## Breast Feeding and Beyond: Best Practices for Feeding an Infant with Cow Milk Allergy

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#### **Disclosure:**

• Member, Nutricia Speaker Bureau

### **Objectives**

- 1. Understand the role of human milk in infants with cow milk allergy (CMA)
- 2. Discuss mother's diet within the management of CMA
- 3. Distinguish differences in composition and categorization of specialized pediatric formulas
- 4. Understand the proper use of specialized pediatric formulas based on evidence

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## **Definition of Cow Milk Allergy**

- Cow Milk Allergy (CMA) is an adverse immune response to proteins - primarily whey and casein protein fractions found in cow milk
- CMA is associated with a spectrum of symptoms which may be elicited by different immune mechanisms:
  - IgE-mediated
  - Non IgE-mediated

Gupta et al, Pediatrics, 2011

#### Symptoms of IgE vs Non-IgE Mediated Allergy

	IgE Mediated	Nor	-IgE Mediated	
	Immediate Reaction: Few minutes to 2 hours	D C	elayed Reaction Often 2 to 7 days	
	Urticaria		Vomiting	
	Angioedema		Constipation	
	Vomiting		Hemosiderosis	
	Diarrhea		Malabsorption	
	Eczema		Villous atrophy	
	Rhinitis	RhinitisEnterocolitisAnaphylaxisProctitis/Proctocoliti		
	Anaphylaxis			
		Fosinop	ohilic Esophagitis (EoE	)
In clinical practice, often not possible to distinguish between IgE and non-IgE mediated based on history and physical exam			Vandennlas et al. <i>Pedic</i>	ıdenj

Combinations of both immediate and delayed reactions of the same allergen can occur in the same patient

M Vandenplas et al. *Acta Pediatrica* 2015 Vandenplas et al, *Pediatr Gastroenterol Hepatol Nutr,* 2014 Koletzko et al, ESPGHAN GI Committee Guidelines, *JPGN*, 2012

## Symptoms of CMA by Organ Involvement

#### Gastrointestinal

- Colic, abdominal pain
- Vomiting, regurgitation
- Anorexia, refusal to eat
- Diarrhea
- Bloody stools
- Iron deficiency anemia
- Constipation
- Failure to thrive
- Dysphagia, dyspepsia

#### Respiratory

- Runny nose
- Chronic coughing
- Wheezing/stridor
- Breathing difficulties

#### Skin

Urticaria
Eczema
Angioedema

Vandenplas et al. Acta Pediatrica 2015

## **Typical Presentation of CMA**

- Cutaneous reactions (eczema)
- Gastrointestinal symptoms (most frequently, bloody stools)
  - Systemic symptoms (emesis, severe diarrhea, abdominal distention) are quite rare and may suggest other allergic disorders such as food protein-induced enterocolitis
- Often occur between 2-6 weeks of life
  - Although some have reported symptoms as early as DOL 1 or as late as 4-6 months

Academy of Breastfeeding Medicine Protocol, Breastfeed Med, 2011

#### **Prevalence of Food Allergy**

- Food allergy affects ~5% of children under the age of 5 yrs
  - NIAID National Institute of Allergy and Infectious Diseases (component of NIH)
- CMA is the leading cause of food allergy in children <3 years of age</li>
  - Affects about 2-3% of infants and young children
  - Natural occurrence of CMA has changed overtime a higher percentage of children's CMA persists into adolescence and adulthood
  - 50-90% outgrow CMA by 3-5 years

Vandenplas et al. *Acta Pediatrica* 2015 Wood et al, *J Allergy Clin Immunol*, 2013 Boyce et al, NIAID Guidelines, *J Allergy Clin Immunol*, 2010

#### **Allergic Reactions to Proteins**

Protein in Cow's Milk Whey 20% Casein 80%

- Both casein and whey can elicit both IgE and non-IgE responses
- Polysensitization to multiple CM proteins in the same patient is common
- Soy proteins may trigger allergic reactions in CMA patients
- 10-14% of CMA infants are also sensitive to soy

