



COW`s MILK PROTEIN ALLERGY

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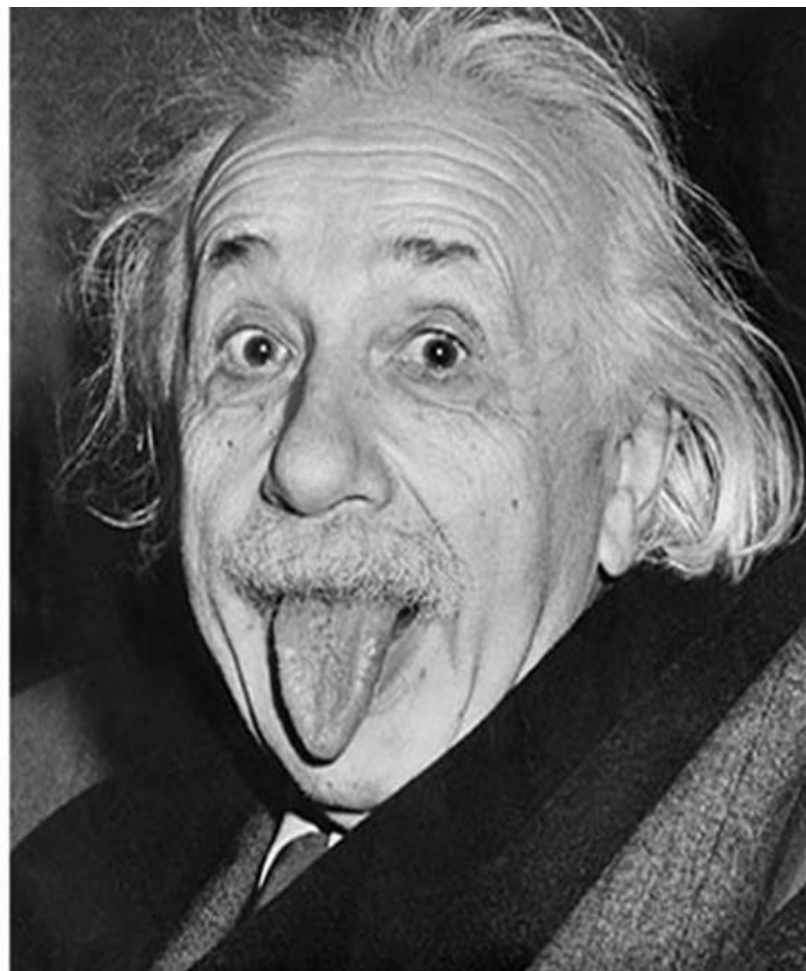
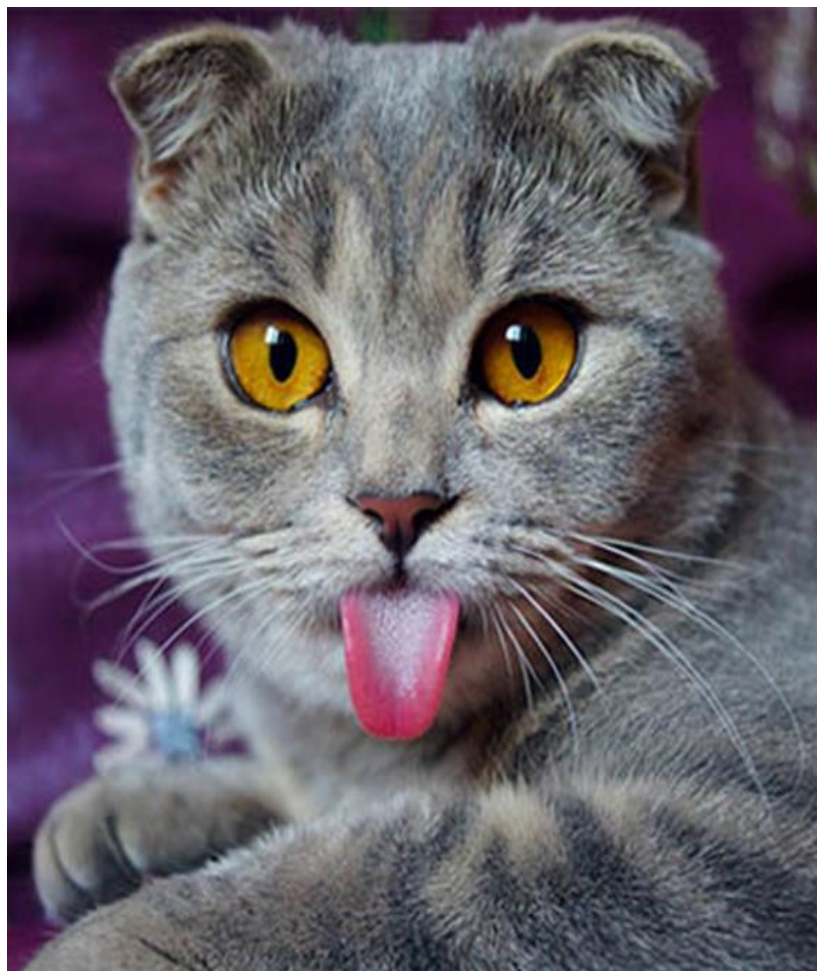
Agenda of the talk

