Food Allergy GI Presentations

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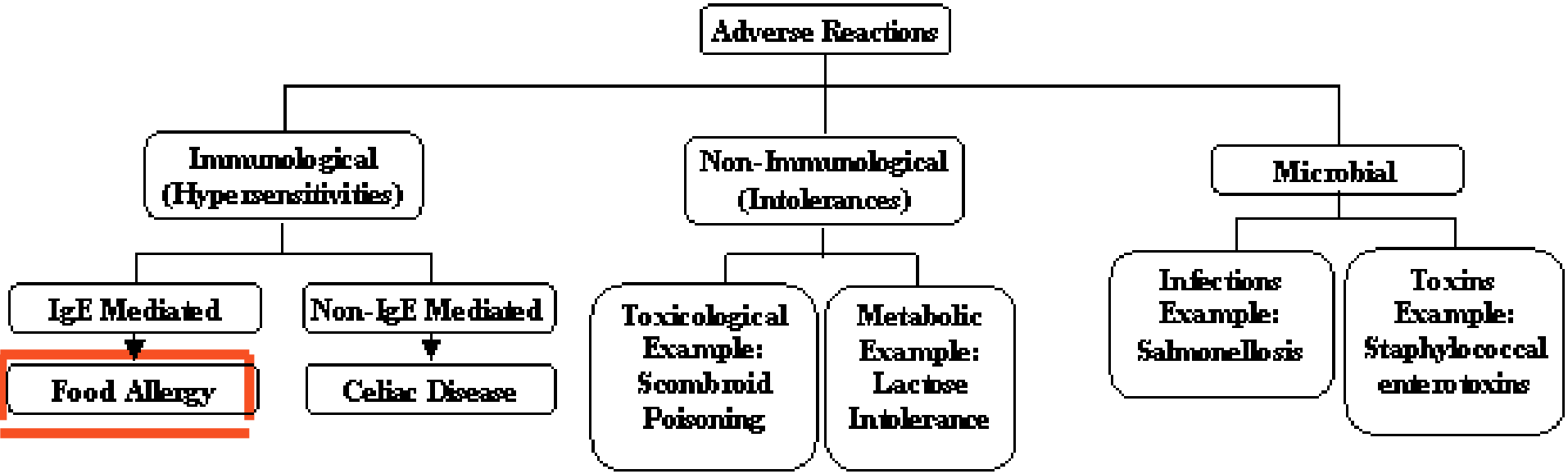
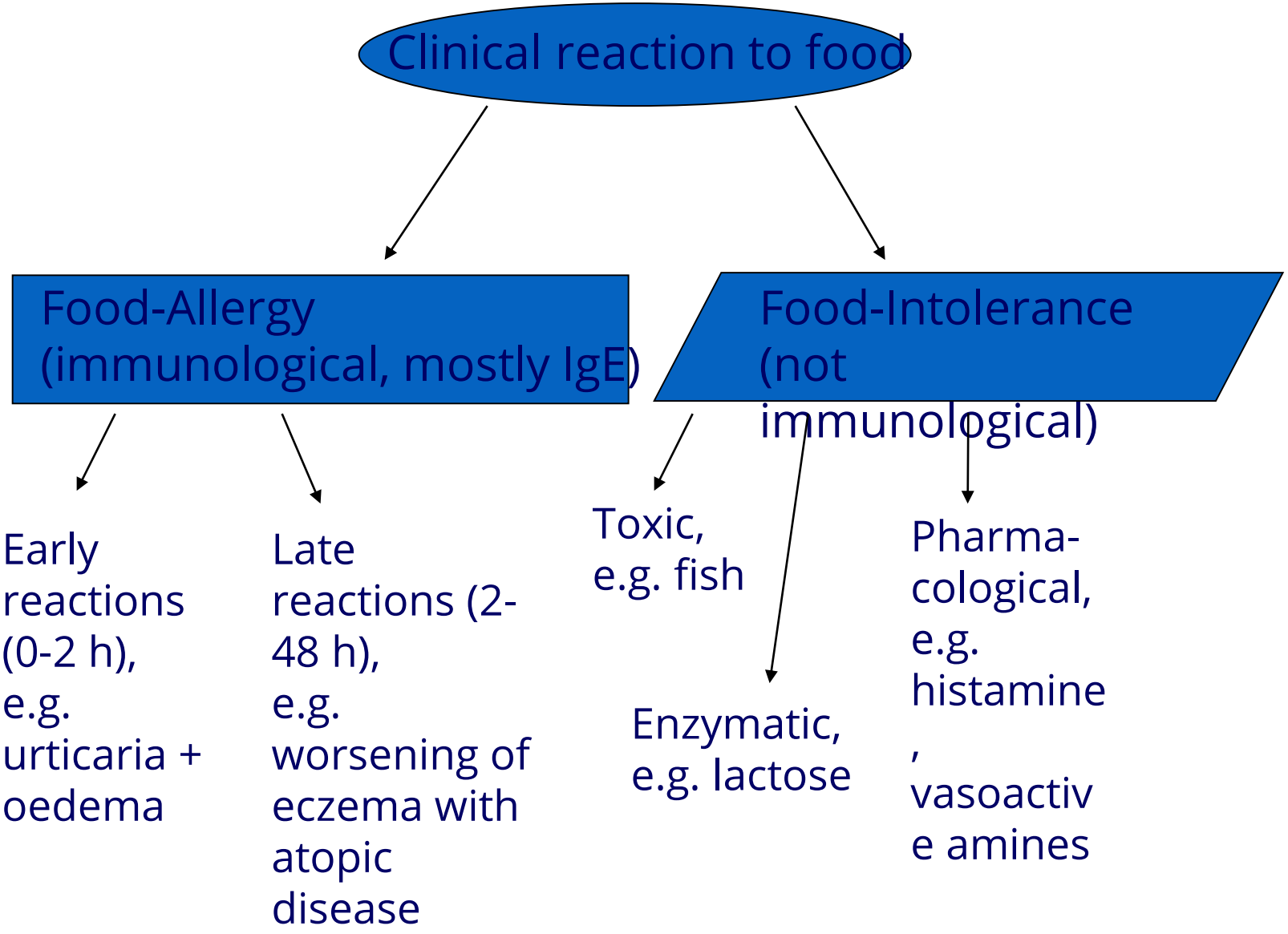
Adverse Reactions to Food



