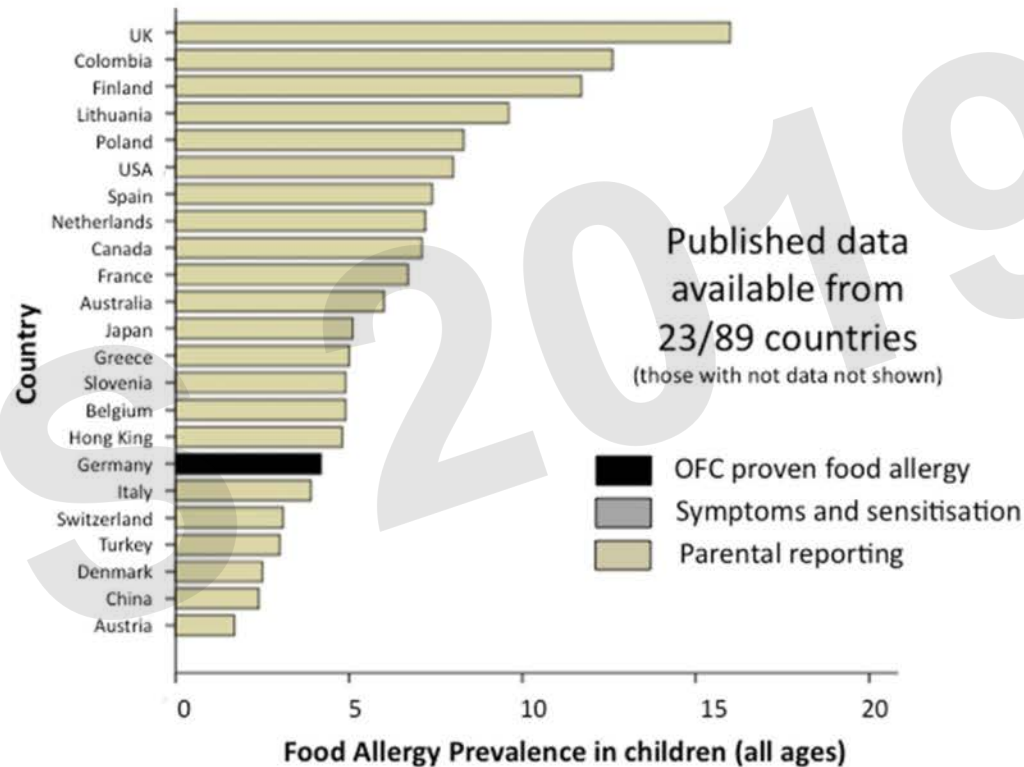
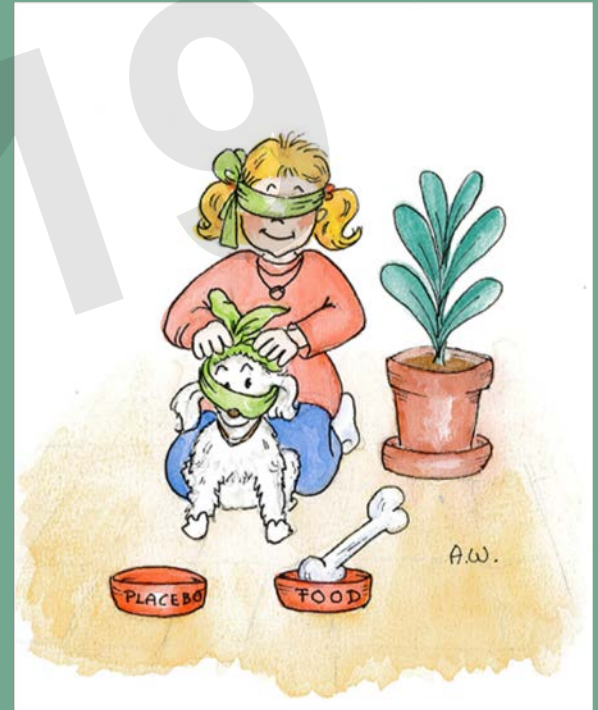


