

Cow's Milk Protein Allergy

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Question 1

A 18 day old baby girl has been brought to you with complaints of passing frank blood in stool (approx. 5ml) on at least 4 separate occasions since birth. She was delivered by normal (vaginal) delivery, birth weight 2.7 kg, first child of parents. She has been actively feeding, alert and has no frequent vomiting. She has been on breast feeds as well as top feeds (lactogen-1) since birth.

How will you approach this child and manage?



Question 2

A 9 month old boy weighing 6.2 kg has been having increased stool frequency and frequent regurgitation of feeds for the past 2 months. His birth weight was 3 kg. He was exclusively breast-fed till 6 months of age and subsequently is on a combination of breast feeds, single toned (Mother Dairy) milk and semisolid weaning foods. He has not responded to anti-reflux measures.

What does he have?

What would you like to do?



Question 3

The infant boy is now 10 months old, he has received over the past 4 weeks, MCT containing infant formula for 10 days followed by a soy formula for the remaining period. His problem remains unresolved and his weight is 6.4 kg.

What will you do now?



Cow's Milk Protein Allergy (CPMA)

Definition: “It is an allergy to both casein and whey protein components of animal milk protein which may manifest with Gastrointestinal symptoms only or symptoms involving other Organ systems of the body (respiratory and skin) in addition to the gastrointestinal tract. Most cases are IGE-mediated (ATOPIC), some may be IGA - mediated.”

Cow's Milk Protein Intolerance (CMPI)

Definition: “It is intolerance to animal milk protein which manifests with symptoms identical to cow's milk protein Allergy but the underlying mechanisms are non – immunological.”



Major Differences Between CMPA and CMPI

CMPA

1. Always immunologically mediated
2. Involvement of organ systems other than GIT well described
3. Blood in stool well-known clinical presentation
4. Reintroduction of animal milk after 2 yrs of age should follow a systematic approach of desensitization exposing child to very gradually increasing quantities of animal milk

CMPI

1. Involves, non-immunological Mechanisms
2. Involvement of organ systems other than GIT unusual
3. Blood in stool not a clinical presentation
4. Reintroduction of animal milk after 2 years of age can be achieved rapidly without a systematic desensitization process



Decoding Cows Milk Protein Allergy (CMPA)



Breast feeding is the best

No interest in any brand promotion



Layout of presentation

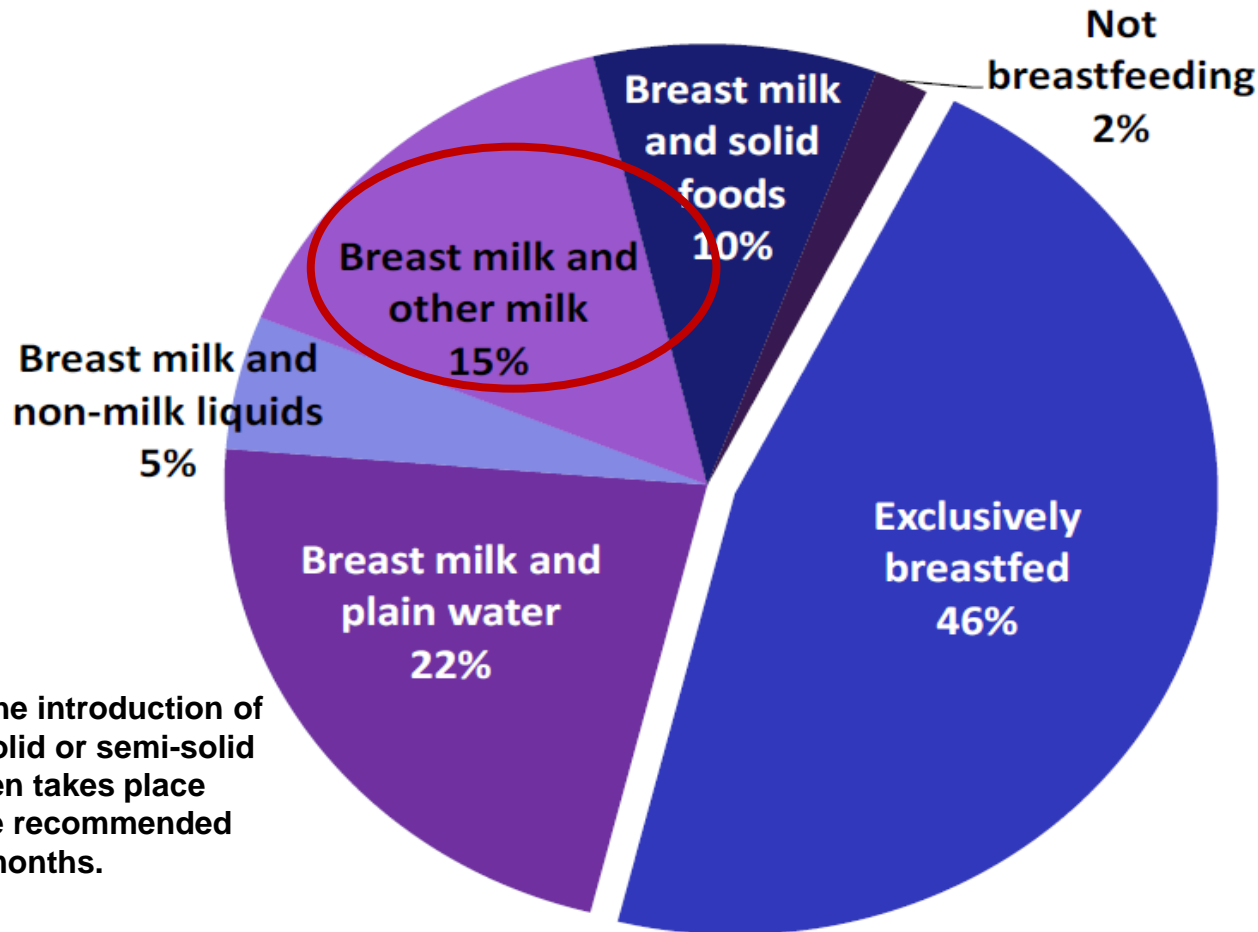
CMPA

Case scenarios – Allergy and Intolerance

Carry home message



Feeding Practices of Infants Under Six Months



Overall, slightly less than half of children under six months of age are exclusively breastfed