http://www.cfsan.fda.gov/~dms/alrgn2.html#ii

Defining Allergy – Atopy – Intolerance



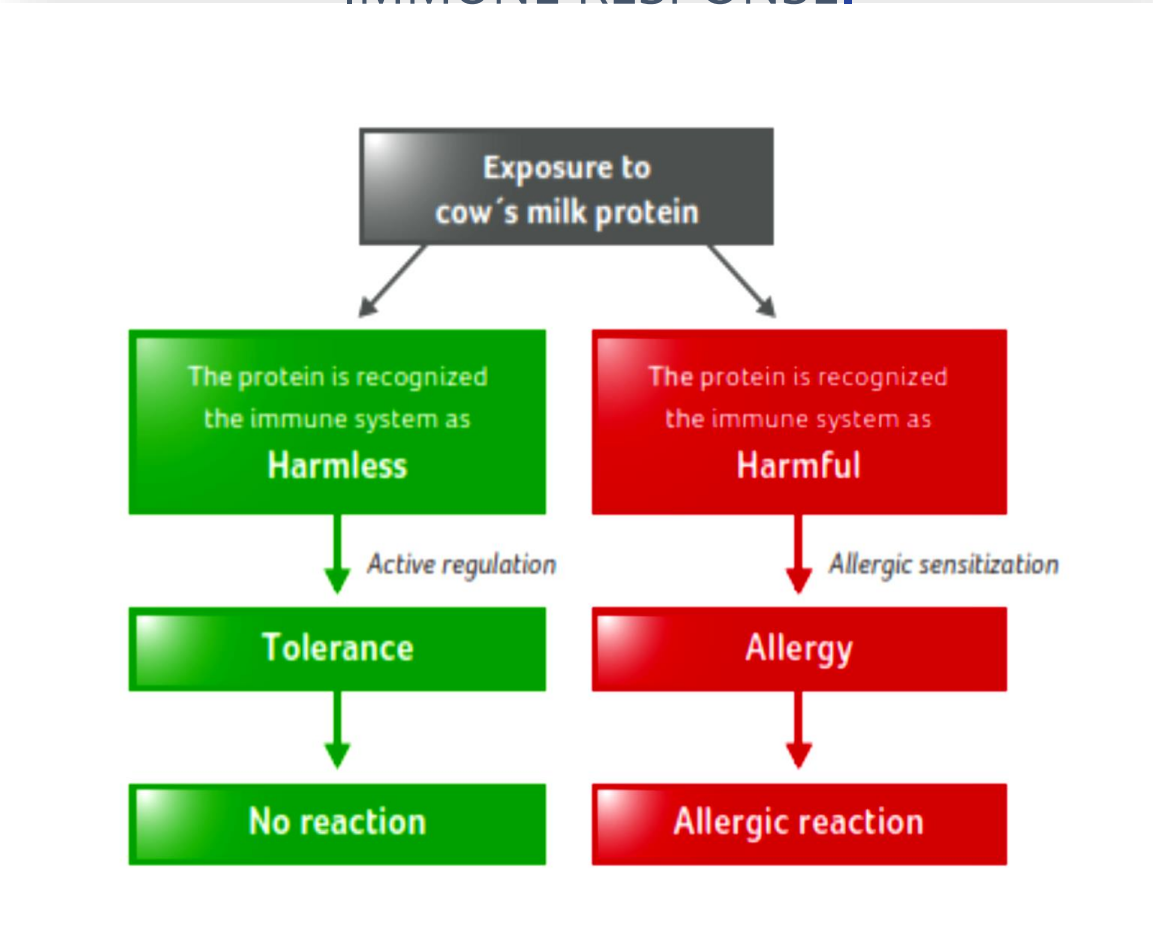
Disorders associated w/ food allergy

Controversial:

- **Migraine headaches**
- **Chronic fatigue**
- **Attention deficit disorder**
- **Autism**
- **Irritable bowel disease**
- **Crohn's disease**

NSTA WEB SEMINARS

UPON EXPOSURE TO COW'S MILK PROTEIN, THE IMMUNE SYSTEM CAN ELICIT A TOLEROGENIC OR A IMMUNOGENIC IMMUNE RESPONSE.

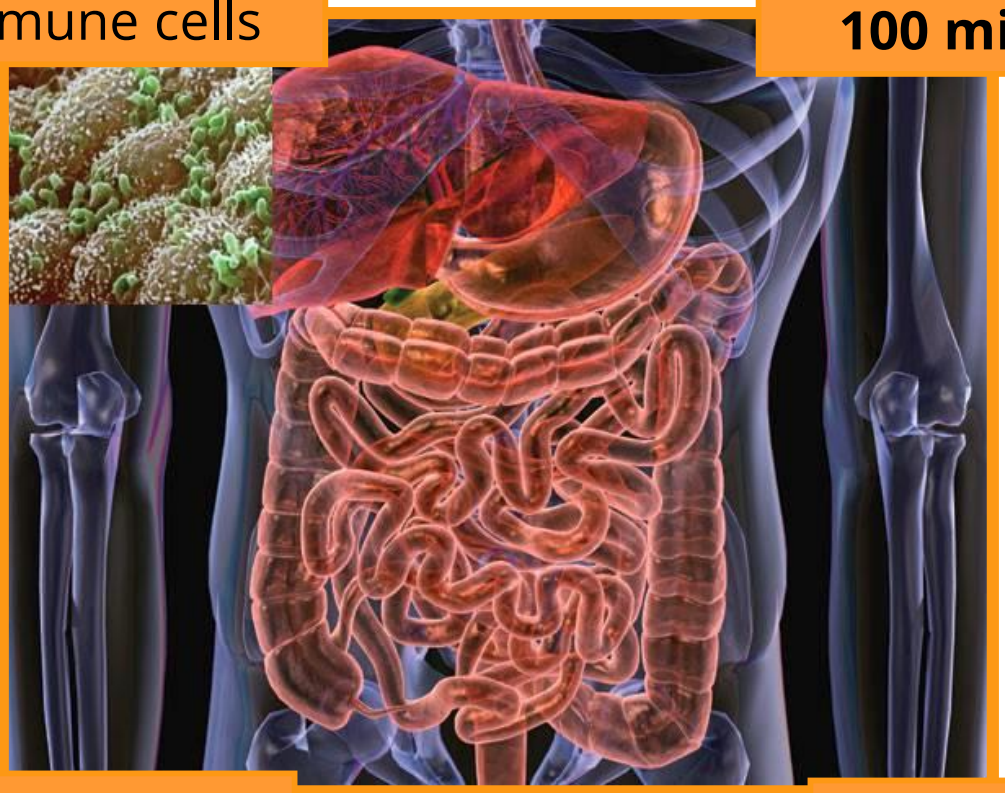


1. Flohr and Mann 2014

The GUT: A Complex Organ

60 -70% of immune cells

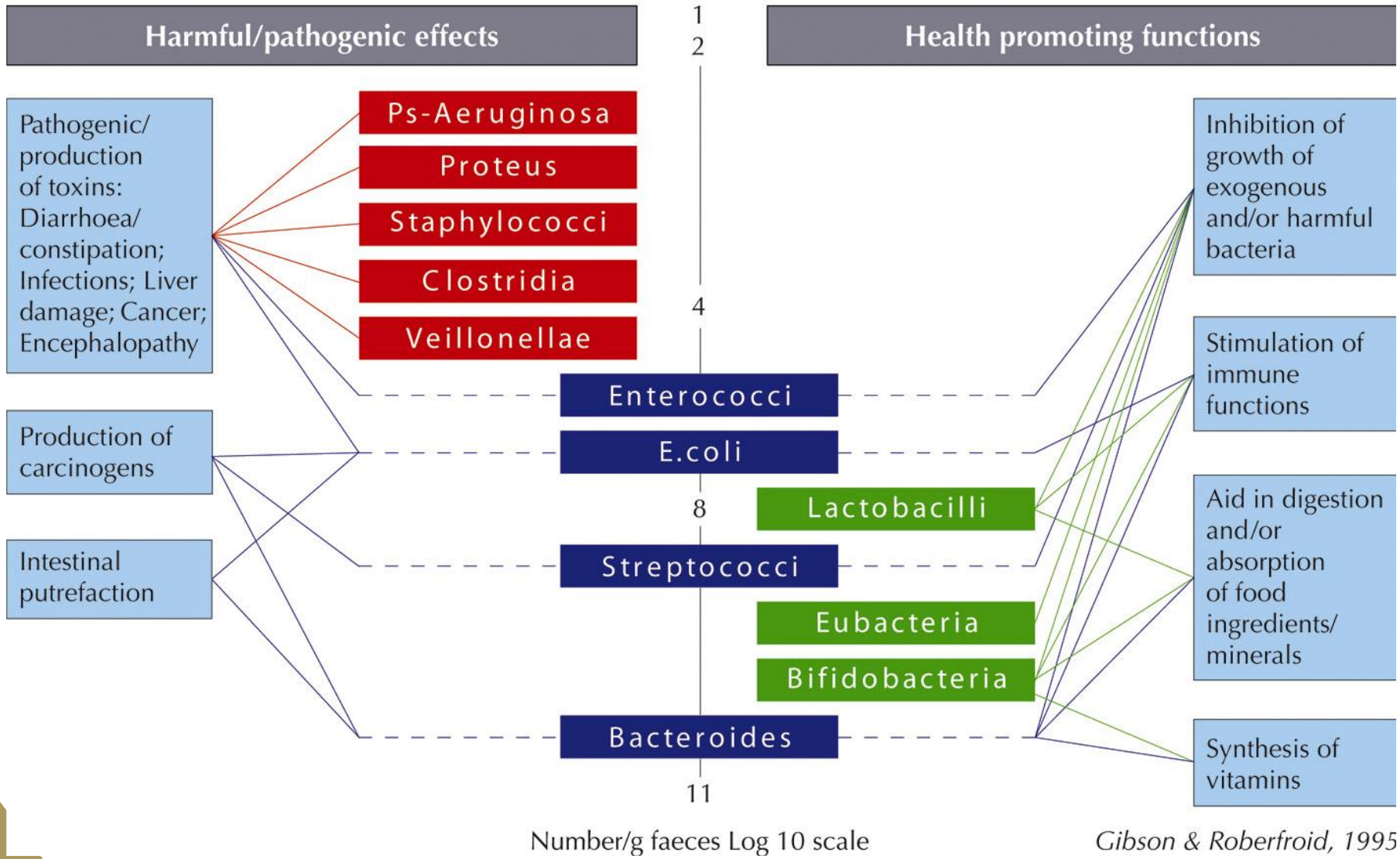
100 million neurons



Surface of approximately **300m²**

100 trillion bacteria " Gut Microbiota"