Vanderhoof et al, *JPeds,* 2015 Rozenfeld et al, *Clin Exp Immunol* 2002 Bhatia and Greer, AAP Committee on Nutrition, *Pediatrics,* 2008

#### CMA affects 3-5% of formula-fed infants, 0.5-1% of breastfed infants



Parent self-report of CMA is 3-18% worldwide









Vandenplas et al. *Acta Pediatrica* 2015 Elizur et al. *Arch Dis Child* 2013

#### **Algorithm for Management of CMA**



\*Severe CMA-related symptoms: severe eczema or enterocolitis with growth faltering, hypoproteinemia, or severe anemia

Vandenplas et al. Acta Pediatrica 2015

Long-Term Management Elimination of CM sources If BM not available, consider eHF or AAF for at least 6 mo or until infant is 9-12 mo of age; monitor for tolerance

## AAP Policy Statement: Breastfeeding and the Use of Human Milk

- All infants should receive human milk
  - Exclusive breastfeeding for 1<sup>st</sup> 6 months
  - Continued breastfeeding as complementary foods are introduced
  - Continuation of breastfeeding at least 1 year or up to 2 years or longer

TABLE 1Healthy People2020(%)	Targets	2010 a	nd
	<b>2007</b> ª	2010	2020
		Target	Target
Any breastfeeding			
Ever	75.0	75	81.9
6 mo	43.8	50	60.5
1 y	22.4	25	34.1
Exclusive breastfeeding			
To 3 mo	33.5	40	44.3
To 6 mo	13.8	17	23.7
Worksite lactation support	25		38.0
Formula use in first 2 d	25.6	—	15.6

<sup>a</sup> 2007 data reported in 2011.<sup>10</sup>

American Academy of Pediatrics Section on Breastfeeding Breastfeeding and the Use of Human Milk, *Pediatrics.* 2012, also update 2015

#### **Maternal Elimination Diet**

- Data not sufficient to recommend elimination diet as a means of <u>preventing</u> allergy (during pregnancy or lactation) for low-risk or even high-risk infants
  - Possible benefits for very high-risk infants with highlymotivated mothers
    - Greater effects for prevention of atopic dermatitis and respiratory allergy rather than food allergy
- 1<sup>st</sup> line of treatment for <u>managing</u> CMA (Recognize this request can be very stressful on new mother)

Academy of Breastfeeding Medicine Protocol, Breastfeed Med, 2011

#### **Management of Breastfed Infants**

- Goal: To continue breastfeeding
- Immediate reaction: maternal elimination diet for 3-6 days
- Delayed reaction: maternal elimination diet up to 14 days
- If no improvement, CMA unlikely and re-evaluate
  - Recognize that proteins other than CM may cause allergic reactions and consider maternal elimination of soy and eggs
  - If improve, consider reintroduction of CM into mother's diet
    - If symptoms return, return to CM-free maternal diet, provide mother with calcium supplements (1000-1200 mg/d)

Koletzko et al, ESPGHAN GI Committee Guidelines, JPGN, 2012 Fiocchi et al (DRACMA), J Allergy Clin Immunol, 2010

#### **Maternal Elimination Diet**

- Eliminate 1 food group at a time and wait a minimum of 2-4 wks
  - If no changes with the infant's symptoms, mother can add this food back into her diet and eliminate another food group
  - Continue until all foods listed have been eliminated
- If eliminating several food groups at once (cow milk, eggs, soy, etc), then wait a minimum of 2-4 wks and reintroduce 1 food group at a time, waiting at least a week before reintroducing another food group
- If eliminating foods doesn't alleviate symptoms, have mother keep strict food diary for 2 weekdays and 1 weekend to pinpoint foods

# Management of Breastfed Infants with Severe Symptoms

- Severe symptoms: severe eczema or enterocolitis with growth faltering, hypoproteinemia, or severe anemia
  - Consider taking off breast milk temporarily and using amino acid (AA)-based formula for several days up to 2 weeks
  - Consider AA-based formula during transition of elimination diet washout period to stabilize the patient's condition