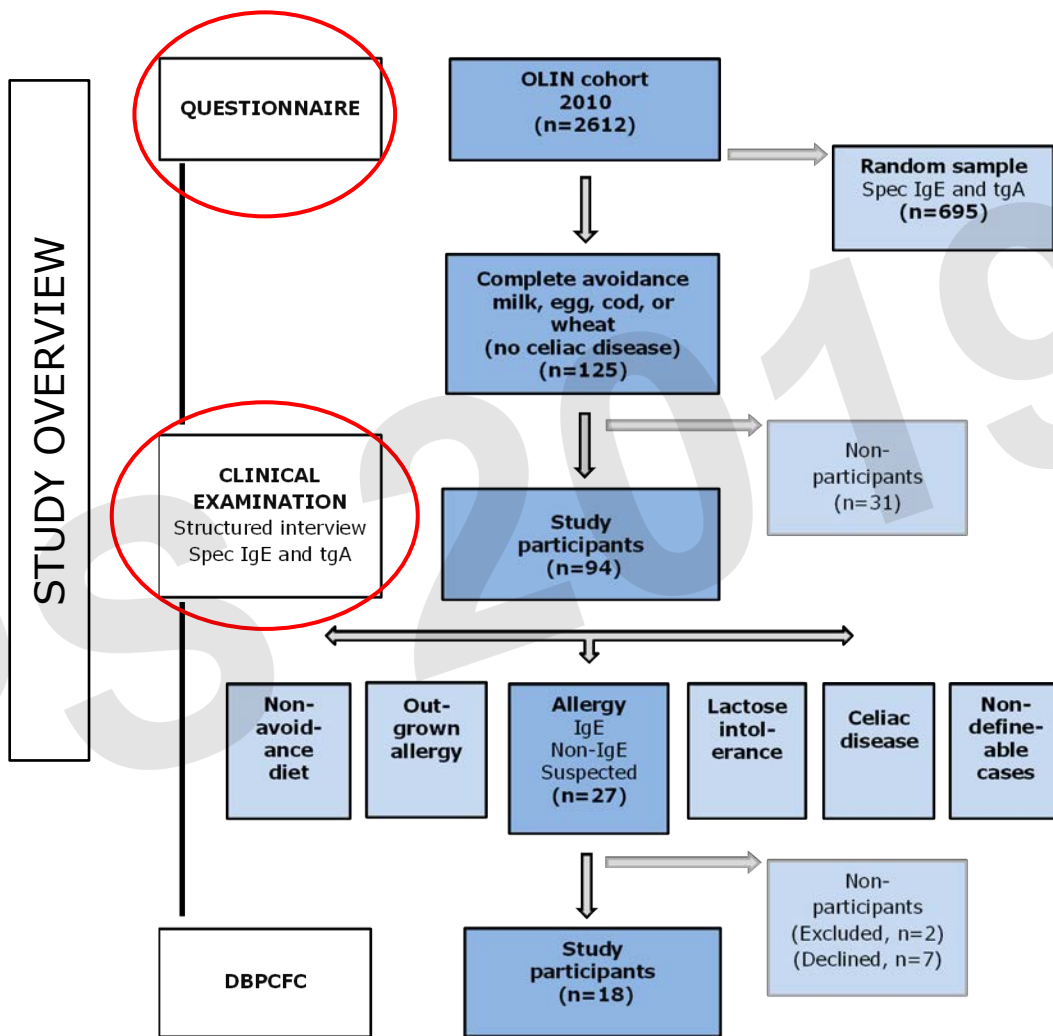
Figure 4 Summary of food allergy prevalence from studies that provided data for children of all ages (generally ranging 0–18 years). Studies are categorised according to level of evidence; OFC proven food allergy (black bars); or questionnaires/parental reporting (yellow bars).

Assessment the prevalence of allergy to cow's milk, hen's egg, cod and wheat among 11-12-year old Swedish children using

- Reported data
- Clinical investigations
- Double-blind placebo-controlled food challenges