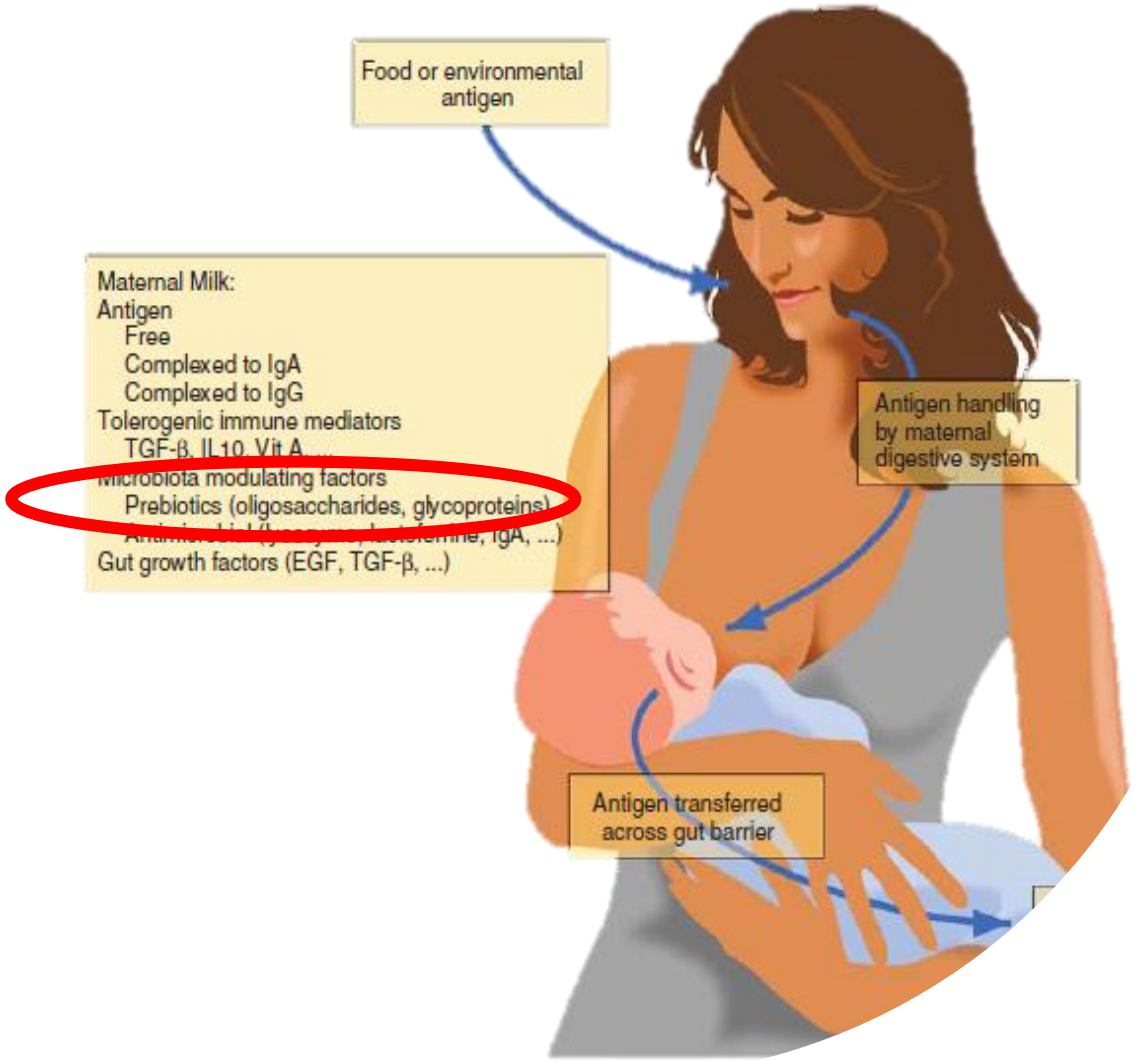
Composition of the Intestinal Flora



BREASTMILK IS THOUGHT TO BE PREVENTIVE BECAUSE OF:

1. Allergen exposure: Exposure to low doses of cow's milk allergen via the maternal diet, enough to be recognized, thereby promoting oral tolerance. Avoidance to higher doses allergens, thereby limiting allergic sensitization

2. Factors in human milk Human milk contains immune modulatory factors that influence the environment in which the protein is presented to the immune system, thereby promoting the induction of tolerogenic immune responses (e.g. immunoglobulins, oligosaccharides, TGF-F).



(Flohr and Mann 2014; Jarvinen, Westfall et al. 2014)

Introduction

- Food allergy affects 6-8% of children <2yr.
- Cow's milk and soybean are the most common cause of food allergic reactions.
- Prevalence in adult is about 0.1% to 0.3%.
- CMA has a wide spectrum of clinical presentations.
  (immediate and delayed onset responses)

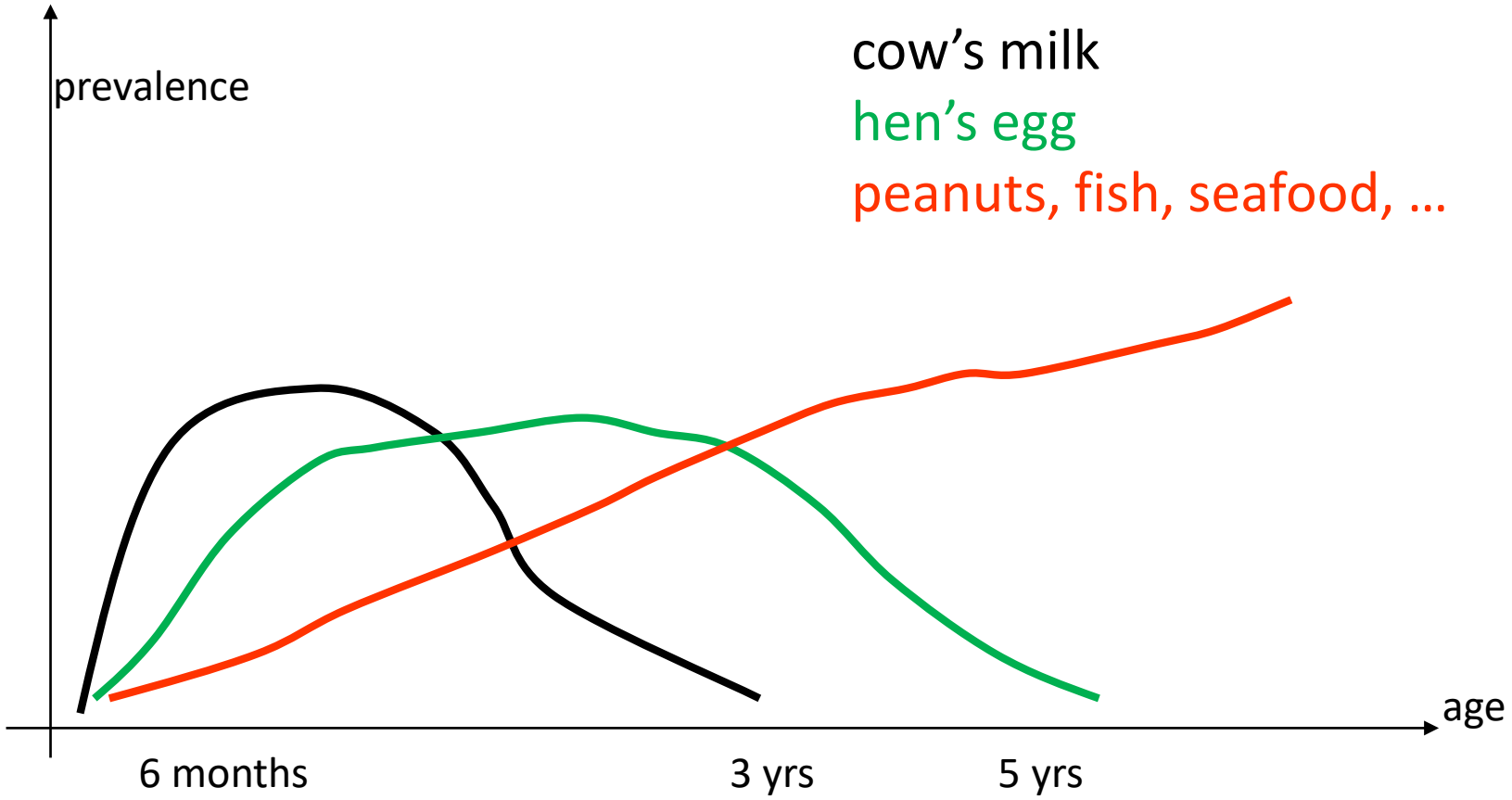
Food allergy prevalence

- Increase in prevalence over past 20 years
- 4% of total US population: Infants > adults