Koletzko et al, ESPGHAN GI Committee Guidelines, JPGN, 2012

#### How long to continue elimination diets?

- Although bloody stools, other symptoms may clear within days, full endoscopic and histologic healing can take several weeks
- Rechallenging within the 1<sup>st</sup> 6 months of elimination often provokes recurrence of bleeding within 72 hours



Recurrence can occur in severely sensitive infants even with as little as a PAT of butter in maternal diet

> Koletzko et al, ESPGHAN GI Committee Guidelines, *JPGN*, 2012 Academy of Breastfeeding Medicine Protocol, *Breastfeed Med*, 2011

#### How long to continue elimination diets?

- Suspected foods should be eliminated from mother's (and infant's) diet until 9-12 months of age AND for at least 6 months after diagnosis
- Most infants will tolerate the allergenic food after 6 months from diagnosis AND at least 9 months old
  - If infant is diagnosed at 2 weeks of age, eliminate the food until infant is 9-12 months of age
  - Rare circumstance of diagnosis at 5-6 mo of age, wait a full 6 months after diagnosis to reintroduce allergens in maternal diet (ie, 12 mo of age)

Academy of Breastfeeding Medicine Protocol, Breastfeed Med, 2011

#### **Management of Formula Fed Infants**

- Start with extensively hydrolyzed formula
  - If no improvement within 2 wks, switch to AA-based formula
- If extremely severe, start with AA-based formula
- If no improvement with AA-based formulas after 2 wks, consider other diagnoses other than CMA

Koletzko et al, ESPGHAN GI Committee Guidelines, JPGN, 2012

## **Peptides vs Free Amino Acids**



- Proteins have been broken down into smaller peptides by enzymatic and heat treatment process
- Size of peptides determines degree of hydrolysis
  - Partially hydrolyzed
  - Extensively hydrolyzed
- Amino acid-based (elemental)

<sup>\*</sup> For illustration purposes only

## **Differentiating Formula Proteins by Size**

- No set criteria for defining degrees of hydrolysis for partially hydrolyzed and extensively hydrolyzed formulas
- Only industry standards
- Protein size matters it is the key factor for allergy
  - Peptides 10-70 kD (particularly 10-40 kD) are associated with allergens

Type of Formula	Size Proteins (kD)	Range of Peptide Sizes	
Whole cow milk	14-67		
Partially hydrolyzed formula (pHF)	<5	~18% of peptides are >6 kD	
Extensively hydrolyzed formula (eHF)	<u>&lt;</u> 3	~1 to 5% are >3.5 kD	
Amino acid-basedDoesformulaMade of		es not contain peptides of 100% free amino acids	

2-10% of infants with CMA may be intolerant to extensively hydrolyzed formulas due to small residual peptides that may provoke reactions in infants allergic to CM

Vandenplas et al, *JPEN*, 2014 Hill et al, *Clin Exp Allergy*, 2007

kD: Dissociation constant

## Hypoallergenicity

- Definitions vary among countries and can create confusion
- American Academy of Pediatrics (AAP): A double-blind placebo controlled trial has to be conducted in infants with documented CMA and results have to show that a minimum of 90% had no allergic reaction to cow milk protein with a 95% CI (<10% of patients can react)
- US: Considered a health claim that requires premarket approval by the FDA
- Only extensively hydrolyzed and amino acid-based formulas are considered hypoallergenic and are appropriate for CMA

AAP Committee on Nutrition, Pediatrics, 2000

#### **Categories of Infant Formulas based on Protein Type**

Intact Protein (Standard Infant Formula)					
Mead Johnson*	Abbott*	Perrigo Nutritionals*			
Enfamil <sup>®</sup> Premium <sup>™</sup>	Similac <sup>®</sup> Advance <sup>™</sup>	Store Brand Advantage & Premium			
Enfamil <sup>®</sup> Newborn <sup>™</sup>	Similac <sup>®</sup> for Supplementation <sup>™</sup>	Store Brand Added Rice Starch			
Enfamil <sup>®</sup> AR™	Similac <sup>®</sup> Sensitive <sup>™</sup>	Store Brand Sensitivity			
Enfamil <sup>®</sup> Prosobee <sup>™</sup> (soy)	Similac <sup>®</sup> for Spit-Up <sup>™</sup>	Store Brand Soy			
Enfamil <sup>®</sup> Enspire <sup>™</sup>	Similac <sup>®</sup> Isomil <sup>™</sup> (soy)				
	Similac <sup>®</sup> for Diarrhea <sup>™</sup> (soy)				

\*Names of products not belonging to Nutricia or Danone are trademarks of other entities.