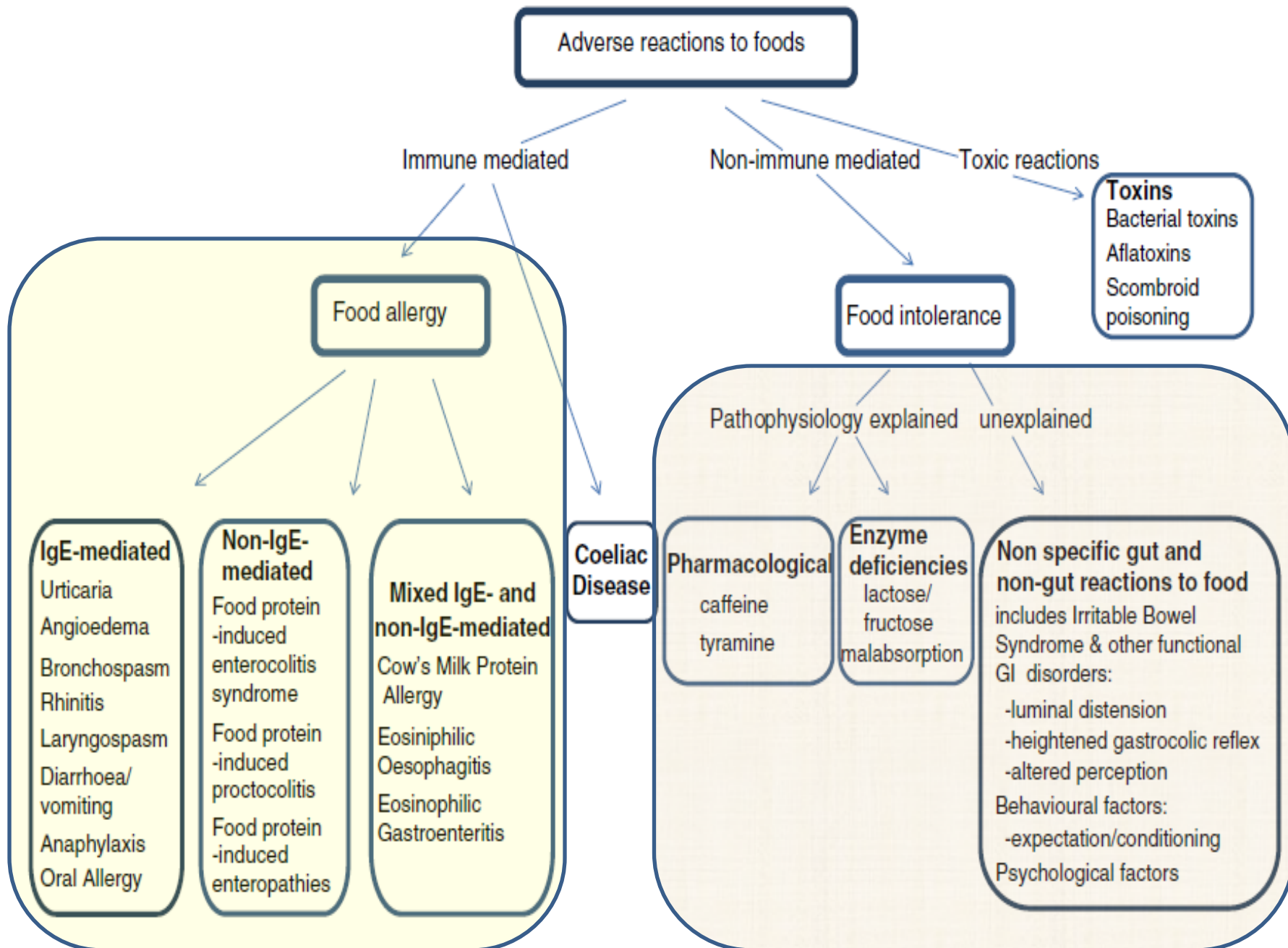
- Definitions
- CMPA Epidemiology and Pathogenesis
- CMPA Diagnosis
- CMPA Management
- CMPA prevention

Adverse Food Reaction

Broad term indicating a link between an ingestion of a food and an abnormal response

Reproducible adverse reactions may be caused by a toxin, a pharmacologic effect, an immunologic response, or a metabolic disorder





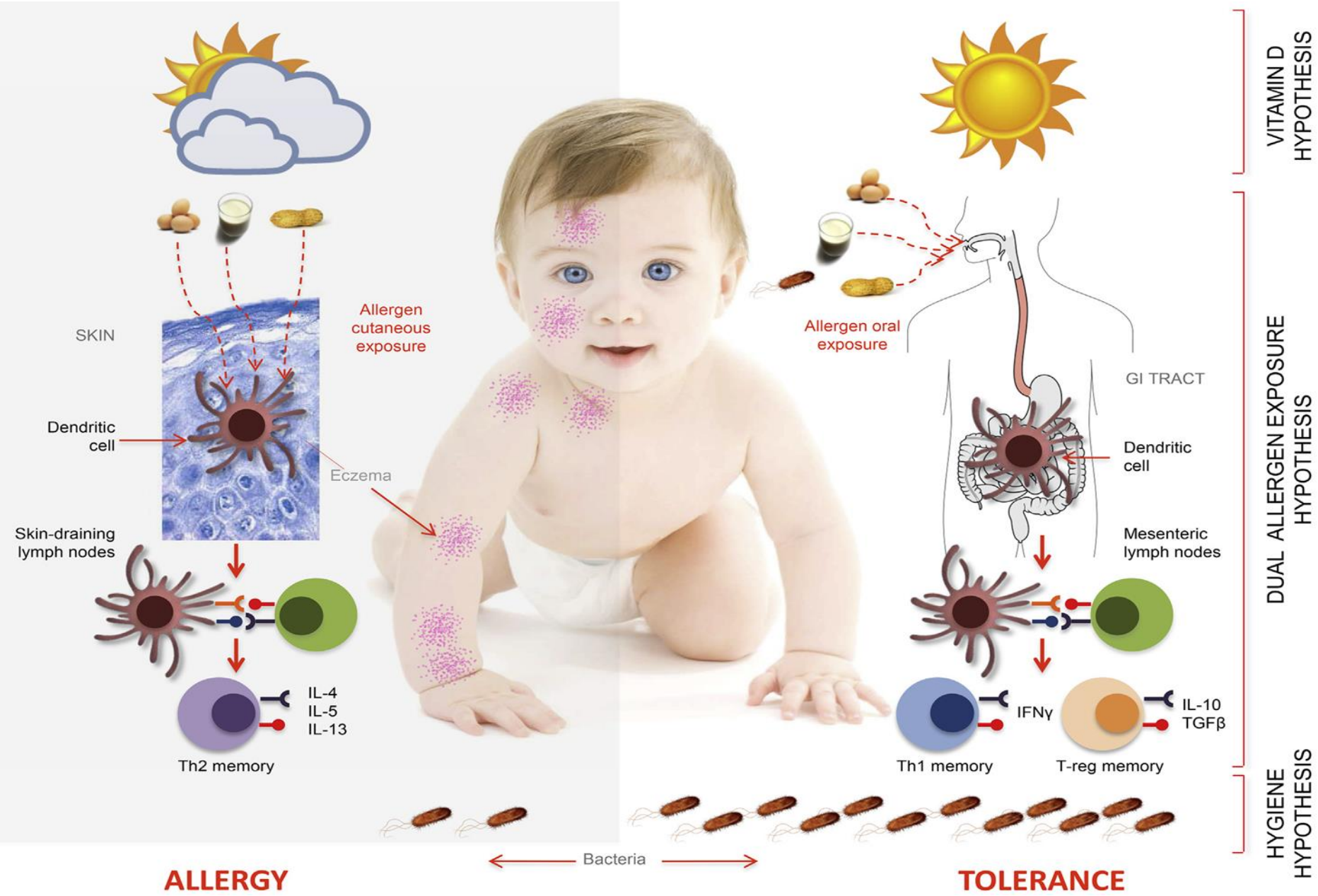
- Food allergy is an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food
- Food allergens are specific components of food or ingredients within, that are recognized by allergen-specific immune cells and elicit specific immunologic reactions, resulting in characteristic symptoms