UMEÅ UNIVERSITY

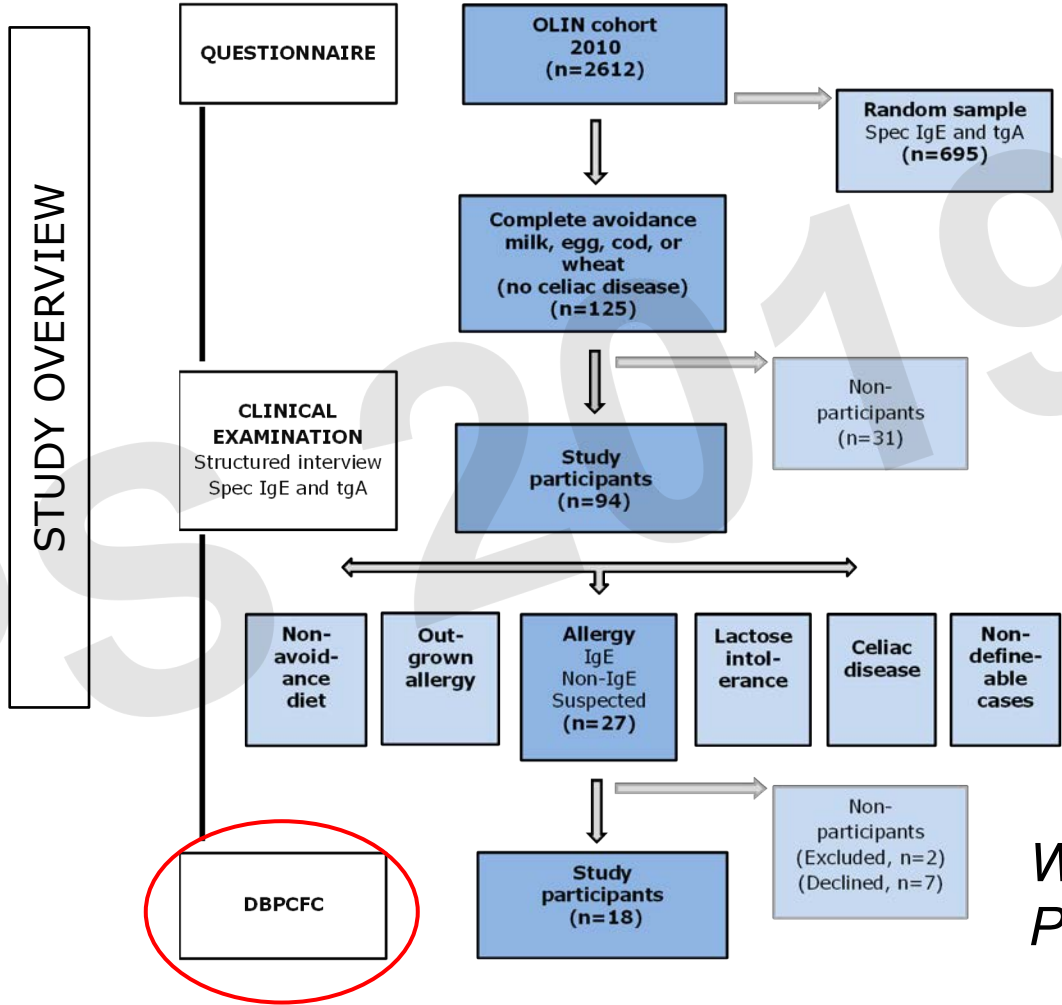


*Winberg et al
PLOS One, 2015*

DISTRIBUTION OF PHENOTYPES OF FOOD HYPERSENSITIVITY (FHS) BASED ON THE CLINICAL EXAMINATIONS, AND THE RELATION TO THE INDIVIDUAL TRIGGERING FOODS

FHS PHENOTYPE	Participants	Triggering foods*			
	(n=94) n (%)	Milk (n=87) n (%)	Egg (n=12) n (%)	Cod (n=16) n (%)	Wheat (n=4) n (%)
ALLERGY					
IgE-mediated allergy	18 (19)	3 (3)	8 (67)	12 (75)	1 (25)
Non-IgE-mediated allergy	6 (6)	6 (7)	0	0	0
Suspected allergy	3 (3)	0	2 (17)	3 (19)	0
Outgrown allergy	18 (19)	28 (32)	0	0	1 (25)
LACTOSE INTOLERANCE					
Lactose intolerance	27 (29)	29 (33)	0	0	0
Suspected lactose intolerance	11 (12)	11 (13)	0	0	0
CELIAC DISEASE					
	1 (1)	0	0	0	1 (25)
NON-DEFINABLE CASES					
Symptoms not definable	2 (3)	3 (3)	0	0	1 (25)
No blood analyses (specific IgE/tTGA)	7 (7)	6 (7)	2 (16)	1 (6)	0
NON-AVOIDANCE DIET					
	1 (1)	1 (1)	0	0	0





