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
Nice to “Meet” You!
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

Symptoms of IgE vs Non-IgE Mediated Allergy

<table>
<thead>
<tr>
<th>IgE Mediated</th>
<th>Non-IgE Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Reaction: Few minutes to 2 hours</td>
<td>Delayed Reaction Often 2 to 7 days</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Constipation</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Hemosiderosis</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Malabsorption</td>
</tr>
<tr>
<td>Eczema</td>
<td>Villous atrophy</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>Enterocolitis</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Proctitis/Proctocolitis</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic Esophagitis (EoE)</td>
</tr>
</tbody>
</table>

In clinical practice, often not possible to distinguish between IgE and non-IgE mediated based on history and physical exam.

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

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

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

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
  • 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

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

- 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

Elizur et al. *Arch Dis Child* 2013
Algorithm for Management of CMA

Breast Fed Baby

Continue BF, mom on CM-free diet 2-4 wks

Symptoms improve/disappear

No

Yes

Consider compliance
Consult specialist
Not CMA?

Formula Fed Baby

No Anaphylaxis

2-4 wks Extensively Hydrolyzed formula

Symptoms improve/disappear

No

Yes

Not CMA

Consider cow milk challenge

CMA?

Yes

FF with Anaphylaxis or BF Baby

with severe CMA-related symptoms* or FTT

2-4 wks AA formula

Symptoms improve/disappear

No

Yes

Not CMA

Consult specialist

Consider cow milk challenge

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


*Severe CMA-related symptoms: severe eczema or enterocolitis with growth faltering, hypoproteinemia, or severe anemia
AAP Policy Statement: Breastfeeding and the Use of Human Milk

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

American Academy of Pediatrics Section on Breastfeeding

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Healthy People Targets 2010 and 2020(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2007</td>
</tr>
<tr>
<td>Any breastfeeding</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>75.0</td>
</tr>
<tr>
<td>6 mo</td>
<td>43.8</td>
</tr>
<tr>
<td>1 y</td>
<td>22.4</td>
</tr>
<tr>
<td>Exclusive breastfeeding</td>
<td></td>
</tr>
<tr>
<td>To 3 mo</td>
<td>33.5</td>
</tr>
<tr>
<td>To 6 mo</td>
<td>13.8</td>
</tr>
<tr>
<td>Worksite lactation support</td>
<td>25</td>
</tr>
<tr>
<td>Formula use in first 2 d</td>
<td>25.6</td>
</tr>
</tbody>
</table>

<sup>8</sup> 2007 data reported in 2011.<sup>10</sup>
Maternal Elimination Diet

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

<table>
<thead>
<tr>
<th>Type of Formula</th>
<th>Size Proteins (kD)</th>
<th>Range of Peptide Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cow milk</td>
<td>14-67</td>
<td></td>
</tr>
<tr>
<td>Partially hydrolyzed formula (pHF)</td>
<td>&lt;5</td>
<td>~18% of peptides are &gt;6 kD</td>
</tr>
<tr>
<td>Extensively hydrolyzed formula (eHF)</td>
<td>&lt;3</td>
<td>~1 to 5% are &gt;3.5 kD</td>
</tr>
<tr>
<td>Amino acid-based formula</td>
<td>Does not contain peptides Made of 100% free amino acids</td>
<td></td>
</tr>
</tbody>
</table>

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
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

# Categories of Infant Formulas based on Protein Type

<table>
<thead>
<tr>
<th>Intact Protein (Standard Infant Formula)</th>
<th>Abbott*</th>
<th>Perrigo Nutritionals*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mead Johnson*</td>
<td>Abbott*</td>
<td>Perrigo Nutritionals*</td>
</tr>
<tr>
<td>Enfamil®Premium™</td>
<td>Similac®Advance™</td>
<td>Store Brand Advantage &amp; Premium</td>
</tr>
<tr>
<td>Enfamil®Newborn™</td>
<td>Similac®for Supplementation™</td>
<td>Store Brand Added Rice Starch</td>
</tr>
<tr>
<td>Enfamil®ART™</td>
<td>Similac®Sensitive™</td>
<td>Store Brand Sensitivity</td>
</tr>
<tr>
<td>Enfamil®Prosobee™ (soy)</td>
<td>Similac®for Spit-Up™</td>
<td>Store Brand Soy</td>
</tr>
<tr>
<td>Enfamil®Enspire™</td>
<td>Similac®Isomil™ (soy)</td>
<td>Store Brand Soy</td>
</tr>
<tr>
<td></td>
<td>Similac®for Diarrhea™ (soy)</td>
<td>Store Brand Soy</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th></th>
<th>Mead Johnson*</th>
<th>Abbott*</th>
<th>Nestle*</th>
<th>Perrigo Nutritionals*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfamil®Gentlease™</td>
<td>Similac®Total Comfort™</td>
<td>Gerber®Good Start®Gentle</td>
<td>Store Brand Gentle &amp; Tender®</td>
<td></td>
</tr>
<tr>
<td>Enfamil®for Supplementation™</td>
<td>Gerber®Good Start®Soothe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfamil®Reguline™</td>
<td>Gerber®Good Start®Protect</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Gerber®Good Start®for Supplementation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gerber®Good Start®Soy</td>
</tr>
</tbody>
</table>

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## Categories of Infant Formulas based on Protein Type

<table>
<thead>
<tr>
<th>Extensively Hydrolyzed Protein</th>
<th>Mead Johnson*</th>
<th>Abbott*</th>
<th>Nutricia</th>
<th>Nestle*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregestimil™</td>
<td>Similac® Alimentum®</td>
<td>- - -</td>
<td>- - -</td>
<td>Gerber® Extensive HA®</td>
</tr>
<tr>
<td>Nutramigen™</td>
<td>- - -</td>
<td>- - -</td>
<td>- - -</td>
<td></td>
</tr>
<tr>
<td>Nutramigen with Enflora LGG™</td>
<td>- - -</td>
<td>- - -</td>
<td>- - -</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amino-Acid Based Protein (&quot;Elemental&quot;)</th>
<th>Mead Johnson*</th>
<th>Abbott*</th>
<th>Nutricia</th>
<th>Nestle*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PurAmino™</td>
<td>Elecare®</td>
<td>Neocate®</td>
<td>- - -</td>
<td>Alfamino™</td>
</tr>
</tbody>
</table>

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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

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

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.
Moovember
Cows Milk Protein Allergy Awareness Month.

2016 National ASTHMA & ALLERGY Awareness Month

United Kingdom

USA
Thank You!

Keli’s Farm
Chalk Mountain, TX
Registered Dietitians (RDs) interested in obtaining 1 CPEU credit please visit:
http://www.NutriciaLearningCenter.com

Information needed:
Event code = GWBFBMA8
Event date = 8.30.16

Question & Answer Session

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