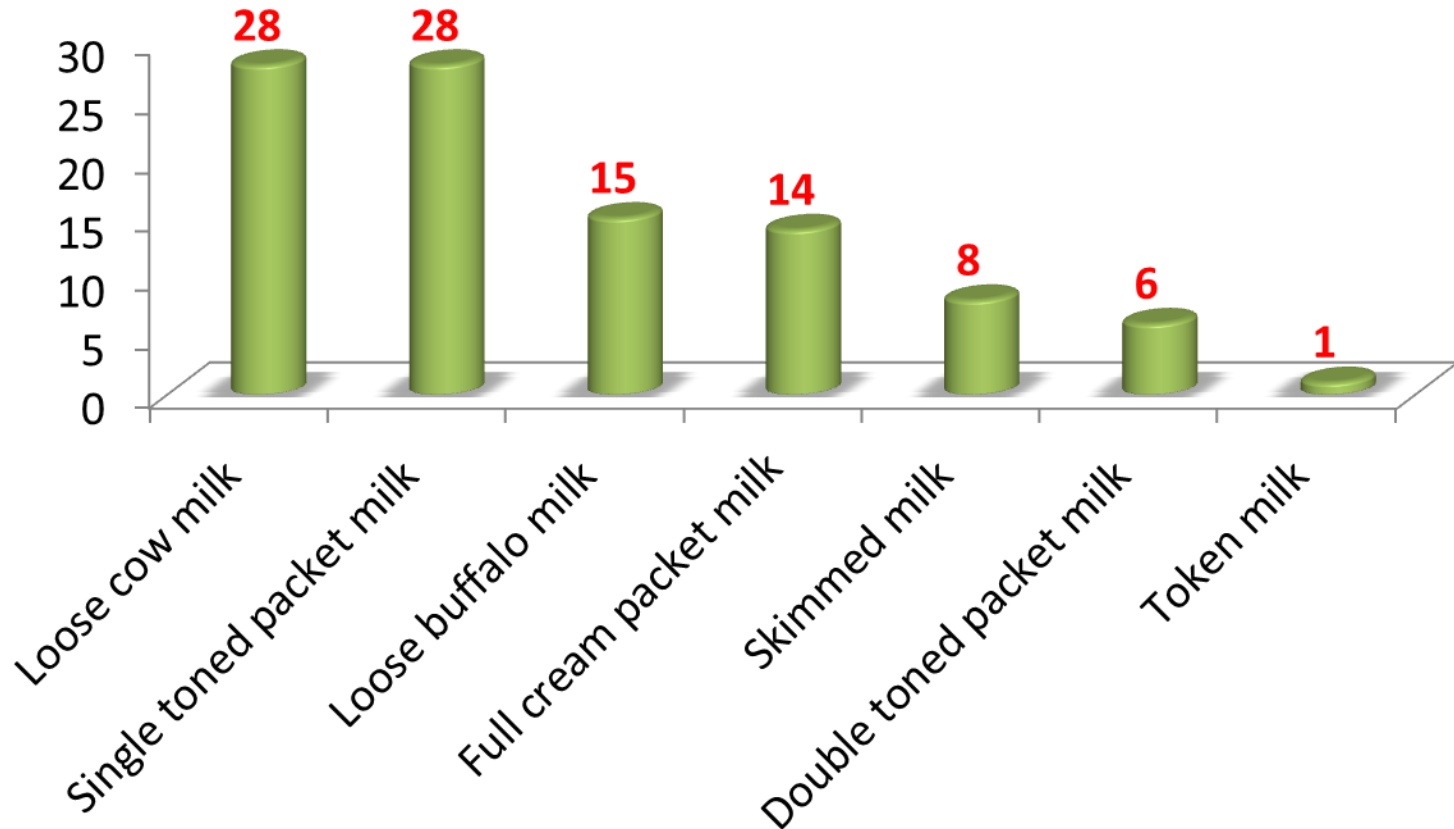
In India, the introduction of liquids, solid or semi-solid foods often takes place before the recommended age of 6 months.

Source
Nutrition in India. National Family Health Survey- 3, 2005-06
Bovine milk usage and feeding practices for infants in India. Indian J Public Health 2012;56:75-81



Feeding Practice - Alternatives

Types of milk purchased for infant feeding (%)



Source
Bovine milk usage and feeding practices for infants in India. Indian J Public Health 2012;56:75-81



Feeding practice – regional differences

Region	Preferred milk for feeding
North	Loose buffalo milk (49%)
East	Cow's milk (65%)
West	Full cream packet milk (27%)
South	Cow's milk (27%)

The **milk is modified** in majority of cases (81%) before fed.

Modification was often done with **sugar** (85%), followed by **water** (49%), biscuits, fennel seeds, cardamom or infant cereals before feeding.

On an average 61% of the infants are given bovine milk.

Source
Bovine milk usage and feeding practices for infants in India. Indian J Public Health 2012;56:75-81



Cow's milk usage in infants - the controversy



Cow's milk usage in infants - the controversy

The Government of India recommends that children should be exclusively breastfed for the first 6 months of life and that children should be given appropriate and adequate complementary feeding in addition to continued breastfeeding from 6 months of age.

The American Academy of Paediatrics (AAP) recommends that whole cow's milk and low iron formulas not be used during the first year of life.

*Source:
Ministry of Women and Child Development, 2006
Pediatric Nutrition Handbook, 7th ed. 2014*



Cow's milk usage in infants- the controversy

Iron Deficiency Anemia (IDA)

Renal Solute Load (RSL)

Risk of Diabetes Mellitus (DM)

Allergy and others



Cow's Milk and Iron Deficiency Anaemia (IDA)

A strong correlation between whole cow's milk use and development of IDA

ESPGHAN and AAP recommend that it is best to delay the introduction of whole cow's milk until the infant is one year old.

Some of the important reasons are;

- Very low content of iron in cow's milk (less than 0.3mg/L to 1 mg/L)
- Reduced bioavailability because of non-heme nature and higher calcium and phosphorus
- Gastrointestinal bleeding (the risk for IDA increases when about 500–1000 ml of whole cow's milk is consumed daily)
- Bovine milk proteins are potent inhibitors of iron absorption.

Source
Alexander KC Leung et al. Whole cow's milk in infancy. Paediatr Child Health Vol 8 No 7 September 2003
Agostoni, Carlo et al.. Journal of Pediatric Gastroenterology & Nutrition: January 2008 - Volume 46 - Issue 1
- p 99-110
Pediatric Nutrition Handbook, 7th ed. 2014



Cow's Milk and Renal Effects

Approximate values per 100ml		Cow milk	Human milk
Sodium	mg	73.00	18.5
Potassium	mg	140.00	47.5
Chloride	mg	103	45
Calcium	mg	120.00	28
Phosphorous	mg	90.00	11

Feeding infants with whole cow's milk narrows the margin of safety in situations that may lead to dehydration, such as when water intake is reduced (eg, vomiting) or water loss is increased (eg, diarrhea, hot environment), whole cow's milk may not supply enough free water. Dehydration may result unless additional water is offered.

Source

Whole cow's milk in infancy. *Paediatr Child Health* Vol 8 No 7 September 2003
Artificial Feeding of Newborns as a Risk Factor for Renal Disease in Childhood. *Human Physiology*, Vol. 29, No. 4, 2003, pp. 510–512.