Sensitization indicates demonstrable IgE antibody to a food without having clinical symptoms on exposure

This does not equate with clinical food allergy

- Tolerance is the suppression of adverse immune responses to non-harmful ingested food antigens





ALLERGY

TOLERANCE

VITAMIN D
HYPOTHESIS

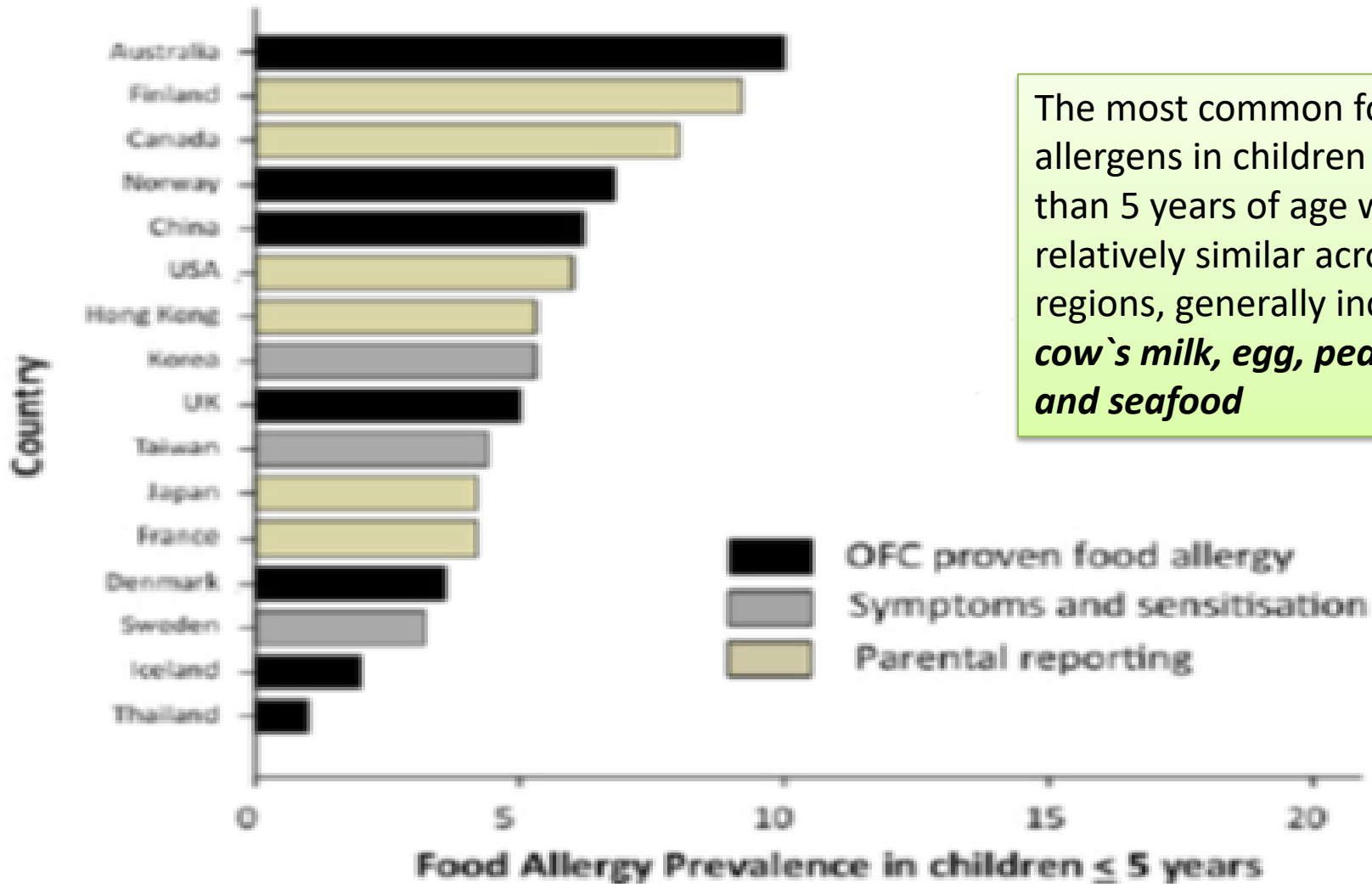
DUAL ALLERGEN EXPOSURE
HYPOTHESIS

HYGIENE
HYPOTHESIS

Food allergy Epidemiology

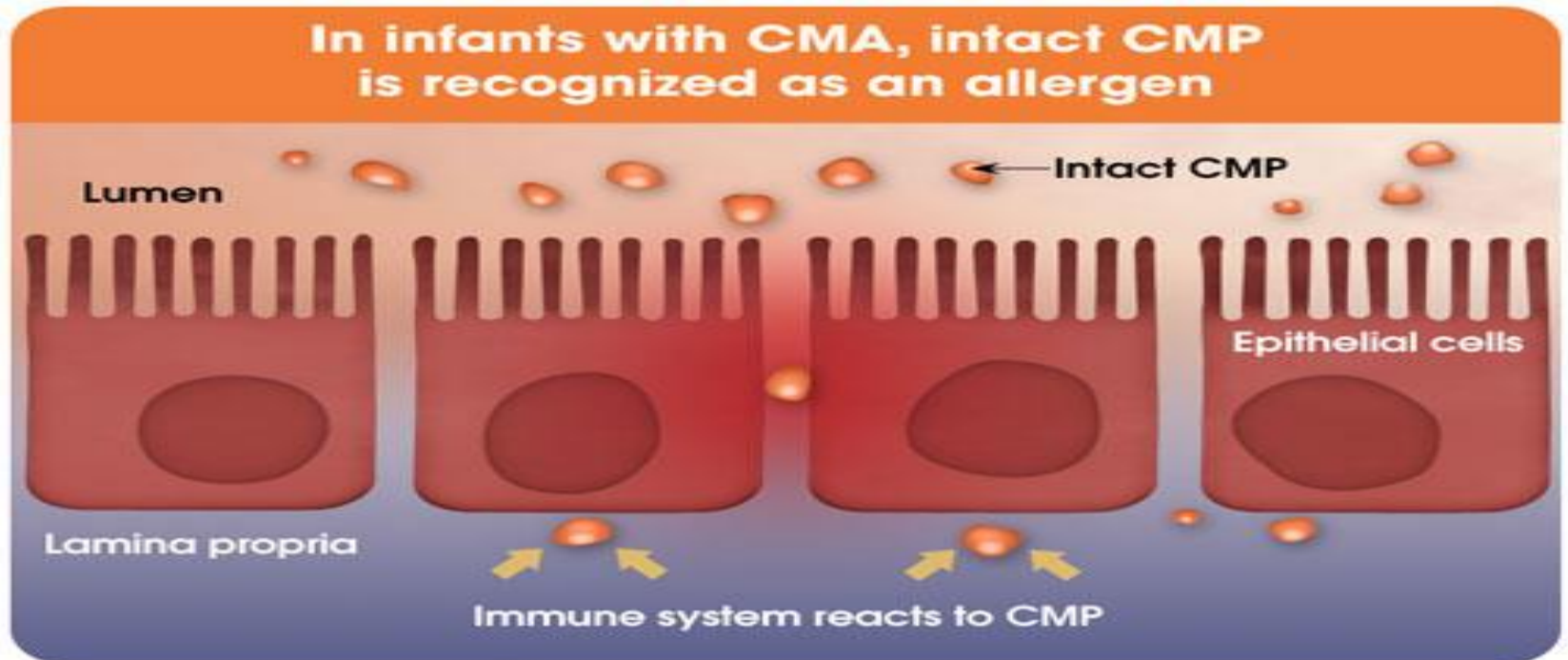
Prevalence of food allergies is rising in both developed and developing countries, especially over the last 10-15 years which increases the personal as well as global health burden

Studies reporting Food Allergy Prevalence in preschool children ≤ 5 years



The most common food allergens in children less than 5 years of age were relatively similar across all regions, generally including ***cow`s milk, egg, peanuts and seafood***

Cow's milk protein allergy (CMPA)



is an immunological reaction to one or more milk proteins

What is the allergen?

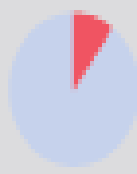





**PATIENTS ARE MORE OFTEN SENSITIZED TO ALPHA (100%)
AND KAPPA CASEINS (91.7%)**

- Cross-reactivity may occur when an antibody reacts not only with the original allergen, but also with a similar allergen
- Adverse reaction to food or aeroallergen might be provoked by another allergen which share structural or sequence similarity
- Milk allergens of various mammalian species cross-react

The greatest homology is among cows, sheep and goats, while proteins in the pig, horse, donkey and camel milk have less structural homology

<p>Cow's milk*</p> 	<p>Beef hamburger</p> 	<p>10%</p> 