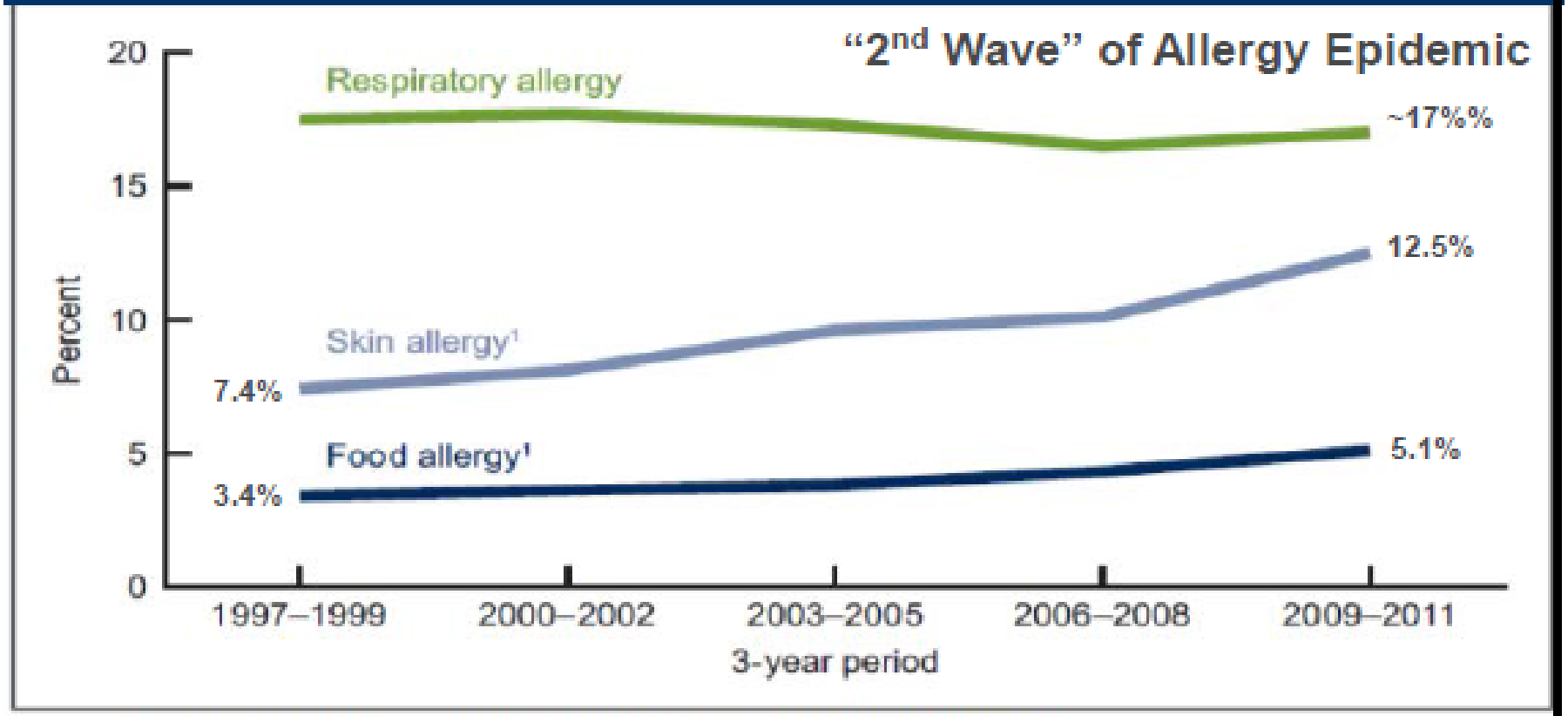
Food	Young children	Adults	
Milk	2.5%	0.3%	80%
Egg	1.3%	0.2%	60-70%
Peanut	0.8%	0.6%	20%
Tree nut	0.2%	0.5%	No
Fish	0.1%	0.4%	No
Shellfish	0.1%	2.0%	No
Other	6%	3.7%	

Sampson, J Allergy Clin Immunol 2004; 113:805-819

Every food has its own story…



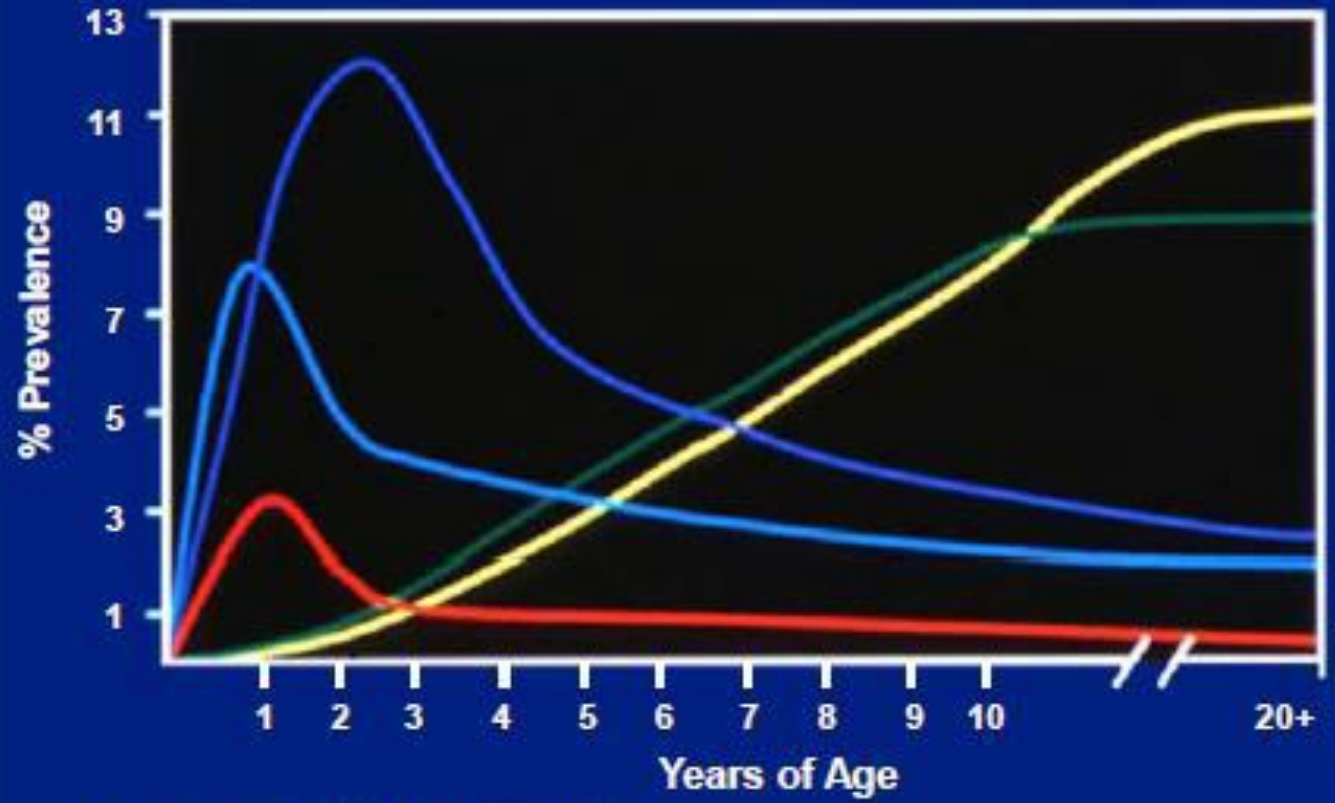
Prevalence of Food and Skin Allergies in the Pediatric Population [1 – 17 years] in the US



¹Significant increasing linear trend for food and skin allergy from 1997–1999 to 2009–2011.
SOURCE: CDC/NCHS, Health Data Interactive, National Health Interview Survey.