Ziegler EE. Milk and formulas for older infants. *J Pediatr* 1990;117:S76-9.
Consumption of cow's milk as a cause of iron deficiency in infants and toddlers. [Nutr Rev.](#) 2011 Nov;69 Suppl 1:S37-42
Nutritive value of Indian foods. NIN, ICMR; 2011



Cow's Milk and Risk of Diabetes

An association between early exposure to cow's milk proteins and risk for type 1 diabetes mellitus has been reported

Cow's milk proteins elicits antibody formation to insulin in some children. Bovine serum albumin may provoke an immunological response in genetically susceptible individuals, which then cross reacts with a beta-cell surface protein.

Destruction of beta cells may lead to the development of diabetes mellitus.

The AAP recommends that in families with a strong history of insulin-dependent diabetes mellitus, breastfeeding and avoidance of commercially available cow's milk and products containing intact cow's milk proteins during the first year of life are strongly encouraged.

Source

Whole cow's milk in infancy. *Paediatr Child Health* Vol 8 No 7 September 2003

Cow's milk and immune-mediated diabetes. [Proc Nutr Soc](#). 2000 Nov;59(4):573-9.

Cow's milk formula feeding induces primary immunization to insulin in infants at genetic risk for type 1 diabetes. [Diabetes](#). 1999 Jul;48(7):1389-94.

American Academy of Pediatrics. Infant feeding practices and their possible relationship to the etiology of diabetes mellitus. *Pediatrics*

1994;94:752-4.

Cow's Milk Exposure and Type I Diabetes Mellitus. *Diabetes Care*, Volume 17, Number 1, January 1994



Cow's milk and allergy

Although controversial, it is believed that increased intestinal permeability may contribute to the high incidence of cow's milk protein allergy.

CMPA is suspected clinically in 1%-17% of infants, while most estimates for the prevalence of CMPA vary from region to region and has been found to be in 2% to 7.5% of infants.

The major allergens from cow's milk have been found to be β -lactoglobulin, α -lactalbumin and caseins.

Treatment of infant formulas by methods such as heating, high pressure treatment and proteolysis offers an efficient way to destroy allergenic epitopes and to reduce their allergenicity.

Source

**Whole cow's milk in infancy. Paediatr Child Health Vol 8 No 7 September 2003*

**Cow's Milk Allergy: A Complex Disorder. J Am Coll Nutr December 2005 vol. 24 no. suppl 6 582S-591S*

Cow's milk allergy in children. CME JANUARY 2011 Vol.29 No.1

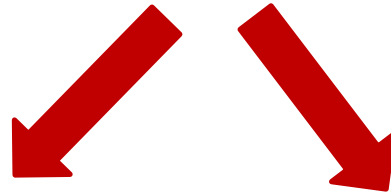
[Patterns of clinical disease associated with cow milk allergy in childhood](#) Original Research. Nutrition Research, Volume 12, Issue 1, January 1992, Pages 109-121.



Let us discuss in details on Cow's Milk Protein Allergy



Adverse Food Reaction



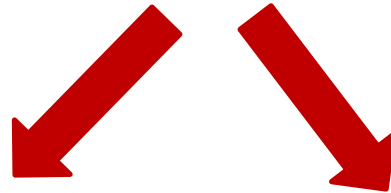
**Immune mediated
Food allergy**

**Non - immune mediated
Primary food intolerance**

J Allergy Clin Immunol Dec 2010



Adverse Food Reaction



**Immune mediated
Food allergy**

**Non - immune mediated
Primary food intolerance**

Mechanism

IgE mediated

Non- IgE
mediated

Mixed IgE and non- IgE
mediated

Cell mediated

Example

Acute urticaria

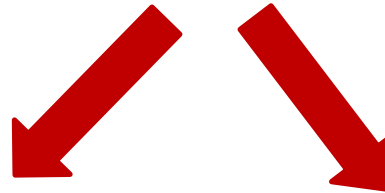
FP induced
enteropathy

Eosinophilic esophagitis

Allergic contact dermatitis



Adverse Food Reaction



**Immune mediated
Food allergy**

**Non - immune mediated
Primary food intolerance**

Mechanism

Example

Metabolic

Pharmacologic

Food factor

Psychologic

Lactose
intolerance

Caffeine -
hyperactivity

Toxin, Infectious organisms

Food phobia

J Allergy Clin Immunol Dec 2010



Common Food Allergens



Food allergy - prevalence (meta analysis of 51 studies)

More than 170 foods have been reported to cause IgE mediated reactions

Diagnostic criteria	Overall Prevalence	Peanut	Milk	Egg	Fish	Crustacean Fish
Self –reported Symptoms: Children	12%					
Self –reported Symptoms: Adults	13%					
Self –reported Symptoms: All ages		0.6%	3%*	1%	0.6%	1.2%
Symptoms plus SPT or serum IgE: All ages	3%	0.75%	0.6%	0.9%	0.3%	0.6%
Food challenge: All ages	3%	NE	0.9%	0.3%	0.2%	NE

No prevalence data of food allergy in India

NE- Not estimated; SPT- Skin prick test

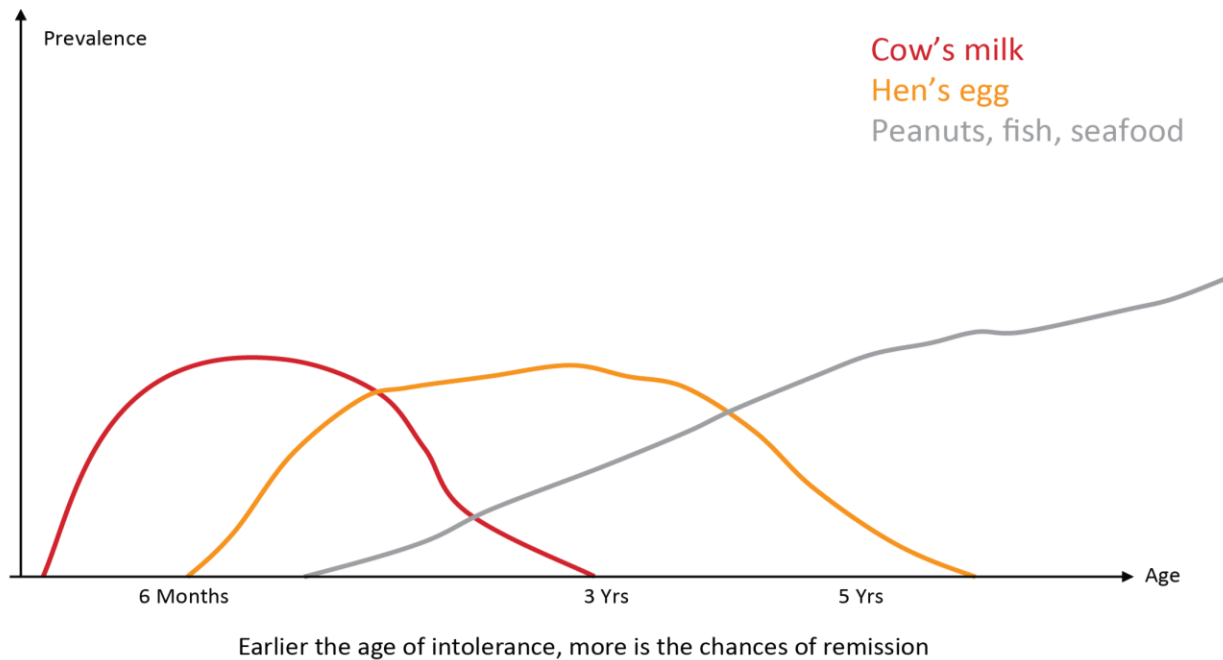
Greater prevalence in children than adults, not specifically estimated but it appears to be about 6% to