<p>Cow's milk*</p> 	<p>Goat's milk goat</p> 	<p>92%</p> 
<p>Cow's milk*</p> 	<p>Mare's milk horse</p> 	<p>4%</p> 

Why?



Cow`s
milk
feeding

Atopy

Maternal
Factors



Atopy: Allergy Genes

- Risk of CMPA increases by 20-40% if one parent had allergic disease
- Risk of CMPA increases by 40-60% if both parent had allergic disease

Cow`s Milk Feeding

- Significantly higher cow`s milk protein compared to breast milk
- Loss of immunomodulators in breast milk
- Different gut microflora

Arch Dis Child. 2007;92:902-908

Maternal Factors

Factors	Inducing	Protective
Antigens	Sensitizing allergens	Tolerizing allergens
Cytokines	IL-4	TGF- β
	IL-5	sCD14
	IL-13	
Immunoglobulins		s-IgA to ovalbumin
Polyunsaturated fatty acids	Arachidonic acid	Eicosapentanoic acid
		α -Linoleic acid
		n-3 Polyunsaturated fatty acids
Chemokines	RANTES	
	IL-8	
Polyamines		Spermine
		Spermidine

Allergy can be immunoglobulin E (IgE)-mediated or non-IgE-mediated

IgE mediated

Minutes to 2 hr

May persist beyond 1 yr of age

Two phases : "sensibilization" and "activation"

Specific serum IgE skin prick test

Non-IgE mediated

Several hours to days

Usually resolved by 1 yr

Reactions mediated by Th1 cells, interactions between T lymphocytes, mast cells and neurons that alters the function of the smooth muscle and the intestinal motility

Oral challenge test

Combinations of immediate and delayed reactions to the same allergen may occur

Prevalence of CMPA in children



European data :
Prevalence: 1.9 - 4.9%
Incidence (below 1 year of age): 2-3%

Clinical Manifestations

Most infants with CMA develop symptoms within the first month after introduction of CMP-based Formula