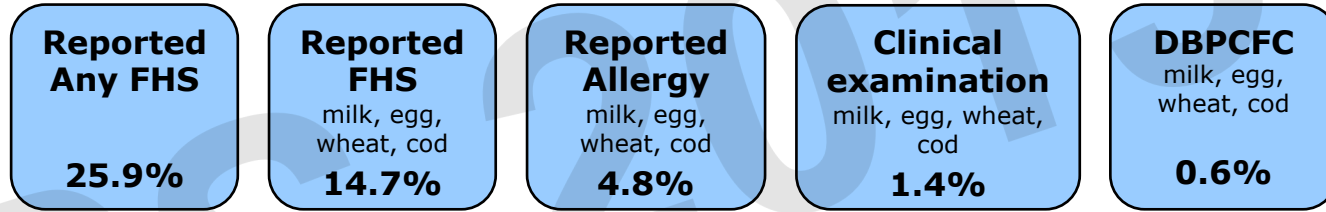
*Winberg et al
PLOS One, 2015*

Assessment of Allergy to Milk, Egg, Cod, and Wheat in Swedish Schoolchildren:

A Population Based Cohort Study

Winberg A, West CE, Strinnholm Å, Nordström L, Hedman L, Rönmark E PLoS One. 2015;10(7):e0131804

Main results:

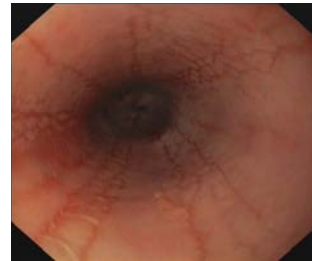


- *The majority of children reporting allergy to milk, egg, wheat or cod were categorized as another FHS-phenotype*



CLINICAL PRESENTATIONS OF CMPA





Presentations of CMPA:

An adverse reaction to milk, mediated by the immune system

IgE-Mediated

- Anaphylaxis
- Urticaria
/ Angioedema
- Immediate GI symptoms
- Food-associated, exercise-induced anaphylaxis

Mixed

- Atopic eczema
- Eosinophilic gastrointestinal disorders

Non-IgE-Mediated

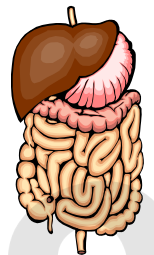
- Food protein-induced enteropathy
- Food protein-induced proctitis/proctocolitis
- Food Protein-Induced Enterocolitis (FPIES)
- Gastroesophageal reflux
- Colic
- Constipation
- Heiner's syndrome*

**Milk-induced pulmonary disease*



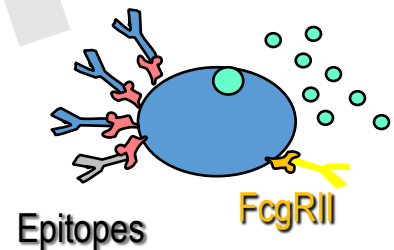
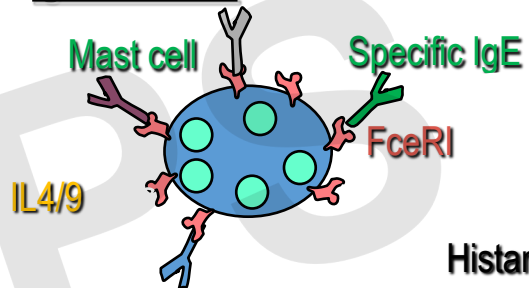
Pathophysiology

Courtesy of Dr K. Järvinen-Seppo



- ◆ Protein digestion, absorption
- ◆ Antigen processing
- ◆ Antigen presentation to T cells

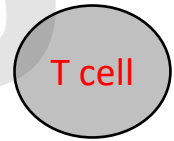
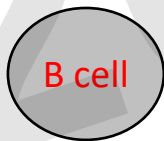
IgE-Mediated