7% in children and 1% to 2% in adults

J Allergy Clin Immunol 2007 Sep; 120(3):638-46



Every food has its own story....



Age at onset



Age	Food
0-1yr	Milk, Egg
1-2yrs	Fish
>2yrs	Fruits, Legumes, Vegetables
>3yrs	Pollen related cross reactivity

Crespo JF. Pediatr Allergy Immunol 1995;6:39-43



CMPA in India (1993)

Etiology of malabsorption in India

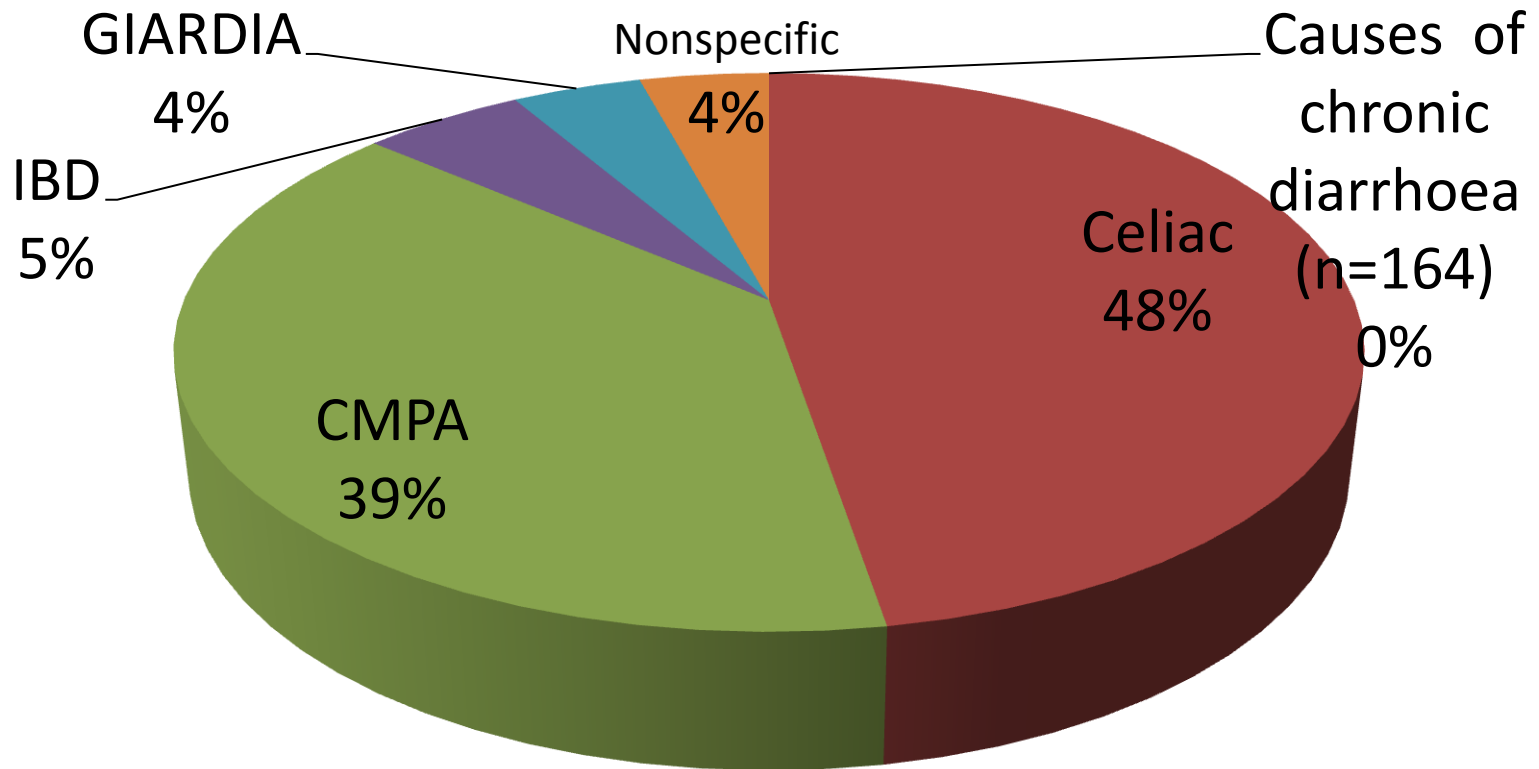
Etiology	Age < 2 years	Age > 2 years
Persistent diarrhea	73 %	0 %
CMPI	13%	0 %
Celiac disease	5 %	43 %
Parasites	3 %	15 %
Tuberculosis	0 %	9 %
Miscellaneous	0 %	24 %

Indian J. Gastroenterol. 1993



CMPA in India (2009)

Causes of chronic diarrhea <3 years (n=164)



Journal of Gastroenterology and Hepatology 2009



Composition of major protein in human and cows milk

Protein	Human milk(mg/ml)	Cows Milk
alpha Lactalbumin	2.2	1.2
alpha s1 casien	0	11.6
alpha s2 casien	0	3
b cassien	2.2	9.6
k cassien	0.4	3.6
g cassien	0	1.6
Immunoglobulin	0.8	0.6
Lactoferrin	1.4	0.3
b globulin	0	3
Lysosome	0.5	trace
Albumin	0.4	0.4
Other	0.8	0.6



Features of CMPA

Cows milk is composed of variety of proteins - Casein (80 %) : α s1-, α s2-, β - and κ -caseins, Whey (20 %) : α lactalbumin, β lactglobulin and others

β lactglobulin being considered as the most important cows milk allergen

Cross reactivity between antigens of different bovine milk



Symptoms of CMPA

< 30 min after ingestion (IgE mediated)