The majority has two or more symptoms from two or more organ systems

Clinical symptoms and signs in the digestive tract may be due to inflammation, dysmotility, or a combination of both

Systems involved

Organ system	Symptom
Systemic	<ul style="list-style-type: none">• Anaphylaxis (flaccidity/floppiness; pallor/cyanosis)• Shock-like symptoms with severe metabolic acidosis, vomiting & diarrhea (FPIES)• Infantile colic
Gastrointestinal (50-60%)	<ul style="list-style-type: none">• Oral allergy syndrome• Vomiting, regurgitation, reflux• Dysphagia; food impaction• Delayed gastric emptying• Abdominal pain• Diarrhea (bloody stools, protein losing enteropathy)• Proctocolitis• Constipation +/- perianal rash• Anorexia, failure to thrive, early satiety• FPIES• Eosinophil infiltration (eosinophilic esophagitis, gastritis, enterocolitis)
Dermatological (5-60%)	<ul style="list-style-type: none">• Urticaria (unrelated to infections, drug intake, or other causes)• Atopic dermatitis• Angioedema
Respiratory (20-30%)	<ul style="list-style-type: none">• Runny nose (rhinitis)• Wheezing, stridor• Chronic coughing (all unrelated to infections)

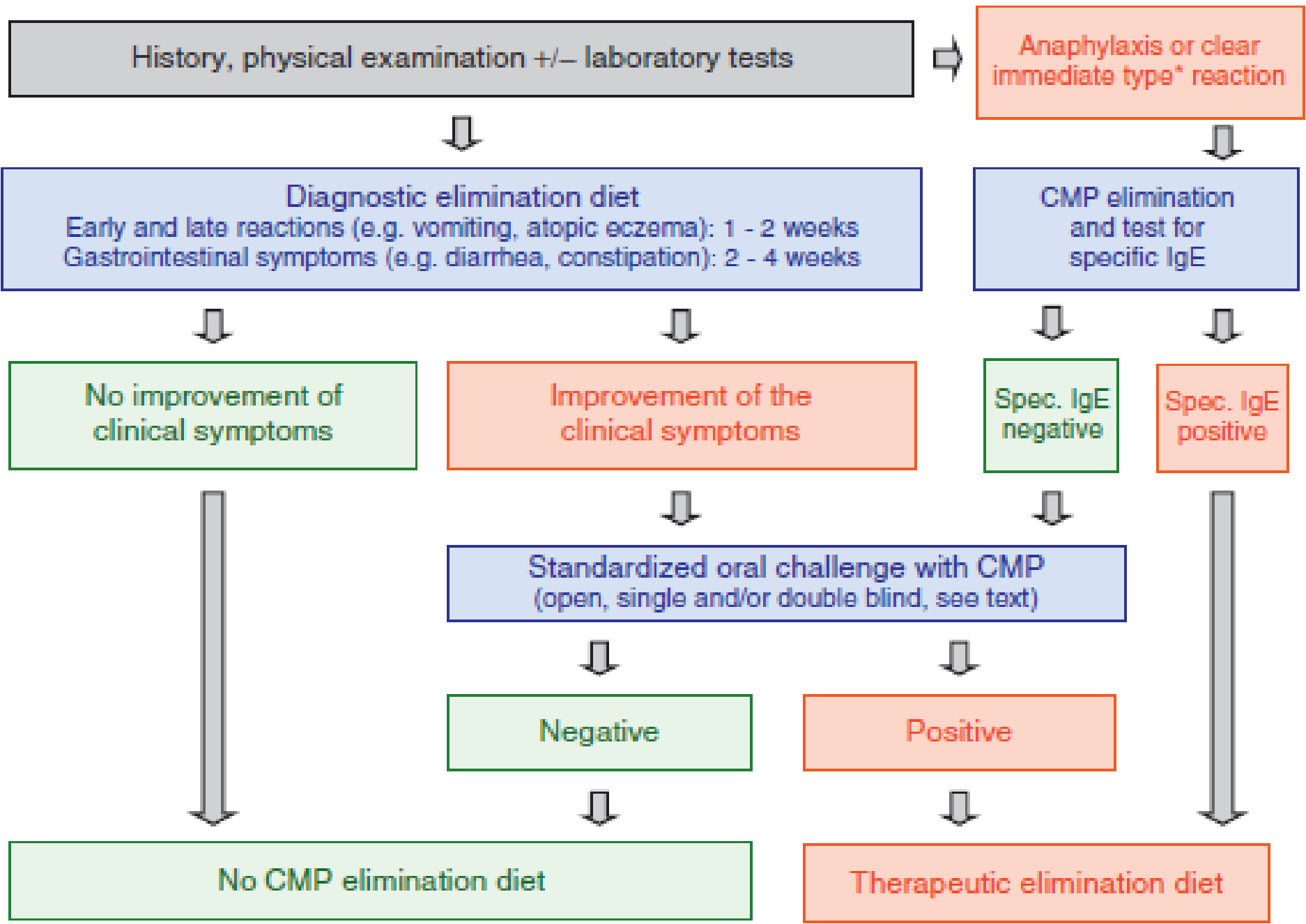
Diagnosis



The First step
History and Physical Examination

Suspect CMPA if:

- Family history of atopy
- Abrupt onset of symptoms (within 2 hrs.)
- Appearance of symptoms within two months after ingesting Cow`s milk protein
- More than two systems involved
- Symptomatic treatment failed



Serum IgE & Skin Prick Test

Multiple guidelines consider them useful or confirmatory for the diagnosis

Limited value in case of non-IgE mediated CMPA

May identify a sensitization to a specific allergen

Positive results in these assays do not necessarily predict the existence of a clinically significant allergy

Skin prick test should preferably utilize fresh foods, thermal processing may destroy heat-labile proteins which contribute to the allergenicity producing false negative results

Recent studies suggest that these two assays are not interchangeable tests as they show only a moderate agreement in young children

One study also suggests SPT results are more closely related to clinical symptoms than sIgE in children under the age of 5

Allergy 2015;70(1):41-48

- Quantification of both of these test results allows prediction of the likelihood of a further reaction and hence is useful for prognostic purposes
- The higher the antibody titer and the larger the diameter of the SPT reaction, the greater is the probability of having a reaction to CMP and allergy persistence



CoFAR

Consortium of Food Allergy Research

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CoFAR MILK ALLERGY RESOLUTION PROBABILITY OVER TIME

To be used for young (less than 15 months old) patients with their presenting (greater than 3 months of age) values; for PST use Milk wheal size minus Saline control wheal size.