NCHS Data Brief #121; May 2013 Jackson KD et al

Prevalence of Food Allergy by Age in the United States



Affects ~12 million Americans

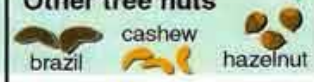
	<3 yrs	Overall
Milk	2.5	0.3%
Egg	1.5%	0.2%
Peanut	1.4%	0.8%
Fish	0.1%	0.4%
Shellfish	0.1%	2.0%

Sicherer SH & Sampson HA. Annu Rev Med. 2009; 60:261-278.

Foods Responsible for Majority of Significant Food Allergy in Infants, Children, and Adults[†]

Infants	Children	Adults
Cows' milk	Cows' milk	Peanut
Soy	Egg	Tree nuts
	Peanut	Fish
	Soy	Shellfish
	Wheat	
	Tree nuts (walnut, hazel, etc.)	
	Fish	
	Shellfish	

[†] Reproduced with permission from the American Gastroenterological Association. Gastroenterology 2001; 120:1023.

If Allergic to:	Risk of Reaction to at Least One:	Risk:
A legume* 	Other legumes 	5% 
A tree nut 	Other tree nuts 	37% 
A fish* 	Other fish 	50% 
A shellfish 	Other shellfish 	75% 
A grain* 	Other grains 	20% 
Cow's milk* 	Beef 	10% 
Cow's milk* 	Goat's milk 	92% 
Cow's milk* 	Mare's milk 	4% 
Pollen 	Fruits/vegetables 	55% 
Peach* 	Other Rosaceae 	55% 
Melon* 	Other fruits 	92% 
Latex* 	Fruits 	35% 
Fruits 	Latex 	11% 

Non-IgE-Mediated Disorders
(most food allergic disorders affecting *ONLY* the gut)

- Dietary Protein Proctitis / Colitis
- Dietary Protein Enteropathy
- Dietary Protein Enterocolitis (or food-protein induced enterocolitis syndrome *FPIES)*

All of these disorders are most frequently caused by ***cow's milk or soy protein*** *& occur mainly in infancy*

INTRODUCTION

- Food protein-induced proctocolitis is a common cause of rectal bleeding in an otherwise healthy young infant, and in most cases resolves by late infancy.

- It is characterized by inflammation of the distal colon in response to one or more food proteins, through a mechanism that does not involve immunoglobulin E (IgE).

- Cow's milk & soy protein are common triggers.

- An association of symptoms to food protein antigens requires demonstration of objective improvement following withdrawal of the suspected food antigen, and in some cases, recurrence following a subsequent oral challenge.

Pathogenesis

- Cow's milk contain Casein (alfaS1, alphaS2, kappa-casein) & whey (α lactalbomin, β lactalbomin, bovine lactoferrin, bovine serum albumin, bovine immunoglobulins) that account for 80 & 20% of total protein respectively.
- Most patients are sensitized to several milk protein.
- Casein , BLG, ALA are major milk allergens and co-sensitization to these three allergens is common.

- Cooking diminishes the allergenicity of whey proteins , particularly β-lactoglobolin.
- This may explain why extensively heat milk (milk in baked goods) is better tolerated by many patients.
- Yogurt cultures, which ferment & acidify milk, diminish the amount of intact whey protein in milk and may result in tolerance of yogurt based dairy products by individuals with CMA exclusively sensitized to whey proteins.

Natural Course

- Tolerance is achieved by many of children with CMA.
- Non – IgE mediated CMA tends to resolve more quickly than IgE- mediated CMA.
- Most with non- IgE mediated become tolerant by 3 y.
- IgE mediated is more consistent (64% by 12Y)

Food Allergy-classification

IgE-mediated:

- Type I hypersensitivity
- Quick onset
- Positive skin prick test or RAST
- Symptoms: "systemic"-urticaria, angioedema, rashes, wheezing, anaphylaxis
- Example "peanut allergy"

Non-IgE-mediated:

- Type IV hypersensitivity (T-cell mediated)
- Late onset
- Negative skin prick test & RAST
- Symptoms: FTT, diarrhea, vomiting, enteropathyor colitis, eczema, rhinitis

EPIDEMIOLOGY

- Food protein-induced proctocolitis appears to be a common cause of rectal bleeding in breastfed or formula-fed infants .

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- The overall prevalence of rectal bleeding attributed to cow's milk protein was 1.6 per 1000 infants .

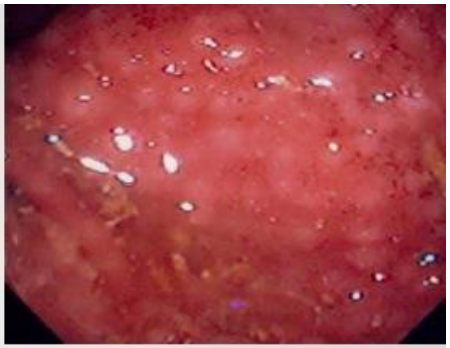
DIETARY TRIGGERS :

- Cow's milk is the most common trigger in most series.
- In a prospective study of 240 exclusively breastfed infants who presented with blood-tinged stools, 88 % were determined to be sensitive to the following foods, as determined by sequential elimination of foods from the maternal diet :

  - Cow's milk – 76 %.
  - Egg – 16 %.
  - Soy – 6 %.
  - Corn – 2 %(all in infants with multiple protein allergies).
  - Multiple (two of the above) – 8 %.

  - No response to maternal dietary restriction – 8 %; they improved after weaning to an extensively hydrolyzed or amino acid-based formula.

Dietary Protein Proctitis /Colitis



- **Age of onset**: first few months of life.
- **Symptoms**: blood-streaked stools w/out frank diarrhea in healthy-appearing infants, fecal WBCs.
- **Lab**: occasional mild peripheral eosinophilia, anemia.
- **Pathology**: focal to diffuse colitis; E◦ infiltration common & nodular lymphoid hyperplasia.
- **Natural history**: symptoms usually resolve within one year
- **Food Challenge Risk**: **Low risk** of severe symptoms

EVALUATION

The diagnosis depends primarily on a focused history and physical examination.

- Evaluate for typical clinical features , which include the onset of small or moderate amounts of rectal bleeding in a young healthy infant.

- If the infant is breastfed, evaluate the mother's diet, including cow's milk or other dairy products (even small amounts), soy, eggs, and corn.

- If the infant is fed formula : type of formula (ie, standard cow's milk/or soy-based formula, or one of several formulas with extensively hydrolyzed proteins [called "hypoallergenic"), + history of formula changes and symptomatic responses.

Evaluation

- PE include a careful inspection of the anus for fissures.
- The clinician should exam one or more stools directly or SE
- Typical stools in proctocolitis are soft or loose, with blood specks or streaks distributed within the stool, ± mucous.
- Stools that are firm with blood streaks on the outside are more typical of anal fissures.
- Warning signs that suggest a diagnosis other than food protein-induced proctocolitis include unwell appearance or fever, poor weight gain, frank diarrhea, forceful vomiting, and/or abdominal distension.

Stool in proctocolitis

Evaluation

- Skin prick testing and in vitro immunoassays for IgE antibodies to foods are **not** recommended for proctocolitis.
- Flexible sigmoidoscopic or colonoscopic evaluation usually is reserved for patients with atypical symptoms or those who do not respond to an elimination diet .
- Biopsies typically reveal high numbers of eosinophils (including eosinophilic abscesses) in the lamina propria and muscularis mucosa . LNH is frequently observed in these infants, but it is unclear whether this finding is associated with food protein-induced disease .
- . Features that are not typical for food protein-induced proctocolitis include cryptitis, crypt abscesses containing polymorphonuclear abscesses, glandular distortion, and Paneth cell metaplasia; such findings suggest an alternate diagnosis, such as early-onset inflammatory bowel disease (IBD)

DIAGNOSIS

- It is a clinical diagnosis. It is suspected in an otherwise healthy infant presenting with small amounts of rectal bleeding.

- The diagnosis is confirmed after resolution of symptoms upon withdrawal of the presumed food antigen.