Immediate Reactions

- Anaphylaxis
- Acute urticaria
- Acute angioedema
- Wheezing
- Rhinitis
- Dry cough
- Vomiting
- Laryngeal edema
- Acute asthma with severe respiratory distress

Late Reactions

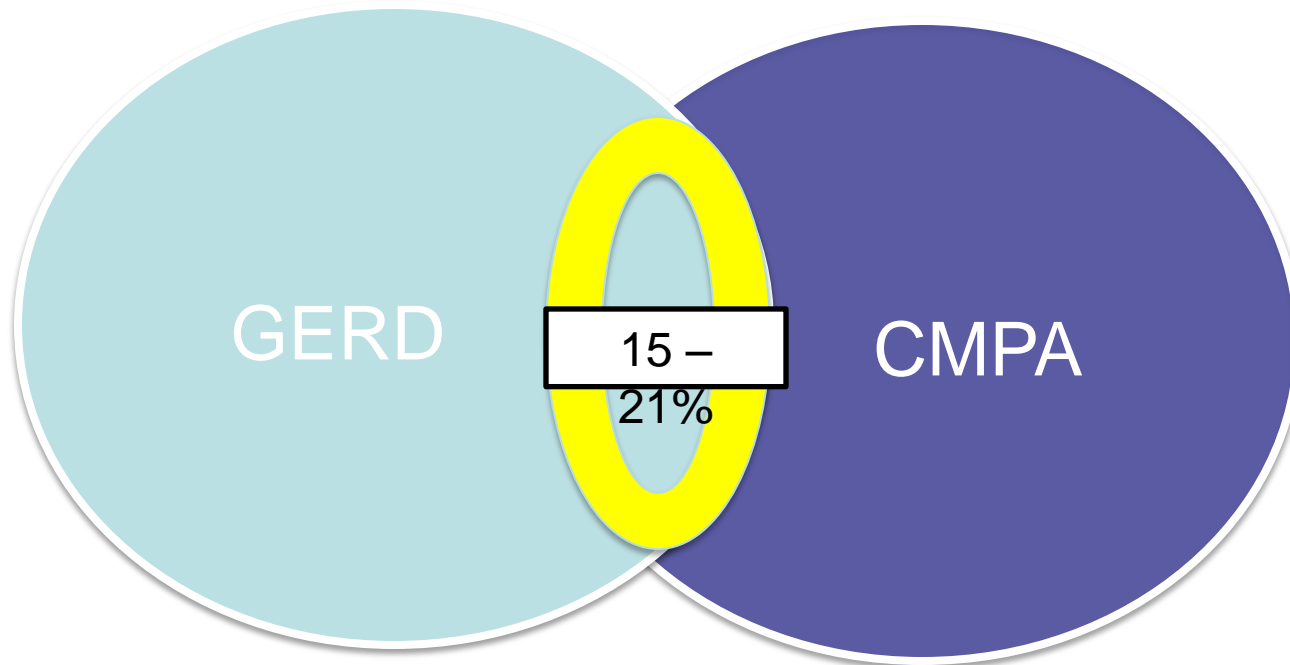
- Atopic dermatitis
- Chronic diarrhea, stool blood, iron deficiency anaemia, gastroesophageal reflux disease, constipation, chronic vomiting, infantile colic
- Poor growth (food refusal)
- Protein-losing with hyperalbuminemia
- Enterocolitis syndrome
- Eosinophilic oesophagogaastroenteropathy confirmed by biopsy

Hours – days after ingestion (Non IgE mediated)



CMPA variants

15–21% of children with suggested or proven GERD and CMPA suffer from both conditions

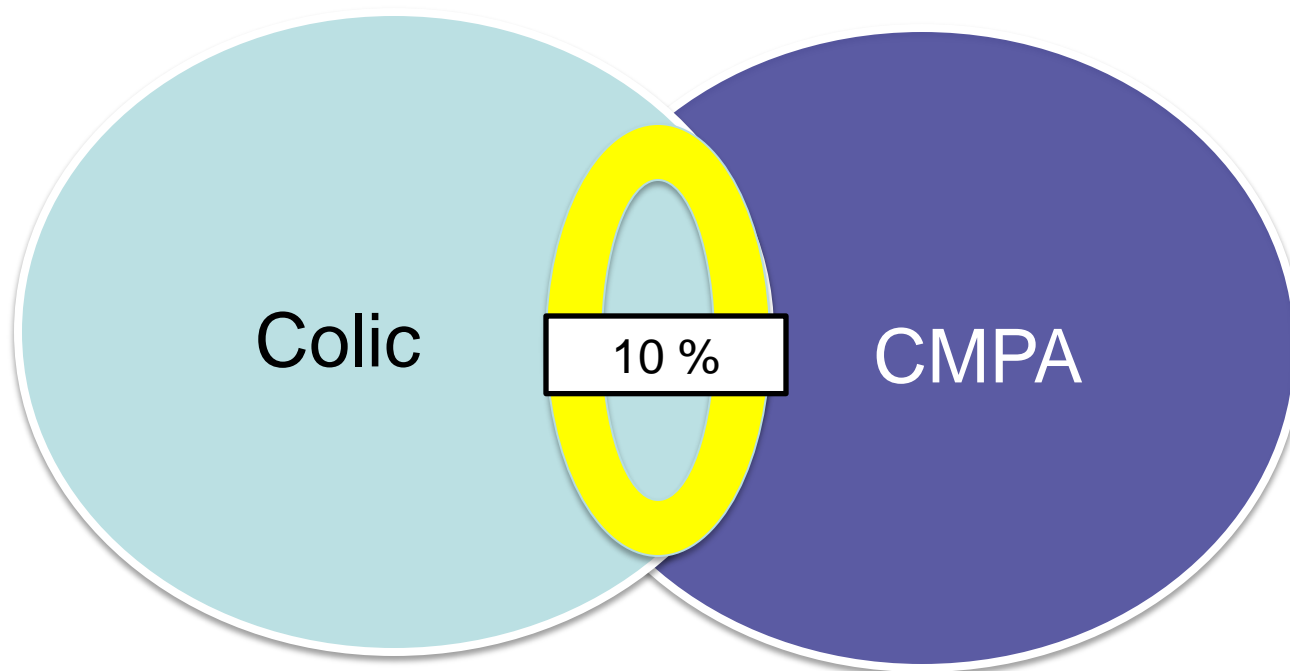


Int Semin Paediatr Gastroenterol Nutr 2002;11:1–7



CMPA variants

10 % of children with Colic and CMPA suffer from both conditions



Int Semin Paediatr Gastroenterol Nutr 2002;11:1-7



Food allergy - Investigations

None of the test prove or disprove diagnosis of CMPA

Elimination diet and re challenge remain the gold standard

Immunocap (IgE against Milk protein) and Skin Prick test may be needed in certain circumstances under specialist



CMPA – What to Avoid

Milk and milk products

Curd, Butter, butter, milk, Ghee, Biscuits,
Breads, sweets, etc.