Milk IgE: KUA/L

Milk PST: MM

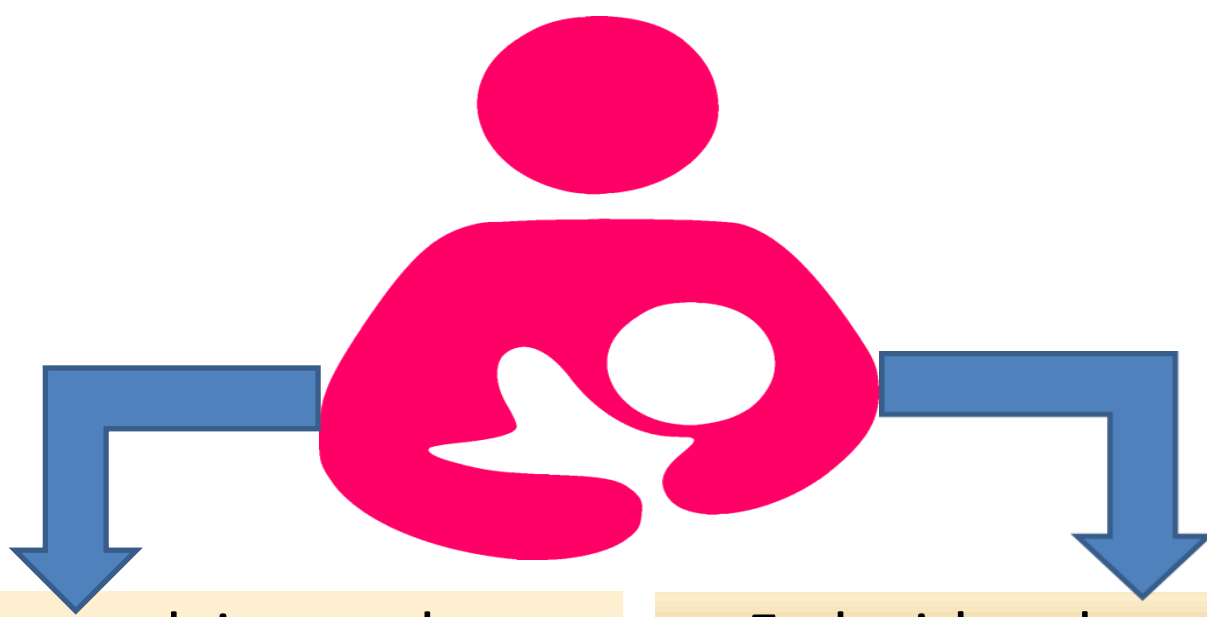
Atopic Dermatitis Status: 0=None or Mild 1=Moderate or Severe

[Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DM, Henning AK, Mayer L, Burks AW, Grishin A, Stablein D, Sampson HA. The Natural History of Milk Allergy in an Observational Cohort. J Allergy Clin Immunol. 2013;131\(1\):1-10.](#)

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To add to home screen, once the desired page has finished loading, tap on the toolbar button with a square and an arrow inside it. A menu should now be displayed on top of your Safari browser window. Select the Add to Home Screen option. This text is editable and can be changed to whatever you desire. It is important, as this is the title which will be shown on the home screen. Once you are done, select the Save button. The shortcut will be a link to this page.



- Eliminate dairy products from maternal diet, supplement mother with Calcium
- Encourage breastfeeding
- Consider Egg, Soy elimination

- Fed with a therapeutic formula for a period of from several days to a maximum of 2 weeks
- AAF for diagnostic elimination in these extremely sick exclusively breast-fed infants



eHF

First choice
Chemical &
Enzymatic Hydrolysis
Small peptides and
AA
Less palatable
More costly

AAF

In infants with
extremely severe or
life-threatening
symptoms
After 2 weeks with
no response on eHF

Soy F

> 6 months who do
not accept the bitter
taste of an eHF, or in
cases in which the
higher cost of an eHF
is a limiting

Confirming Diagnosis of CMPA

Oral Challenge Test

Challenge procedure may be omitted because either the likelihood of CMPA is extremely high or an allergen challenge procedure would be too risky (eg, history of anaphylaxis in a sensitized child)

Challenge

Open vs DBPCFC

Formula

Cow`s milk formula

Fresh Cow`s milk

Lactose-Free Formula

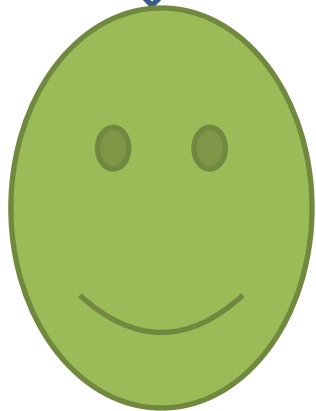
Volume

Small

Increase gradually

Interpretation

No Allergic symptoms after Two weeks



Objective symptoms and positive specific IgE

CMPA confirmed,
Elimination treatment

Uncertain symptoms /severe eczema

Do
DBPCFC

Management of Cow`s Milk Protein Allergy

Strict avoidance of CMP is presently the safest strategy for managing CMPA



Hypoallergenic formulas

The ideal protein hydrolysed formulas should:

1. not contain peptides larger than 1,5KD
2. contain no intact proteins
3. demonstrate no anaphylaxis in animals
4. reveal protein determinant equivalents less than 1/1,000,000 of original protein
5. Most importantly, the formula must be demonstrated safe in milk allergic infants by both double-blind placebo-controlled

Extensively hydrolyzed Formulas

- First choice
- No complete avoidance of CMP: could lead to persistence of allergy or induce severe reaction
/Better in inducing tolerance
- Palatability
- Cost
- Higher renal solute load
- Might induce delay in intestinal enzymatic maturation