Histamine:
flushing, vasodilation,
pruritus,
bronchoconstriction

Tryptase: vascular
permeability

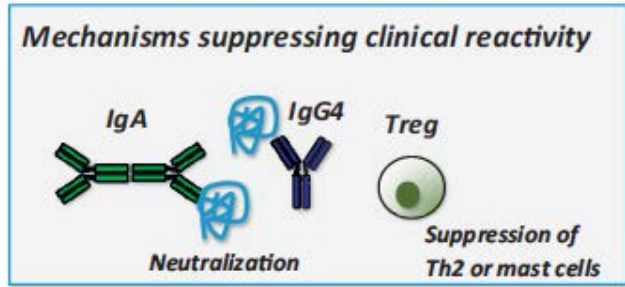
Lipid mediators

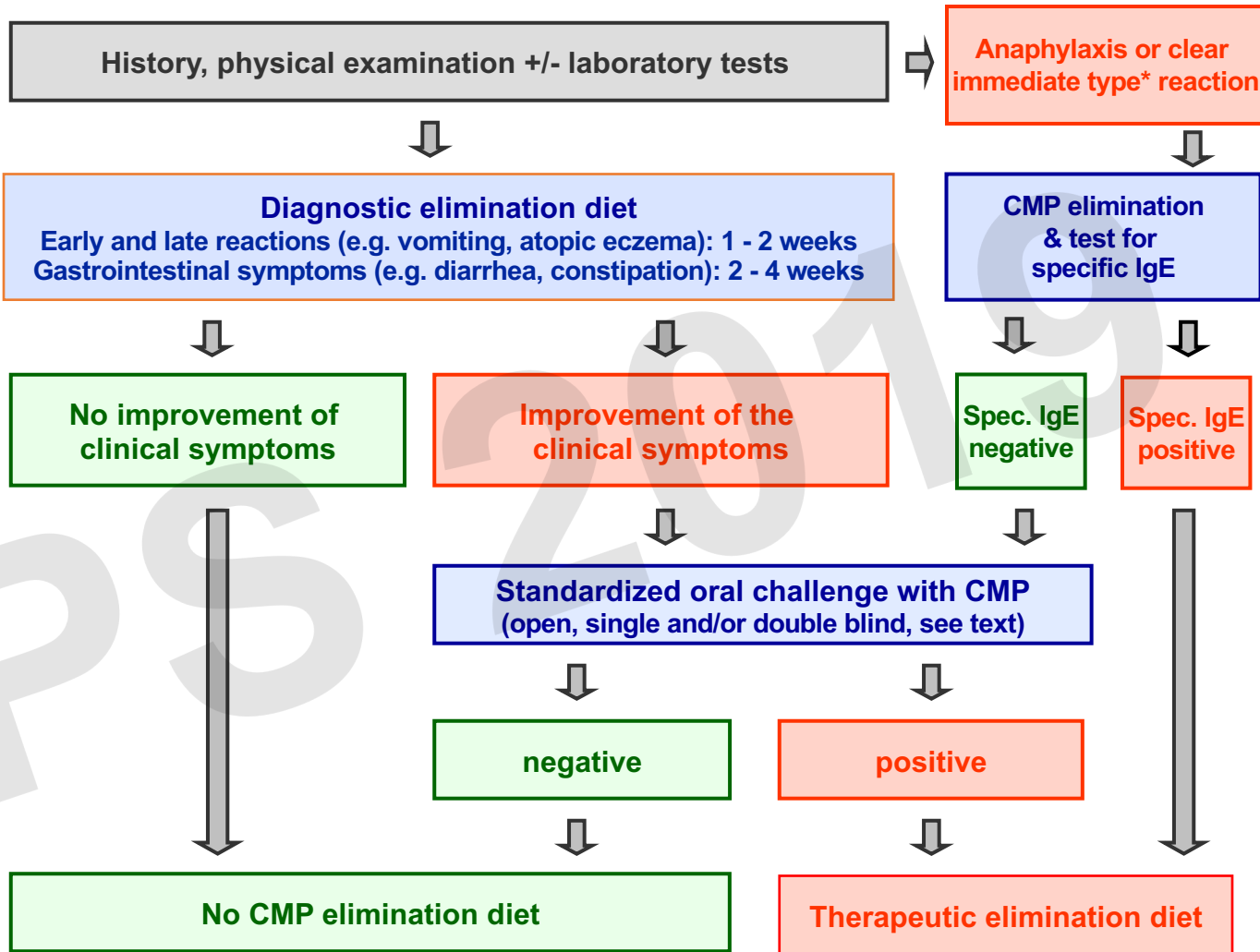


IL-4

Non-IgE Mediated

IL5/13, CCL26, TSLP
TGFb





TREATMENT

Breast-fed infants:

- Mothers should be encouraged to breastfeed while avoiding all milk and milk products
- If the infant receives complementary feeding or drugs- must be free of milk protein
- Dietary counseling needed
- If severe symptoms plus growth faltering/hyponatremia/ and/or severe anemia- use a therapeutic formula (days- to 2 weeks)



UMEÅ UNIVERSITY

*ESPGHAN guidelines. Koletzko S et al.
JPGN 2012;55:221-9.*

TREATMENT

Non-breast-fed infants:

