Evidence Based Approach to Cow’s Milk Protein Intolerance

JONATHAN CORDOVA, DO

OCTOBER 1, 2016
Disclosures

- No financial disclosures

- I will not discuss off-label use and/or investigational use in my presentation
Objectives

1. Recognize common and not so common manifestations of cow’s milk protein intolerance (CMPI)

2. Evaluate evidence-based diagnostic approaches to CMPI

3. Identify appropriate management strategies for CMPI

4. Discuss some novel concepts regarding management
Case #1

K.M. is a 12-week old male

Hematochezia and reflux symptoms
  o Arching
  o Spit ups
  o Fussiness

Formula fed- (standard cow’s milk formula)
  o 2-3 oz every 2-3 hours

Otherwise healthy, growing and developing appropriately

Normal exam
Case #1

**Diagnosis:** Cow’s Milk Protein Intolerance

**Plan**
- Empiric trial of extensively hydrolyzed formula
- Reflux precautions
  - Small frequent feeds
  - Frequent burping
  - Elevate head of crib

**Follow up**
- Hematochezia resolved
- Arching and fussiness improved
Case #2

T.C. is a 4 month-old female

Presented to ED in hypovolemic shock 2º to vomiting and diarrhea

Hospital Course

- Sepsis work up negative, s/p 48-hours of broad spectrum antibiotics
- Heme positive stools
- Mild eczema
- Formula fed (standard cow’s milk formula)
  - 3-4 oz every 3 hours (vomiting for the past 2 weeks)
Case #2

Diagnosis: Cow’s Milk Protein Intolerance

Plan
◦ Empiric trial of an amino acid formula

Follow-up
◦ Re-presented to the ED within 48-hours in hypovolemic shock
◦ Parents report she no longer would take the amino acid formula so they gave her the previously tolerated formula
◦ Positive allergy testing for CMP-IgE

◦ Monitored for a few days on an extensively hydrolyzed formula
◦ Symptoms resolved
Cow’s Milk Protein Intolerance

Milk Allergy = Cow’s Milk Allergy = Cow’s Milk Hypersensitivity

CMPI is the leading cause of food allergy in infants and young children
- Casein: αs1-, αs2-, β- and κ-casein
- Whey: α-lactalbumin, β-lactoglobulin

GI manifestations are non-specific and overlap with other disease processes

At presentation can be very difficult to distinguish from physiologic infantile gastroesophageal reflux (GER)

Lifschitz, 2014
How Common?

Recent meta-analysis indicates about 3-7% of all infants are affected by food allergies, of which cow’s milk protein is the most common in 2-3%.

- ~ 50% develop tolerance by 1 year of age
- > 75% by 3 years of age
- > 90% by 6 years of age
- < 1% of children > 6 years old affected

Koletzko, 2012
Clinical Presentation

Within the first 6 months of life

Majority have > 1 symptom involving > 1 organ systems
- GI tract
- Skin

GI symptoms may be due to
- Inflammation
- Dysmotility
- Both

### TABLE 1. Some symptoms and signs related to CMPA

<table>
<thead>
<tr>
<th>Infants and toddlers</th>
<th>Older children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Frequent regurgitation</td>
<td>Food impaction</td>
</tr>
<tr>
<td>Colic, abdominal pain</td>
<td>Regurgitation</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Anorexia, refusal to feed</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Diarrhea ± intestinal protein or blood loss</td>
<td>Anorexia, early satiety</td>
</tr>
<tr>
<td>Constipation ± perianal rash</td>
<td></td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Diarrhea ± intestinal protein or blood loss</td>
</tr>
<tr>
<td>Occult blood loss</td>
<td>Constipation</td>
</tr>
<tr>
<td>Iron-deficiency anemia</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Occult blood loss</td>
</tr>
<tr>
<td></td>
<td>Iron-deficiency anemia</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>Runny nose</td>
<td>Runny nose</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Wheezing</td>
</tr>
<tr>
<td>Chronic coughing (all unrelated to infections)</td>
<td>Chronic coughing (all unrelated to infections)</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Urticaria (unrelated to infections, drug intake, or other causes)</td>
<td>Urticaria (unrelated to infections, drug intake, or other causes)</td>
</tr>
<tr>
<td>Atopic eczema</td>
<td>Atopic eczema</td>
</tr>
<tr>
<td>Angioedema (swelling of lips or eyelids)</td>
<td>Angioedema (swelling of lips or eyelids)</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Shock-like symptoms with severe metabolic acidosis, vomiting, and diarrhea (FPIES)</td>
<td></td>
</tr>
</tbody>
</table>

CMPA = cow’s-milk protein allergy; FPIES = food protein–induced enterocolitis syndrome.

Lifschitz, 2014; Koletzko, 2012
# IgE- vs. Non-IgE Mediated

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IgE-mediated</th>
<th>Non-IgE-mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of exposure to reaction</td>
<td>Minutes to 2 h</td>
<td>Several hours to days</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild to anaphylaxis</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Duration</td>
<td>May persist beyond 1 year of age</td>
<td>Usually resolved by 1 year</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Specific serum IgE, skin prick tests</td>
<td>Oral challenge</td>
</tr>
</tbody>
</table>

*Lifschitz, 2014*
Diagnostic Challenge

Challenge remains in making the correct diagnosis while assuring optimal growth and development.