AAF

Provide protein as AA with no peptide

AAFs are suitable first line formulas for cow's milk allergy but are usually reserved, because of their higher cost, for those infants with :

- Multiple food allergies
- Severe cow's milk allergy
- Allergic symptoms or severe atopic eczema when exclusively breast fed
- Severe forms of non-IgE mediated cow's milk allergy such as eosinophilic oesophagitis, enteropathies and FPIES
- Faltering growth
- Reacting to or refusing to take eHF



Palatable

Less expensive

Can be used in infants after 6 months of age

Concomitant soya protein allergy affects about 1 in 10 infants with cow's milk allergy, occurring equally in IgE mediated and non-IgE mediated cow's milk protein allergy



- Stable, less allergenic food
- Enzymatic proteolysis of rice protein
- Fortification with (ess. AA ,Fe , Zn)
- No growth issues
- Safe in case of Cow`s milk and soy protein allergy
- Ten years in use
- The availability is an issue

PHF

means

Partially Hydrolyzed
Formula

**Not hypoallergenic and
shouldn't be used in
suspected, proven cow's
milk allergy or diagnostic
exclusion diet**

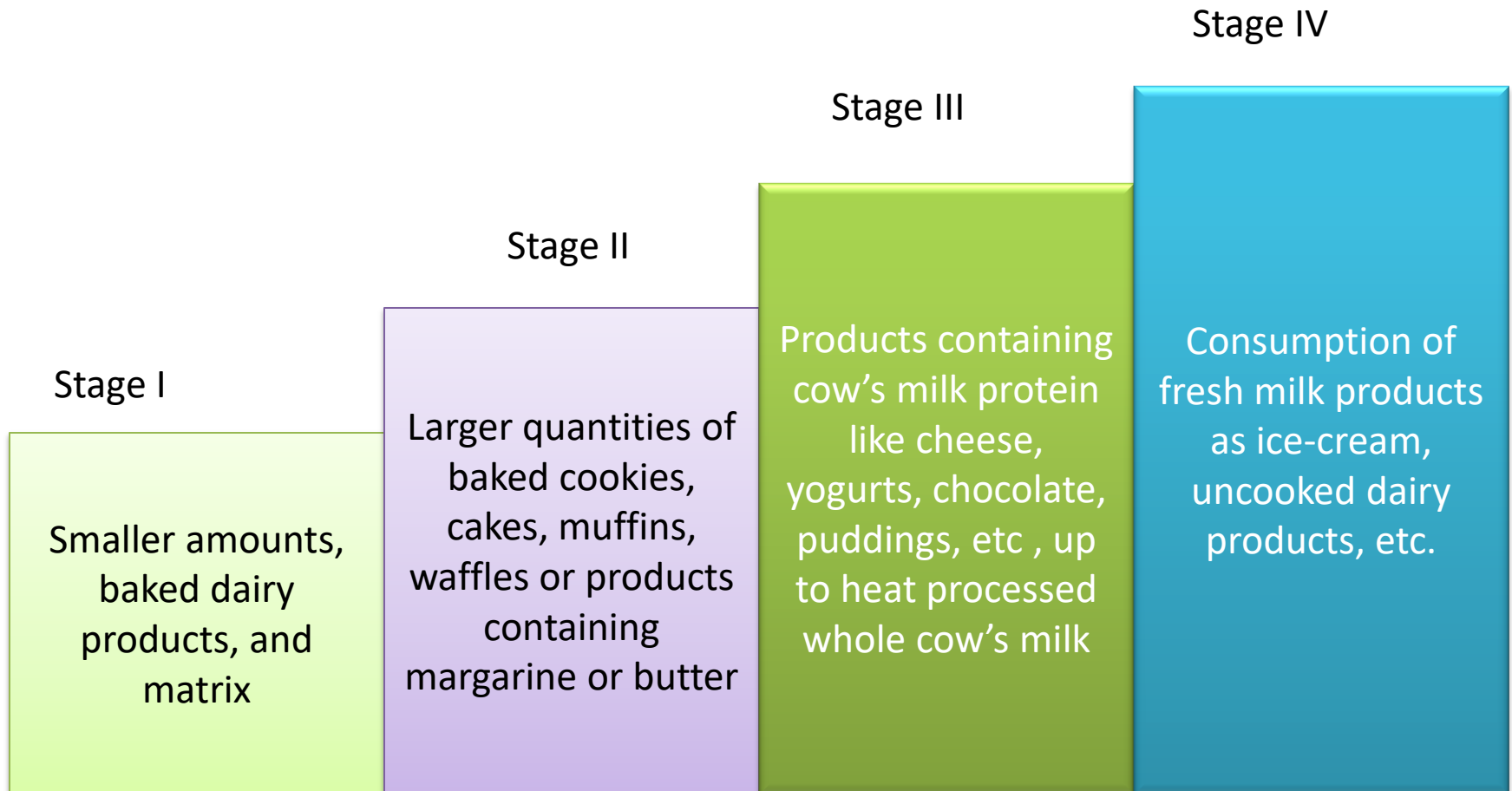


Milk reintroduction

- The speed with which this tolerance develops varies greatly, so the appropriateness and timing of reintroduction should be individually assessed
- Re-evaluation every 6 months
- Non- IgE mediated allergy will resolve more rapidly than IgE mediated allergy
- Dropping in the sIgE level / smaller SPT wheel predict achievement of tolerance
- Home Vs. Hospital reintroduction
- Very slow and meticulous process
- Counseling and training of parents play an important role in achieving the tolerance

Milk Ladder

Stepwise movement from more denatured/ Low protein dose to less denatured/ high protein dose



Probiotics



Evidence showed that probiotics may promote the gut immune regulation and the allergenic tolerance
eHF supplemented with L. GG induce oral tolerance more than non-supplemented formula