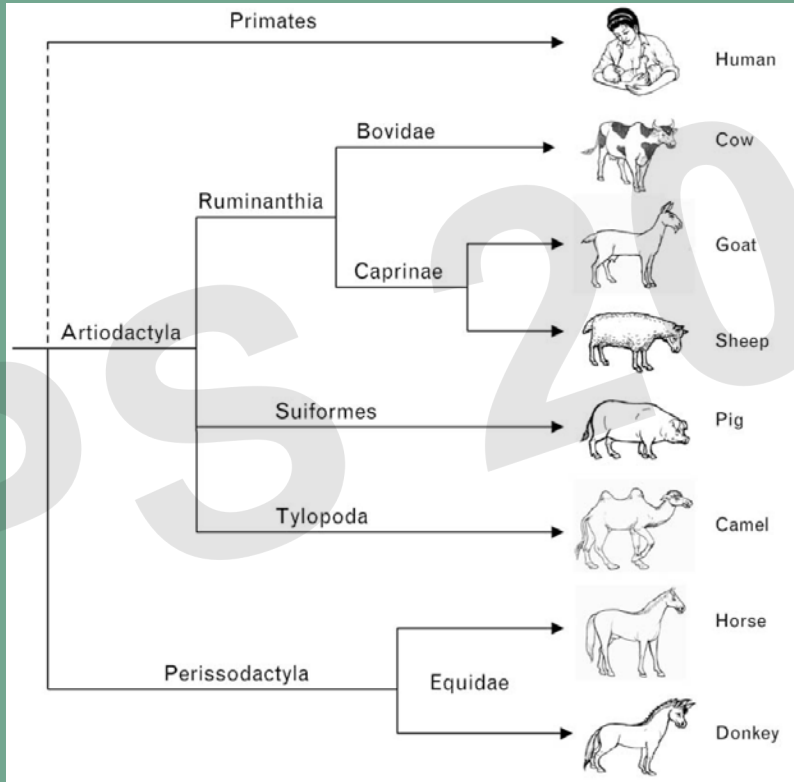
- Formula, any complementary feeding or drugs- must be free of cow's milk protein and other unmodified animal milk proteins (e.g. goat's milk and sheep's milk)
- Elimination diet usually starts with an extensively hydrolyzed formula (eHF) with proven efficacy in infants
- If extremely severe or life-threatening symptoms an amino acid formula (AAF) may be the first choice



UMEÅ UNIVERSITY

*ESPGHAN guidelines. Koletzko S et al.
JPGN 2012;55:221-9.*

Cow's Milk Allergens



Caseins (80%)

- α s1-casein 32%
- α s2-casein 10%
- β -casein 28%
- κ -casein 10%

Whey proteins (15%)

- β -lactoglobulin 10%
- α -lactalbumin 5%

TREATMENT

Toddlers and children:

- A nutritionally adequate elimination diet can be provided by solid foods and liquids free of cow's milk protein from 2 years of age
- Goat's and sheep's milk protein should be eliminated due to high cross-reactivity with cow's milk protein
- Dietary counseling needed



UMEÅ UNIVERSITY

*ESPGHAN guidelines. Koletzko S et al.
JPGN 2012;55:221-9.*

Middle East Consensus Statement on the Prevention, Diagnosis, and Management of Cow's Milk Protein Allergy

Yvan Vandenplas, Ahmed Abuabat^{*}, Suleiman Al-Hammadi[†], Gamal Samy Aly[‡],
Mohamad S Miqdady[§], Sanaa Youssef Shaaban^{||} and Paul-Henri Torbey[¶]

Department of Pediatrics, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium, ^{}King Abdullah Bin Abdul Aziz University Hospital, Princess Nora Bint Abdulrahman University, Riyadh, Kingdom of Saudi Arabia, [†]Department of Pediatrics, College of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates, [‡]Department of Child Health and Nutrition, Institute of Postgraduate Childhood Studies, Ain Shams University, Cairo, Egypt, [§]Division of Pediatric Gastroenterology, Hepatology & Nutrition, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates, ^{||}Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt, [¶]Department of Pediatrics, Hôtel-Dieu de France, St. Joseph University, Beirut, Lebanon*