- Patients with atypical features at presentation, or those who do not respond to a careful and consistent elimination of the suspect food, should undergo a more extensive evaluation.

- This may include flexible sigmoidoscopy or colonoscopy for infants with persistent rectal bleeding; allergy testing for those with food-induced vomiting or other features of immunoglobulin E (IgE)-mediated disease ; or other testing guided by the infant's symptoms.

DIFFERENTIAL DIAGNOSIS

Anal fissure – Is the most common cause of rectal bleeding in patients younger than one year

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Necrotizing enterocolitis (NEC) – About 90 % of infants with NEC are born prematurely. Term infants who develop NEC typically have a preexisting illness. Overall, 75% of cases present within the first month of life.

Intussusception – Typically episodes of sudden-onset severe, crampy, progressive abdominal pain, accompanied by inconsolable crying and drawing up of the legs toward the abdomen. As symptoms progress, increasing lethargy may develop. It is most common in infants and children between 6 and 36 months of age, and uncommon prior to three months of age.

Infection – bacterial enteric pathogens and occasionally rotavirus. Infants presenting with rectal bleeding accompanied by fever, abdominal pain, and tenesmus, particularly if there is a history of exposure to contacts with similar symptoms.

Meckel's diverticulum – painless rectal bleeding in an otherwise healthy individual. Symptomatic presentation during the neonatal period is rare.

D/D

- Food protein-induced enterocolitis syndrome (FPIES) – For infants with gastrointestinal symptoms triggered by exposure to specific foods (typically cow's milk or soy), the differential diagnosis includes FPIES.
- FPIES may have acute or chronic symptoms, and may include vomiting, diarrhea (with or without blood), and weight loss . Infants with FPIES are generally sicker than those with food protein-induced proctocolitis and enteropathy.
- Food protein-induced enteropathy – inflammatory response to food causes small bowel injury, leading to malabsorption, intermittent vomiting, diarrhea, failure to thrive, and rarely, bloody stools.
- The diagnosis is suspected based upon the clinical features and should be confirmed by endoscopy with biopsy of the proximal small intestine to confirm villus injury
- Other causes of bloody stools in infants include swallowed maternal blood, intestinal duplication cysts, vascular malformations, early onset IBD, andLNH.
- Infants with Hirschsprung disease with enterocolitis, or malrotation with volvulus, can have bloody stools as well as marked abdominal distention, vomiting, and/or other symptoms of obstruction.

MANAGEMENT

- *Exclusively breastfed infants* — Continued breastfeeding should be encouraged if the mother is willing to eliminate completely the suspect food from her diet.

- Cow's milk should be eliminated first, unless there is good evidence implicating some other specific food. **All** dairy products should be completely eliminated, including butter.

- All other mammalian milks (eg, goat's and sheep's milk) should also be eliminated because of cross-reactivity between these antigens.

- For infants with severe symptoms, it may be helpful to accelerate the transition by using an amino acid-based formula rather than breast milk for three to five days, while the mother pumps and discards her breast milk to maintain lactation.

- The majority of breastfed infants with food protein-induced proctocolitis respond to elimination of cow's milk from the mother's diet; only a few require elimination of multiple proteins .

- Most infants will improve within a few days up to two weeks.

- If the infant's symptoms fail to resolve, then the first step is to review the mother's diet carefully .

- If cow's milk was completely eliminated for at least two weeks and the infant remains symptomatic, then soy, followed by egg, should also be removed from the mother's diet .

Formula-supplemented or -fed infants

- For formula-fed (cow's milk- or soy-based) should be replaced with an extensively hydrolyzed formula .
- Changing to a soy-based formula is generally not recommended because a substantial percentage of children will be sensitive to both cow's milk and soy proteins .
- Many infants will have loose green stools when fed an extensively hydrolyzed formula, and this does not generally indicate ongoing colitis.
- Approximately 5 to 10 % of infants do not respond to feeding with an extensively hydrolyzed cow's milk formula and should be given an amino acid-based formula.
- infants on an extensively hydrolyzed formula recover more rapidly when the formula is supplemented with the probiotic lactobacillus GG .
- Referral to a pediatric gastroenterologist is recommended if the infant fails to improve or the diagnosis is not clear.

Evaluating response

- — Visible bleeding usually improves within 72 hours, occasionally takes up to two weeks to disappear.
- Testing of stools for OB+ is not generally necessary in this setting and may confuse the situation because microscopic blood or polymorphonuclear leukocytes in the stool may persist for several weeks.
- Occasional recurrence of bleeding is common in breastfed infants, probably because of inadvertent maternal intake of small amounts of the triggering protein (eg, in meals from restaurants)
- If bleeding recurs, we suggest a careful review of the mother's diet for possible sources of milk or other suspected proteins, before considering progressive dietary restrictions.

Reintroduction

- For infants who become asymptomatic after elimination of cow's milk (or other suspected antigenic protein), the standard timetable for reintroduction has been at one year of age and is usually successful.
- Before reintroduction of the protein, stools should be normal and tests for occult blood should be negative.
- Experience indicates that by six months of age, about 50 % of breastfed infants will tolerate the resumption of the offending protein; by nine months of age, 95 % will tolerate resumption of the offending protein in the maternal diet or in formula .
- So it may be possible to successfully reintroduce the offending protein into the diet as early as six months of age.

- Reintroduction of standard cow's milk- or soy-based formula can be done at home, unless the infant presented originally with severe diarrhea and/or vomiting.
- Such symptoms suggest concomitant enterocolitis and/or hypersensitivity, in which case, supervision of the food challenge in the physician's office is appropriate.
- For infants who are breastfeeding, similar parameters can be used to guide reintroduction of these proteins to the mother's diet.
- Patients receiving an amino acid-based formula may be switched to one containing highly hydrolyzed protein for a few months before trying a formula with whole protein.
- For infants who had moderate or severe symptoms ,we suggest reintroducing the food protein gradually over three to five days, while observing the infant's stools for grossly visible blood or diarrhea. The success of this strategy may not be immediately apparent, since it may take up to three days for the hematochezia to recur after the reintroduction of the protein. :

Approach for infants with cow's milk protein-induced proctocolitis is as follows

- **Breastfed infants** : Mother adds one ounce of cow's milk (or dairy equivalent) to her diet, and increases by one ounce each day for five days.

- **Formula-fed infants**
  - First feed – Add one teaspoon (5 mL) of standard cow's milk-based formula (or unmodified cow's milk if the child is older than one year) to the child's usual hypoallergenic formula.
  - Second feed – Substitute 1 ounceof standard cow's milk formula, instead of 1 ounce of the usual hypoallergenic formula.
  - Third feed – Substitute 2 ounces (60 mL) of standard cow's milk formula, instead of 2 ounces of the usual hypoallergenic formula.
- This stepwise is continued if tolerated until the full feed consists of the standard cow's milk-based formula or unmodified cow's milk.

- For infants who had mild symptoms (eg, semi-formed stools with small amounts of visible blood), milk protein can be introduced more rapidly.

- If symptoms of recur, diet restriction for an additional five to six months before attempting to reintroduce the food.

Management of younger siblings

- The risk of proctocolitis in siblings of an affected infant is low.
- Do not suggest avoidance of cow's milk protein for the sibling unless he or she displays symptoms suggestive of protein intolerance.
- If the mother chooses to breastfeed, there is no need for dietary restriction if the infant is asymptomatic
- . For infants who are fed formula, some choose to use a hydrolyzed formula rather than a cow's milk-based formula, but ???.

If an infant has an IgE-mediated food allergy, younger siblings are thought to be at somewhat increased risk for allergic disease. For those who cannot be exclusively breastfed, feeding with a hydrolyzed formula is recommended.

- **PROGNOSIS** — The prognosis is excellent. Nearly all infants will be able to tolerate cow's milk and soy products by one year of age .Progression to persistent food allergy or chronic colitis including inflammatory bowel disease (IBD) is extremely rare.