Protocol in CMPA - Nutshell

Dairy free diet for child and mother (if being breastfed) for 2- 4 weeks

If improvement - rechallenge with cows milk after 1-3 months

If symptoms recur, confirms diagnosis. Rechallenge after 1 year of age or after 6 months of the reaction



Case Scenario 1

3 month old infant c/o visible specks of blood with mucus for past 7 days

Exclusively breast fed, not sick, growing well

Stool culture – E coli, treated with 2 courses of antibiotics; oral f/b parenteral

USG – normal. No intussuception

Blood test – Hb 10.5, Platelet 3.5 lac, INR 1.1, APTT 32 (Control 30)



Case Scenario 1



Sigmoidoscopy
aphthous
ulcerations

Histology (Rectal biopsy)
Increased eosinophils > 6/hpf



Case Scenario 1

Diagnosis: Allergic Proctosigmoiditis

What dietary advise ?

Stop Dairy products in mother; Continue breastfeeding !

Wean with Dairy free diet

Calcium supplements for mother



CMPA - Breastfeeding

A breastfed baby can develop CMPA due to secretion of bovine protein (beta lactoglobulin) through breast milk when the mother is ingesting bovine milk

Incidence - 0.5 % of exclusively breastfed infants may develop CMPA as opposed to 3 % otherwise. Most of these are mild to moderate

CMP present in breast milk is 100 000 times lower than that in cow's milk

Treatment includes stoppage of dairy products in mother



J. Pediatr. 1982



Case Scenario 2

6 month old infant with recurrent vomiting since past 1 month

Treated with Domperdione, Lansoprazole & Ondansetron by 2 doctors, no response

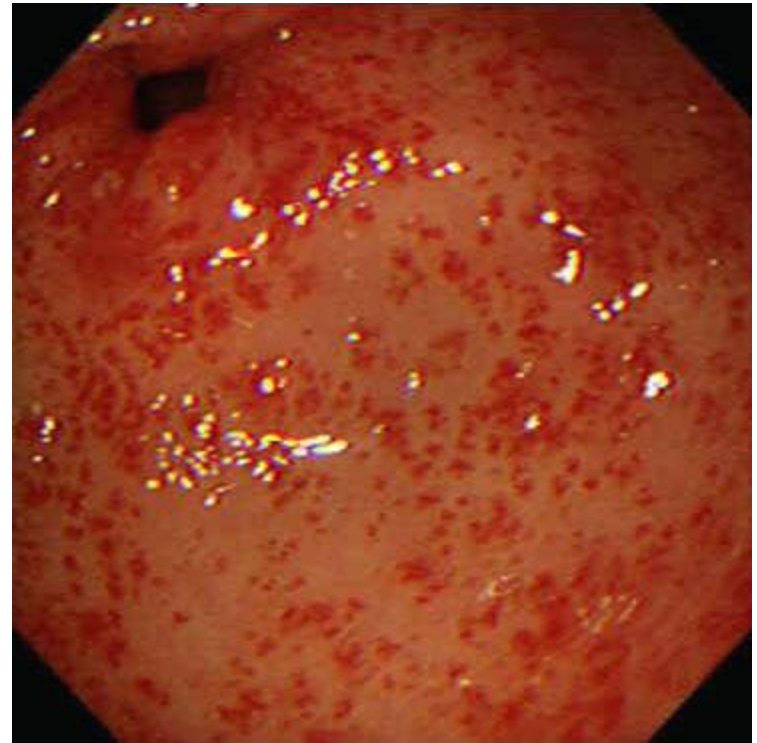
Developed one episode of hematemesis Hb 6.8, received Packed RBC



Case Scenario 2

UGI Endoscopy –
Hemorrhagic Gastritis

Histology - Increased
Eosinophils



Diagnosis: CMPA



Case Scenario 2

Infant was started on dairy free diet

Repeat endoscopy after 1 month – normal

No further vomiting or GI bleed

Milk challenge after 6 months, no reaction, now tolerating dairy products



Case Scenario 3

2 yrs old girl child

Post weaning intolerance to cow's milk

Not able to tolerate milk products

2/3 episodes of post exposure Urticarial rash



OFC



Open food challenge is consistent with diagnosis of Food allergy (Grade C evidence)



OFC

After a physical examination

A drop of the formula is put on the lips

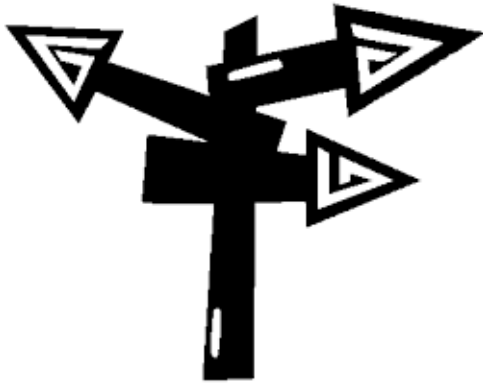
If no reaction occurs after 15 min, the formula is given orally and the dose is increased stepwise (0.5, 1.0, 3.0, 10, 30, 50 to 100 ml) every 30 min

Child should receive at least 250 ml of cow's milk-based formula each day for the next week and the parents told to observe the child for late reactions



What next?

Eliminate cows milk from diet



Consider alternative



CMPA – Options

Breastfeeding/ Relactation

Extensively hydrolyzed formula/Amino acid based formula

Soya Milk

Non dairy food



CMPA – Options in India

Breastfeeding/ Relactation

Soya Milk

Non dairy food



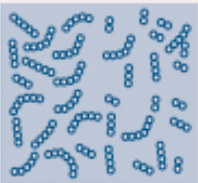
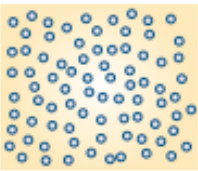


Non Dairy Food

Chicken feeds: Comminuted chicken available in predigested form for use in CMPA

Rice: In infants older than 4 months (sometimes in 2 months old)



	Protein Structure in Infant Formulas	Type of Protein	Formulas Available*	Hypo-allergenic	Contains Milk Proteins (Whey or Casein)	Protein Type
<p style="writing-mode: vertical-rl; transform: rotate(180deg);">MOST ALLERGENIC</p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);">NON-ALLERGENIC</p>		Dairy and soy-based	Enfamil Lipil ^{®1} Smilac Advance ^{®2} ProSobee ^{®1}	No	Yes	Complete protein chains that can trigger an allergic reaction.
		Partially Hydrolyzed	Gentlease ^{®1} Good Start ^{®3}	No	Yes	Protein chains are partially broken down into pieces.
		Extensively Hydrolyzed	Nutramigen ^{®1} Alimentum ^{®2} Pregestimil ^{®1}	Yes	Yes	Protein chains are broken down into pieces. Although these formulas are called hypoallergenic, they can still trigger an allergic reaction.
		Amino acid-based	Neocate[®] Infant (100% amino acid-based)	Yes	No	No intact protein chains, based on individual, non-allergenic amino acids. No peptide links to trigger an allergic reaction.