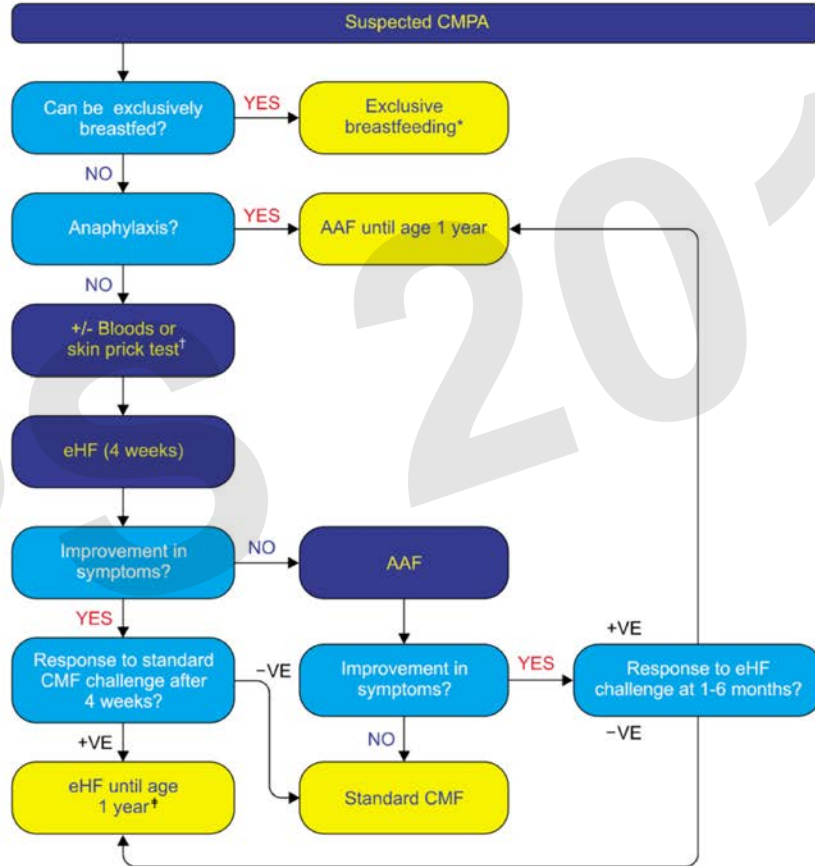


Fig. 2. An algorithm for the treatment of CMPA. *Breast-feeding mothers should exclude all products containing CMP from their diet and take calcium supplements. †IgE-specific test or skin prick test can be performed if laboratory facilities are available. †Soy formula can be used if eHF is unavailable or unpalatable. CMPA: cow's milk protein allergy, AAF: amino acid formula, CMF: cow's milk formula, eHF: extensively hydrolyzed formula, +VE: positive, -VE: negative.

RESOLUTION OF CMPA

IgE-mediated:

Cow's milk allergy: 79% by 16 years ¹

Recurrence is extremely uncommon

Recognition of linear epitopes ²

Tolerance of baked milk ³

Non-IgE-mediated:

Proctocolitis most outgrow by 1 year

FPIES: most outgrow by 3-4 years of age

EoE: variable

¹ Skripak JACI 2007,

² Järvinen JACI 2002,

³ Nowak-Wegrzyn

JACI 2008



REEVALUATION

- "There is insufficient evidence to recommend an optimal interval before reevaluation"
- The duration of the milk elimination diet depends on
 - Age
 - Severity of symptoms
 - Positivity of specific IgE to cow's milk protein
- In clinical practice challenge with cow's milk is performed after maintaining a milk-free diet for 3 months (mild disease) up to at least 12 months (severe disease)



UMEÅ UNIVERSITY

*ESPGHAN guidelines. Koletzko S et al.
JPGN 2012;55:221-9.*

CMPA

Common in infancy

If suspected, strict allergen avoidance is initiated

Diagnosis relies on a **controlled oral food challenge**

Reevaluation important



Umeå University

Pediatric study nurses

Pediatric laboratory analysts

Dr Kotryna Simonyté Sjödin

A/Prof Patrik Rydén

Dr Andreas Sjödin

Prof Olle Hernell

Prof Marie-Louise Hammarström

**Participating
families**

Univ. of Western Australia

Prof Susan Prescott

Prof Meri Tulic

Dr Debbie Palmer

**Funding
Bodies**

SciLife Lab/Karolinska Institute

Prof Lars Engstrand

Dr Daniel Lundin

Dr Maike Seifert

Dr Hugo Wefer