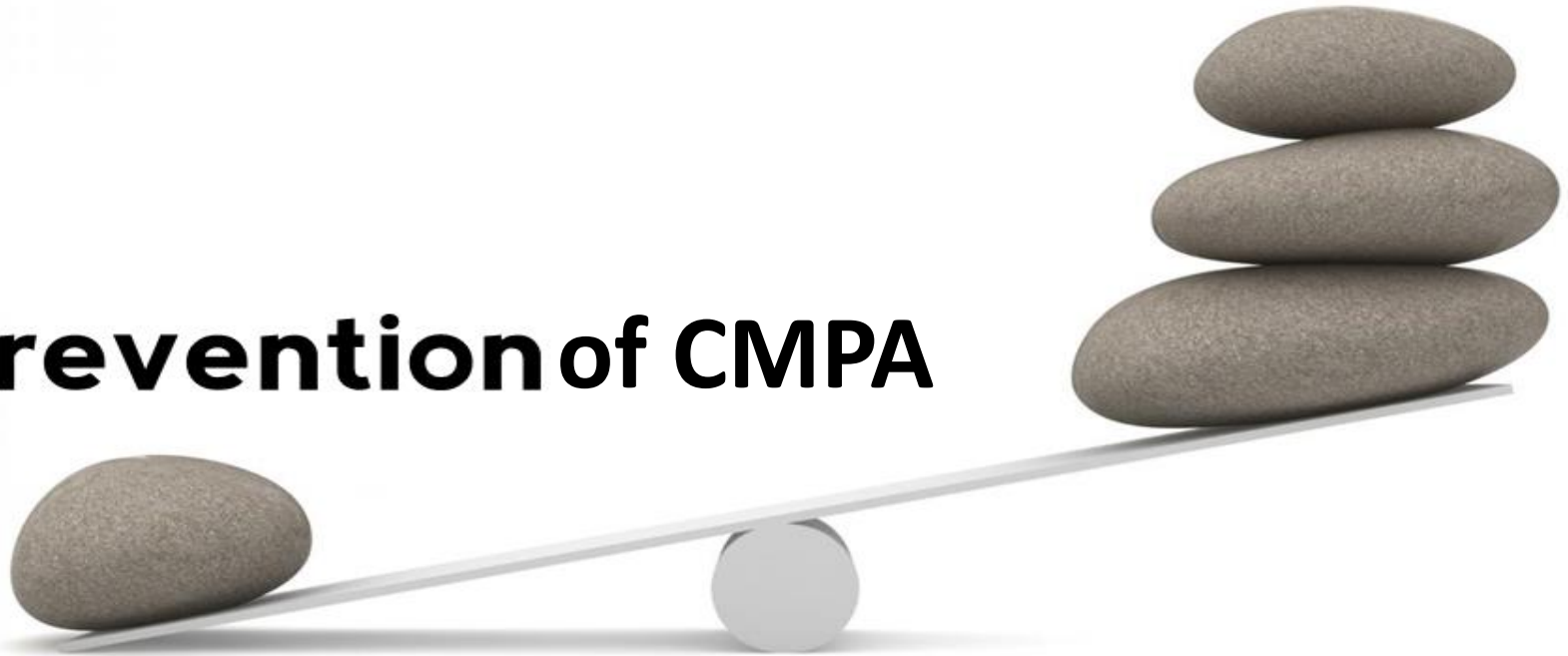


Cow`s milk protein Allergic infants are at increased risk of failure to thrive:

More pronounced in a subgroup of patients with early onset than in those with later of symptoms

Prevention of CMPA

Cure





Cow's milk antigen avoidance during pregnancy and lactation is not recommended

Dietary restrictions on the nutrition of the pregnant woman and her fetus should be considered harmful

Prebiotics and probiotics may help in prevention of allergy studies to suggest that probiotic supplementation of mothers during pregnancy and lactation may prevent early atopic disease in infants

Supplementation with LCPUFAs during pregnancy and postnatally conflicting evidence

Pediatrics 2008;121:183-91.

Pediatr Allergy Immunol 2008;19:1-4.

Lancet 2003;361:1869-71.

Br Med J 344:e184



If the baby can be breastfed exclusively,
Exclusive breastfeeding until 4-6 months



- Decrease exposure to exogenous antigens
- Provide substances capable of protecting the infant against infections
- Induce maturation of the gastrointestinal mucosa
- Promote the development of healthy gut microbiota
- Grant immunomodulatory and anti-inflammatory benefits

J Allergy Clin Immunol 2013;131:1565-73.
Br J Dermatol 2009;161:373-83.



If the baby can't be breastfed exclusively,
Assess allergy risk (F.Hx. of atopy)

YES

Start pHF until 4-6
months
And solid foods as
normal

NO

Start CMF

Not Assessed

Start pHF until assessment
done

Recommendations on primary prevention of Food Allergy, incorporating current Guidelines of the ESPACI / ESPGHAN 2008

Interventions	Recommendations
Immunomodulation	Still experimental
Pregnancy diet	Not recommended
Breast feeding	Exclusive breast-feeding strongly recommended for at least 4 months and should be continued till the first 6 months of life.
Lactation diet	Milk and egg avoidance is not routinely recommended but may be offered on a case-by case basis to highly motivated families; if instituted ,mother must take supplemental calcium
Soy formula	Not recommended
Protein hydrolysate formula	A formula with confirmed reduced allergenicity is strongly recommended if infant is to be bottle-fed or as a supplement to breast milk.
Delayed introduction of solid foods	Solid food may be added at 6 months (after 17 weeks but no later than 26 weeks)

CONCLUSIONS



In summary

Food allergy is on the rise

Cow's milk protein allergy is the leading cause of food allergy in young children

Impaired tolerance of new allergen result in allergy

CMPA might be IgE or non-IgE mediated

CMPA is a multi-organ disease

Accurate diagnosis depends on elimination and re-introduction of cow's milk protein and observe for symptoms progression

In infants with established CMPA:

- If breastfed: Continue breastfeeding, mother to avoid dairy products –
- If formula fed: Switch to eHF or AA formula(superior to Soy F)

To prevent allergy in atopic families:

- exclusive breastfeeding if possible
- starting infants on eHF

Dietary restriction during pregnancy and delayed introduction of solid food have no role in preventing allergy

CMPA patients are at increased risk of FTT, and need nutritional follow up