Different formulas

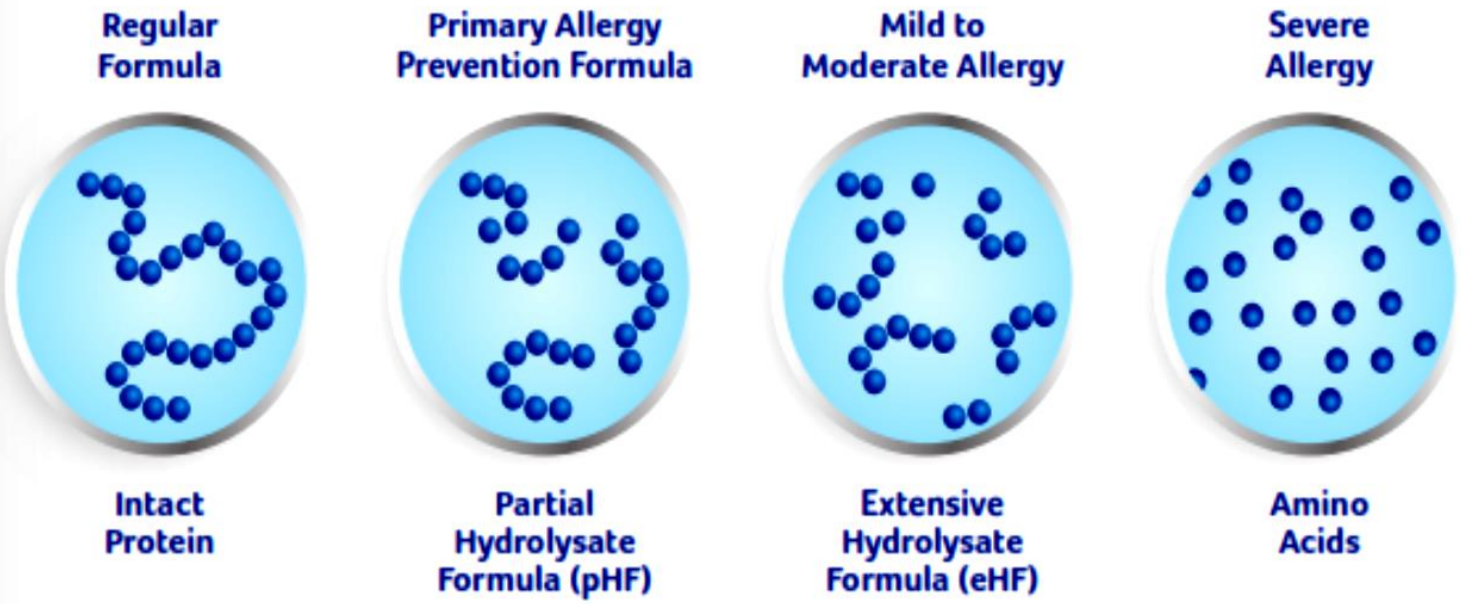
The types of formula available include the fallowing:

- Conventional cow's milk (CM) formulas.
- Partial whey hydrolysate formulas (PHF-W)
- Extensive casein or whey hydrolysate formulas (eHF-C/eHF-W).
- Soy protein based formulas
- Amino acid-based formulas.

_ Protein hydrolysates are termed Partial or extensive "depending on the degree of hydrolysis and ultrafiltration.

_ Allergenicity decreases as the extent of hydrolysis and filtration increases.

Hydrolysis reduces the molecular weight and peptide size, and so the allergenicity



Management (soy based formula)

- Soy based formulas are widely used for feeding infants allergic to CM.
- Children with CMA have 20-50% allergy to soy based formulas.
- In the first 6 mo of age it is not recommended to use .
- It may be an option in infants older than 6 mo who do not accept the bitter taste of an e HF, or in cases in which the higher cost protein has been established.

High risk infant

If there is at least one first degree relative (parent / sibling) with documented allergic condition(AD, asthma, food allegy).

- For prevention of allergic diseases in high risk infants:

- Avoidance of milk is not recommended for nursing mothers.
- Hydrolyzed formula is recommended for formula-fed infants or for supplementation for breast –fed infants (PHF or eHF) instead of CM/soy formula.??
- Not delaying in introduction of solid foods into the diet beyond what is generally recommended for all infants.
- Highly allergenic foods (egg, peanut, tree nuts, dairy products other than CM, fish) can be gradually and carefully introduced to high risk infants who have already tolerated the less allergenic foods(rice cereal, pureed fruits,vegtables, and meats).
- Cow's milk should be avoided in all infants < 1 Y for reasons unrelated to allergy.

Current Recommendations for Practice

Preventive Measures

Mother is atopic:

- Mother eliminates all sources of her own allergens prior to and during pregnancy to reduce IgE and IgG4 in the uterine environment
- Continues to avoid her own allergens during lactation
- Exclusive breast-feeding without exposure of infant to external sources of food allergens for 6 months

Current Recommendations for Practice (continued)

Father and or siblings atopic; mother is non-atopic:

- No recommendations for mother to restrict her diet during pregnancy
- No recommendations for mother to restrict her diet during lactation unless the baby shows signs of allergy
- Exclusive breast-feeding for 4-6 months

Current Recommendations for Practice (continued)

- Some studies suggest that maternal avoidance of the most highly allergenic foods during lactation may reduce sensitization of infant with family history of allergy
- Foods to be avoided:
  - **Peanuts - Shellfish - Eggs**
  - **Tree nuts - Fish - Milk**
- Benefits of this remain to be proven; the strategy is recommended by some authorities
- Hypoallergenic infant formulae if breast-feeding not possible

Current Recommendations for Practice (continued)

- No family history of allergy:
  - Good nutrition practices for mother from preconception onwards
  - Good nutrition practices for early infant feeding
  - Breast-feeding is the best possible source of nutrition and protection
  - Allergen avoidance is unnecessary unless the infant demonstrates signs of allergy

Current Recommendations for Practice (continued)

- If infant demonstrates overt signs of allergy (eczema; gastrointestinal complaints; rhinitis; wheeze)
  - Identify specific food trigger by elimination and challenge
  - Exclusive breast-feeding with mother excluding her own and baby's food allergens
  - If breast-feeding is not possible, extensively hydrolyzed casein formula
- Careful monitoring of mother's diet during lactation for nutritional adequacy, especially of vitamins and trace elements

Measures to Reduce Food Allergy in Infants with Symptoms of Allergy or at High Risk Because of Genetic Background

1. Exclusive breast-feeding for the first 6 months
2. Total maternal avoidance of:
   - any food inducing allergy symptoms in the infant
   - any food inducing allergy symptoms in mother

- **Eggs**
- **Cow's milk and milk products**
- **Peanuts**
- **Nuts**
- **Shellfish**

As a preventive measure initially if not avoided in above categories {clinicians disagree about

Measures to Reduce Food Allergy in Infants (continued)

3. Colostrum as soon after birth as possible: provides sIgA which is absent in newborn
4. Avoid infant formulae in the newborn nursery: NO exposure to formulae in the hospital
5. Avoid small supplemental feedings of infant formulae at widely spaced intervals
6. If formula is unavoidable introduce in incremental doses over a 3-4 week period

Measures to Reduce Food Allergy in Infants (continued)

7. Introduce solid foods after 6 months starting with the least allergenic. Use incremental dose introduction to promote oral tolerance
8. Delay the most allergenic foods until after 12 months:
   - Cow's milk
   - Eggs
   - Soy
   - Shellfish
   - Fish
   - Beef
   - Chicken
   - Wheat
   - Citrus Fruits
   - Tomatoes
9. Delay peanuts and nuts until after 2-3 years

Infant Formulae for the Allergic Baby
Current Recommendations

- Cow's milk based formula if there are no signs of milk allergy
- Partially hydrolysed (phf) whey-based formula if there are no signs of milk allergy
- Extensively hydrolysed (ehf) casein based formula if milk allergy is proven

Development of Tolerance

- 25% of infants lost all food allergy symptoms after 1 year of age
- Most infants will outgrow milk allergy by 3 years of age, but may become intolerant to other foods
- Tolerance of specific foods :

  After 1 year:

  - 26% decrease in allergy to:
    - Milk
    - Egg
    - Soy
    - Wheat
    - Peanut
  - 2% decrease in allergy to other foods