*Examples – not a complete list

¹Mead Johnson Nutrition

²Abbott Nutrition

³Nestle Nutrition



AAP Committee on Nutrition 2014



Soy formula recommended for

- Term infants with IgE mediated allergy to cow milk
- Term infants with galactosemia.
- Term infants with transient lactase deficiency

Note: neither AAP 2008 statement nor 2014 handbook put age limit

Pediatric Nutrition, 7th edition, AAP Committee on Nutrition, Elk Grove Village, Illinois, 2014, p 75



Concern Regarding Growth

AAP: “isolated soy protein-based formulas may be used to provide nutrition for normal growth” *Pediatrics* 2008; 121:1062

ESPGHAN: “soy protein formulae can be used for feeding term infants but have no nutritional advantage over cows-milk protein formulae” *JPGN* 2006;42:352

Soy formulas support growth **equivalent to that of breastfed and cow milk-based formula fed infants. Bone mineralization is similar in full-term infants fed soy and cow milk-based formulas."**



Reproductive and Endocrine Outcomes

No Differences for:

Missed periods

Spotting

Cramps

Breast tenderness

Pregnancy

Pregnancy outcomes

Height

Weight

Age of sexual maturation

Menstrual cycle length

Regularity of menses

Menstrual flow

Bottom line

- Soy formula fed subjects **no different from cow's milk** formula fed subjects on almost all outcomes evaluated
- Given >30 variables
- Findings were **“reassuring about the safety of soy infant formula”**

Strom et al., JAMA 2001;286:807-814



Indications for Soy Formula: What do the doctors really do?

United Kingdom: direct count of feeding and diagnoses

National database query for feeding prescriptions

- Infants < 12 months, and
- Diagnosis of cow milk allergy by GP

Overall, 60% given soy formula, 18% eHF

For infants < 6 months, 76% soy, 21% eHF

5% of soy fed infants switched to another formula

29% of eHF infants switched to another formula

Sladkevicius, et al. J Med Economics 2010;13:119



Case Scenario 4

2 month old infant c/o diarrhea (8-10 stools/day) – 5 days, no blood, perianal excoriation +

Exclusively breast fed

Weight gain acceptable to doctor

Stool examination – reducing substance positive !

What dietary advise?



Stool and urinary sugars in normal neonates

R. COUNAHAN and J. WALKER-SMITH

From Queen Elizabeth Hospital for Children and the Mother's Salvation Army Hospital, London

Stool reducing substance > 0.5 gm% (++) – 32 %

Stool pH < 5 – 10%, < 6 - 25 %



(Trace – 100 mg%, 1 + - 250 mg%, 2 + - 500 mg%, 4+ - > 1gm%)



Case Scenario 4

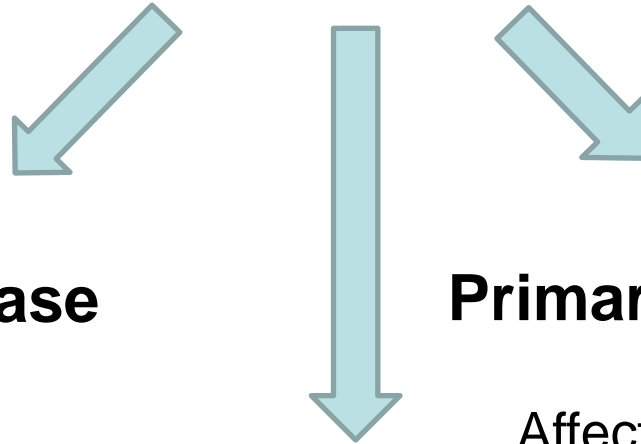
Diagnosis: Pseudo diarrhea/Fore milk diarrhea

Treat lactose intolerance only if above associated with severe diarrhea

Continue breastfeeding, Give more of hind milk



Lactose intolerance



Congenital lactase deficiency

Very rare, autosomal recessive, presents at birth, common in Finland

Primary lactase deficiency

Affects adults, genetic, most common

Secondary lactase deficiency

Caused by injury to small intestine, usually in infancy



	Cows milk allergy	Lactose intolerance
Type of adverse reaction	Allergy – immunological	Intolerance – non immunological
Pathological molecule	Bovine milk protein	Lactose - carbohydrate
Organ involvement	GIT, Skin, Respiratory	GIT
Common GIT symptom	Vomiting, Colic, small or large bowel diarrhea, GI Bleed	Small bowel diarrhea, Colic, flatulence, perianal excoriation
Age group affected	Infancy and toddler	All age group
Treatment	Stoppage of all dairy products, change to non dairy protein or hydrolyzed formula	Reduction of lactose, can continue dairy protein
Result of treatment	Qualitative – all or none phenomenon	Quantitative – response as per reduction of lactose



CMPA in Breast Fed Infant- Principles of Management

1. Breast feeding should be promoted for the primary prevention of allergy
2. Allergen avoidance



Baby



Mother



In Infants with Atopic Dermatitis

Sensitized to



4 times



8 times

Younger the infant and/or the more severe the atopic dermatitis, the stronger the association

Pediatr Allergy Immunol 2002;13:234-42



First Line Elimination Diet

- Milk



- Egg



- Peanuts



Second Line Elimination Diet

Excluding fish, wheat and other gluten-containing grain products

Demanding for the mother → risk of consuming unbalanced diet

Require the advice of an experienced dietician

If the mother has a certain suspicion on any other food elimination diet should be adapted accordingly