#### **Categories of Infant Formulas based on Protein Type**

Partially Hydrolyzed Protein					
Mead Johnson*	Abbott*	Nestle*	Perrigo Nutritionals*		
Enfamil <sup>®</sup> Gentlease <sup>™</sup>	Similac <sup>®</sup> Total Comfort <sup>™</sup>	Gerber <sup>®</sup> Good Start <sup>®</sup> Gentle	Store Brand Gentle & Tender <sup>®</sup>		
Enfamil <sup>®</sup> for Supplementation <sup>™</sup>		Gerber <sup>®</sup> Good Start <sup>®</sup> Soothe			
Enfamil <sup>®</sup> Reguline <sup>™</sup>		Gerber <sup>®</sup> Good Start <sup>®</sup> Protect			
		Gerber <sup>®</sup> Good Start <sup>®</sup> for Supplementation			
		Gerber <sup>®</sup> Good Start <sup>®</sup> Soy			

\*Names of products not belonging to Nutricia or Danone are trademarks of other entities.

#### **Categories of Infant Formulas based on Protein Type**

Extensively Hydrolyzed Protein					
Mead Johnson*		Abbott*		Nutricia	Nestle*
Pregestimil <sup>™</sup>		Similac <sup>®</sup> Alimentum <sup>®</sup>			Gerber <sup>®</sup> Extensive HA <sup>®</sup>
Nutramigen™					
Nutramigen with Enflora LGG <sup>™</sup>					
Amino-Acid Based Protein ("Elemental")					
Mead Johnson*		Abbott*		Nutricia	Nestle*
PurAmino™		Elecare®		Neocate®	Alfamino™

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#### **Probiotics and CMA**

- Probiotics: Live microorganisms that, when administered in adequate amounts, confer health benefits on the host
- Human milk is a rich source of probiotics (Lactobacillus, Bifidobacterium, and many more)
- Infant microbiome is critical in development of immune system
- Not all probiotics are the same or achieve the same results – they are strain- and dose-specific
- More research currently being done

Chau et al, *JPeds*, 2015 Tamburini et al, Nature Med, 2016

#### What about Lactose Intolerance?

- Avoidance of lactose with CMA is no longer warranted based on data (previous concern about reacting to residual proteins in lactose)
- However, patients with CMA may develop secondary lactose intolerance
  - Lactose-free extensively hydrolyzed formulas may be beneficial in some extreme cases

Koletzko et al, ESPGHAN GI Committee Guidelines, JPGN, 2012

#### What about Iron Deficiency in CMA?

- Risk of iron deficiency due to GI lesions, bloody stools
- ~1-3% incidence in CMA infants
- AAP and World Health Organization do not list CMA among the common causes of iron deficiency
- Iron should only be administered for repletion based on lab values for hemoglobin, red blood cell indices, or ferritin levels
- Over supplementation can be detrimental and may increase risk of infection or impair growth

Vanderhoof et al, J Pediatr, 2015

#### **Take Home Messages for Today**

- All mothers should be educated that breast milk is the best nutrition source for infants
- Most common symptoms of CMA: eczema, bloody stools
- Allergy to cow milk protein is the #1 food allergy of infants
- Maternal elimination diets for breastfed infants can offer relief but may take up to 2-4 weeks to see improvements
- Start with extensively hydrolyzed formula for most formula fed CMA infants
- Amino acid-based formula is first choice formula for infants with severe CMA or those who do not respond to extensively hydrolyzed
- Thorough understanding of specialized formulas, their indications, and nuance considerations related to CMA are critical for successful nutrition management of the breastfed infant with CMA





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#### Cows Milk Protein Allergy Awareness Month.

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