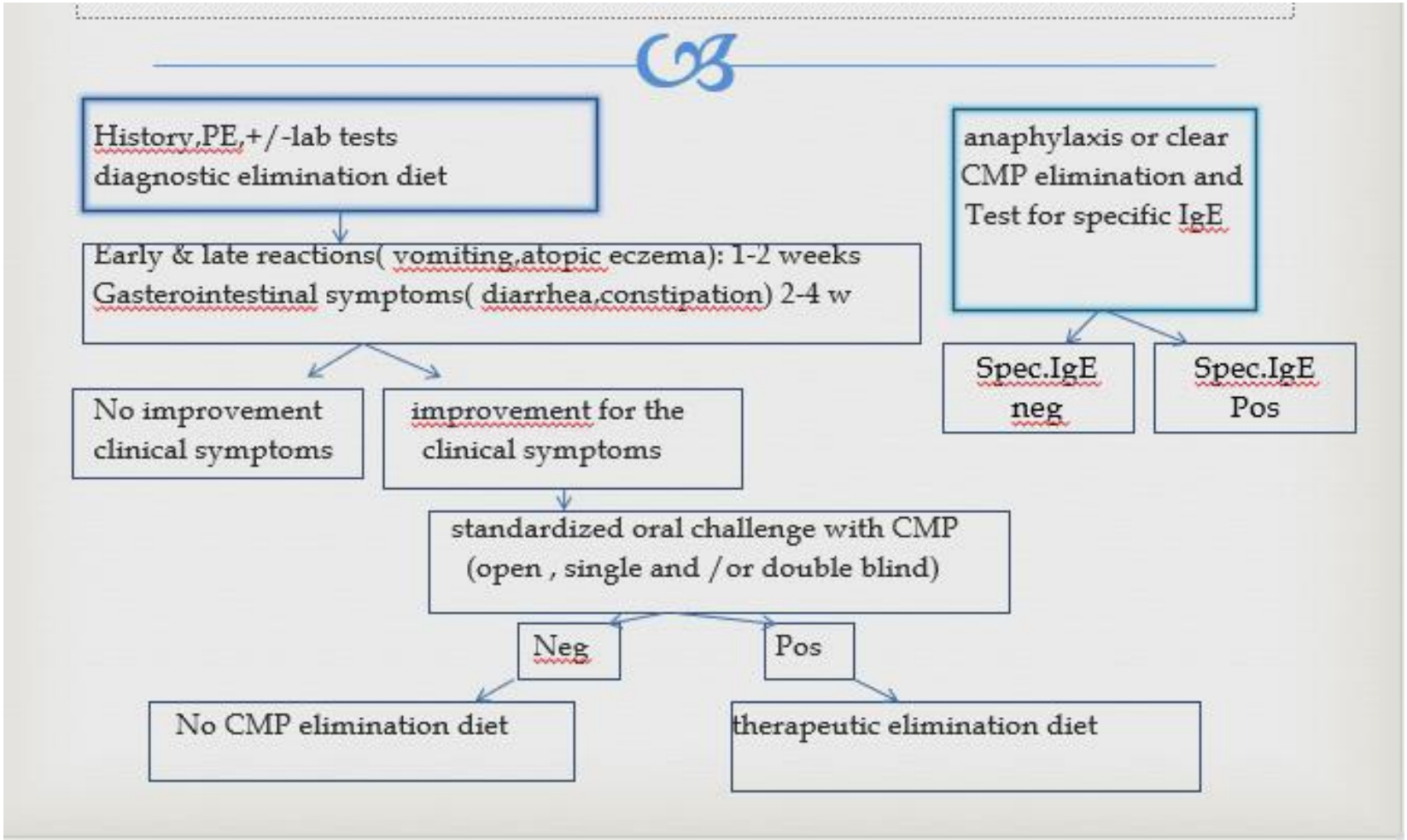
Prognosis

[Study: Bishop et al 1990]

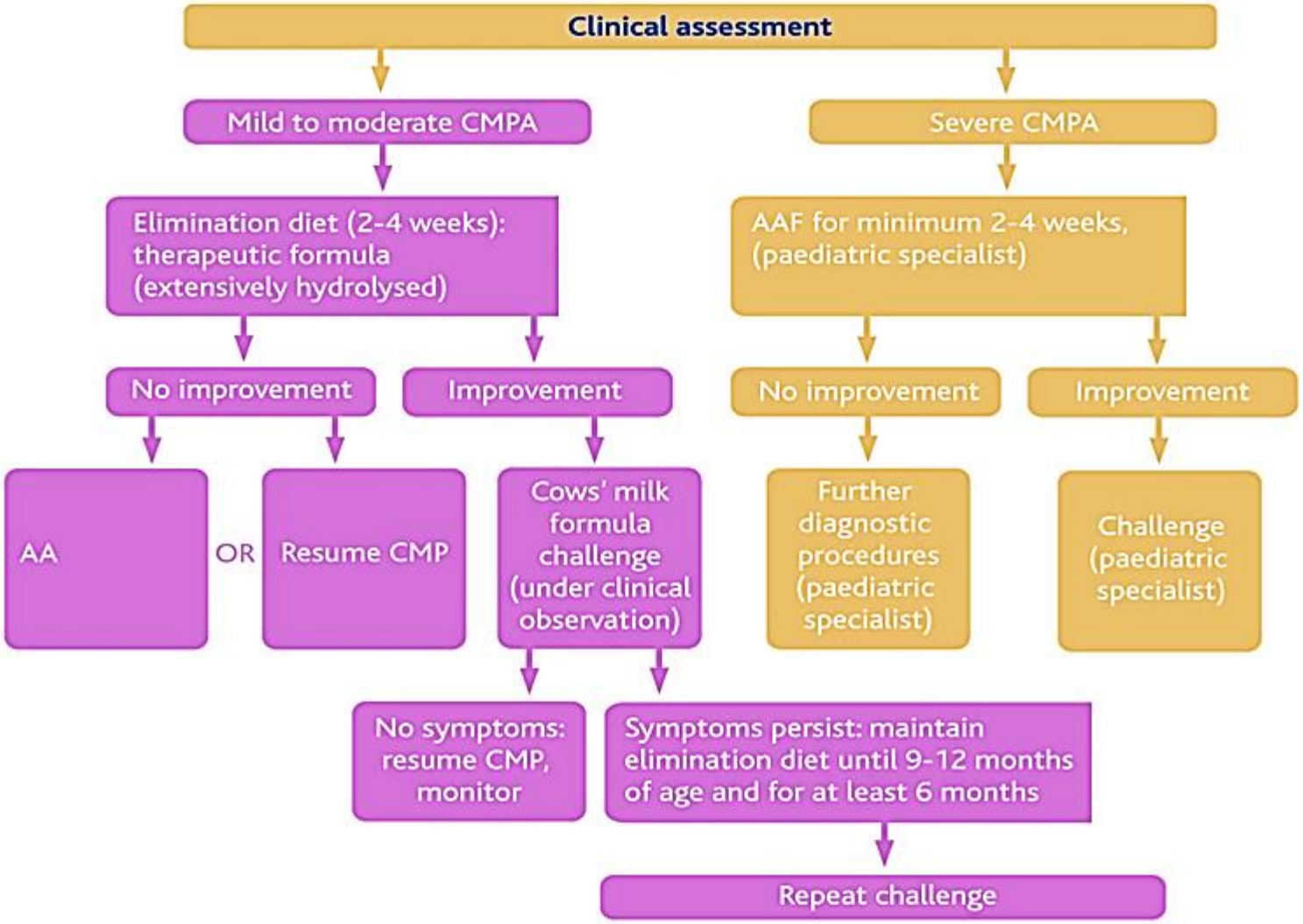
- Age at which milk was tolerated by milk-allergic children:
  - 28% by 2 years of age
  - 56% by 4 years of age
  - 78% by 6 years of age

- About 25% of allergic children develop respiratory allergies

- Allergy to some foods more often than others persists into adulthood:
  - Peanut - Tree nuts
  - Shellfish - Fish
  - Soy


History,PE,+/-lab tests
diagnostic elimination diet
Early & late reactions(vomiting,atopic eczema): 1-2 weeks
Gasterointestinal symptoms(diarrhea,constipation) 2-4 w
No improvement
clinical symptoms
improvement for the
clinical symptoms
anaphylaxis or clear
CMP elimination and
Test for specific IgE
Spec.IgE
neg
Spec.IgE
Pos
standardized oral challenge with CMP
(open , single and /or double blind)
Neg
Pos
No CMP elimination diet
therapeutic elimination diet

Management of CMPA in formula-fed infants*



*Adapted from Vandenplas Y *et al.* Arch Dis Child. 2007; 92 (10): 902-908.