JPGN 2012;55.221-229

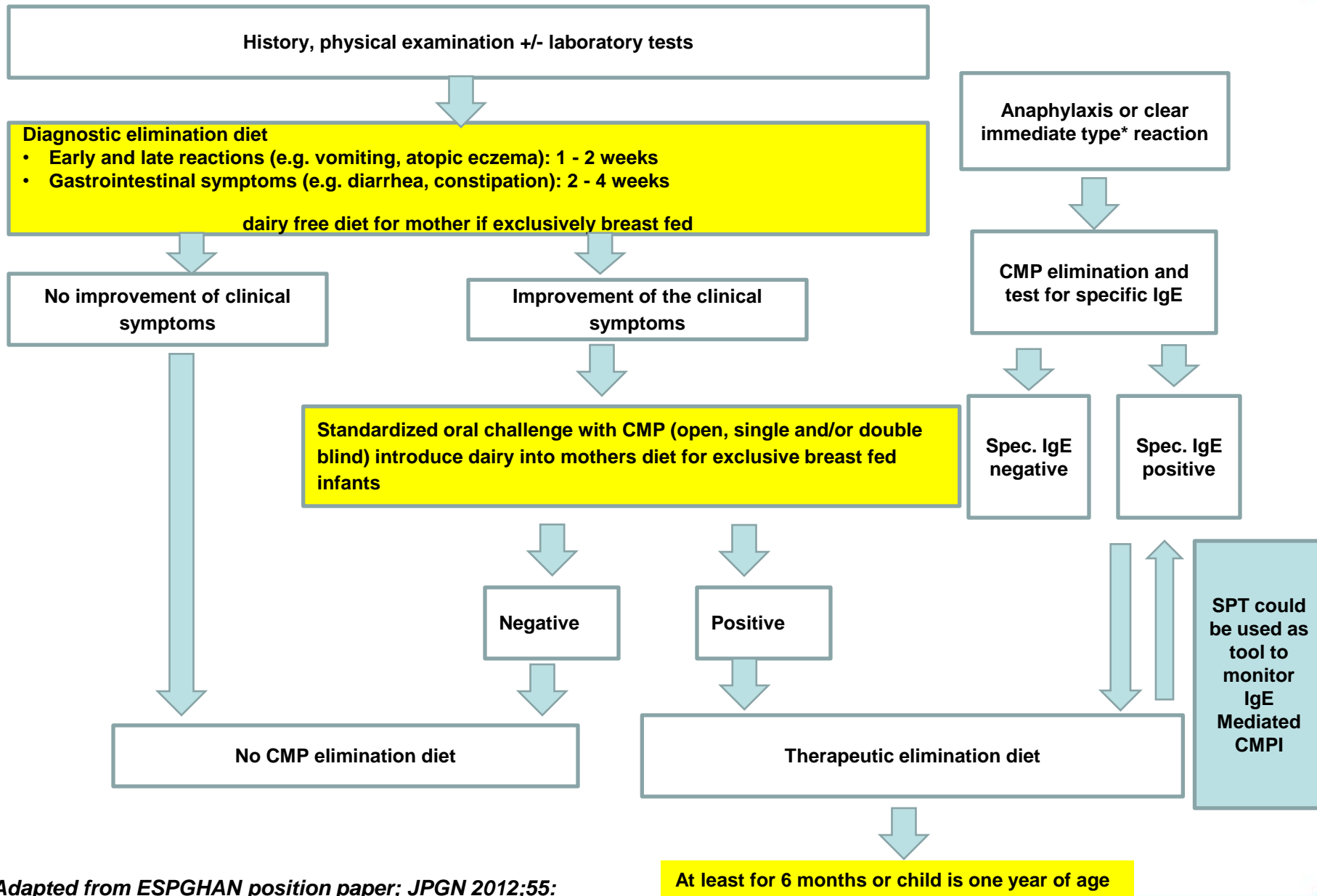
(JPGN 2012;55: 221–229)

MEDICAL POSITION PAPER

Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines

**S. Koletzko, †B. Niggemann, ‡A. Arato, §J.A. Dias, ||R. Heuschkel, ¶S. Husby, #M.L. Mearin,
**A. Papadopoulou, ††F.M. Ruemmele, ‡‡A. Staiano, §§M.G. Schäppi, and ||||Y. Vandenplas*





Adapted from ESPGHAN position paper; JPGN 2012;55: 221–229

At least for 6 months or child is one year of age



Food Allergy – Safety Measure



Carry Home Message

CMPA may present with gastrointestinal respiratory or skin manifestation

First manifestation is generally in infancy

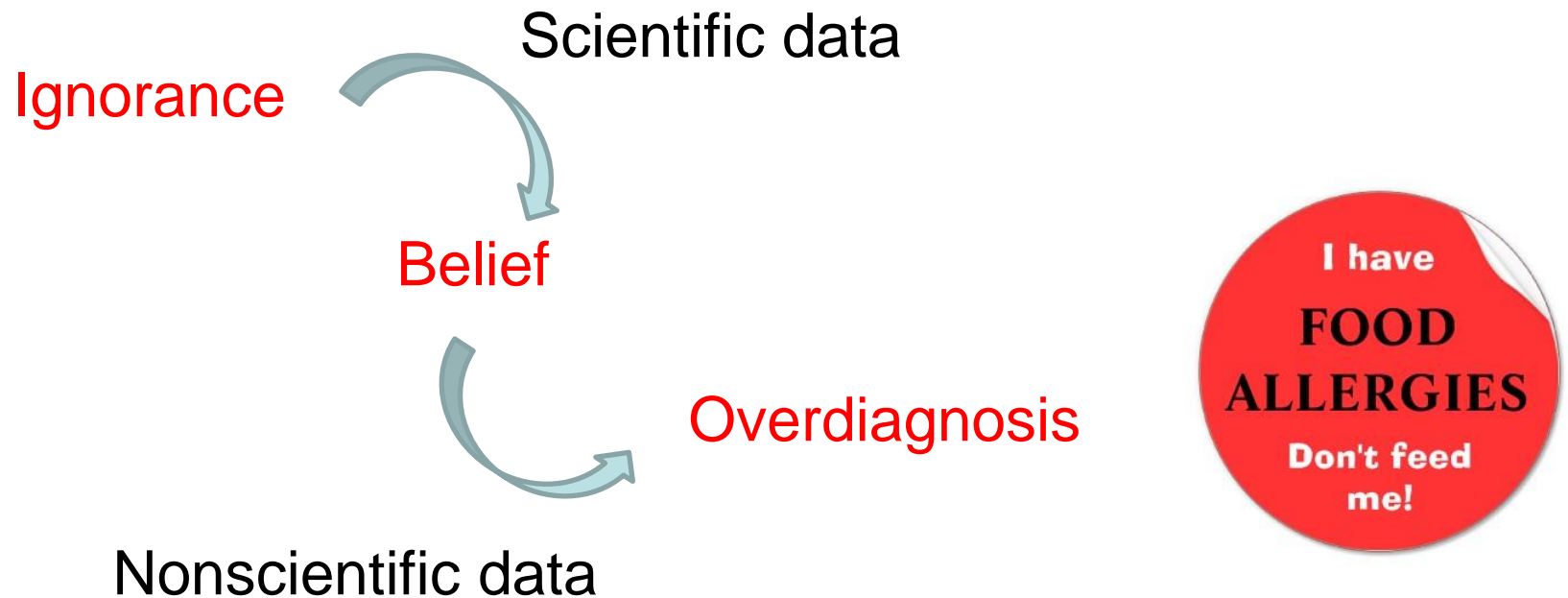
Recurrent vomiting, GI bleeding, diarrhea are common GI manifestations





Conclusion: Food Allergy... Myth or reality?

... A Reality... surrounded with lot's of myth



THANK YOU!!