Eliminating cow’s milk without appropriate substitutions can lead to malnutrition and/or specific nutrient deficiencies.

A diet that is not indicated or continued when the child may have already developed tolerance **may:**
- Impair growth
- Affect quality of life of both the child and family
- Incurring significant cost

Lifschitz, 2014
Approach in Clinical Practice

Thorough History and Physical Exam
- Can usually be enough to suspect CMPI
- ± laboratory tests

*Confirmation of CMPI should be based on eliminating CMP with subsequent resolution of symptoms that recur after reintroduction*
Role for Allergy Testing?

Useful in the right clinical setting (CMP-IgE, Skin Prick Test)
- History of anaphylaxis, multiple food allergies, family history of allergies

Children with GI manifestations are more likely to have a negative specific IgE compared with those with skin manifestations
- Negative test does not exclude CMPI

Atopy Patch Test
- No current agreement on standardization and preparation/application of antigen as well as subjectivity to interpretation
- *Cannot be recommended at present time*
Is there a Role for Endoscopy?

In most cases....unnecessary

- Unexplained significant and persistent GI symptoms, failure to thrive, ongoing iron deficiency anemia
  - Attempting to rule out other organic causes

- Endoscopic appearance and histology are neither specific nor sensitive for CMPI alone
  - Erythema, erosions, mucosal atrophy
  - Eosinophilic infiltration into the lamina propria, increased lymphocytes, plasma cells or neutrophils
How to Approach Breastfeeding vs. Formula Feeding

Encourage mothers to continue to breast feed while avoiding dairy (soy)
  ◦ Can take up to 72 hours to clear breast milk

Trial of a maternally restricted diet for at least 2 weeks
  ◦ No improvement → consider alternate diagnosis
  ◦ Improvement → consider a CMP oral challenge
    ◦ Symptoms return → continue a dairy (soy)- free diet and supplement mother with calcium (1000 mg/day) and offer dietary counseling

  ◦ No data to suggest further elimination of other foods (eggs, gluten, etc.)
How to Approach Breastfeeding vs. Formula Feeding

Avoid cow’s milk protein based formula

Proven efficacy with change to an extensively hydrolyzed formula (eHF)
  ◦ No improvement → consider trial of an amino acid formulas (AAF)

If infant is extremely sick, can stabilize with an AAF as first choice
What is the Role of Soy?

Reports estimate anywhere from 14-60% cross-reactivity to soy protein in those allergic to cow’s milk protein.

Soy protein based formula
- AAP recommends against use in the first 6 months of life due to uncertain absorption of minerals and trace elements.

- **However, consider if child > 6 months old and has known tolerance to soy if:**
  - eHF not accepted
  - Too expensive
  - Strong parental preference (vegan diet)

Ludman, 2013
Diagnostic Elimination of CMP

Appropriate when CMPI is suspected

Elimination should be for a *limited* period of time but should be long enough to judge whether symptoms resolve or not

- Immediate Reactions: 3-5 days
- Delayed Reactions: 1-2 weeks
- GI manifestations: 2-4 weeks
Diagnostic Elimination of CMP

If there is NO improvement in symptoms, then CMPI is less likely

Infants with significant GI symptoms with no improvement on extensively hydrolyzed formulas may benefit from further observation on amino acid formula before CMPI is excluded

- Could be reacting to oligopeptides in eHF

- If symptoms do not improve on AAF, then highly unlikely that symptoms are due to CMP
Oral Food Challenge

Significant improvement on a diagnostic elimination should be confirmed by standardized oral challenge under medical supervision

- Can be done safely at home in the right setting

- Preferably in the hospital/clinic setting if:
  - History of immediate allergic reaction
  - Unpredictable reaction (IgE-mediated who have never been exposed to CMP)
  - Severe atopic eczema (due to difficulty in accurately assessing a reaction)

Gold Standard:
- Double-Blind, Placebo-Controlled, Food Challenge
Open Food Challenge

**Open Challenge**

- Cow’s milk formula given in a stepwise fashion at 30-minute intervals
  - Delayed Reactions: 1, 3, 10, 30 and 100 mL
  - Immediate Reactions: 0.1, 0.3, 1, 3, 10, 30 and 100 mL

- No reaction → milk should be continued at home everyday with at least 200 mL/day for at least 2 weeks
  - No symptoms after 2 weeks → CMPI can be excluded

- If symptoms recur, DBPCFC is recommended to allow elimination of bias by caregiver or physician
  - *Not typically done in clinical practice*
What Should I Do in My Clinical Practice?

Clear, immediate/ severe reactions

→ CMP should be strictly avoided

- Recommend allergy testing
  - If positive → Oral challenge can be omitted and child should avoid CMP for 1 year before an oral challenge is performed in the hospital
  - If negative → Oral challenge should be done in the hospital

Neither clear nor severe reactions (GI symptoms and eczema)

- Recommend elimination diet followed by oral challenge
- Allergy tests in this setting are not cost-effective
  - Can recommend for + challenge to assess risk of immediate reaction at later challenges
  - +IgE at time of diagnosis predicts longer period of intolerance
What are My Treatment Options?

Strict avoidance of cow’s milk protein is the safest strategy
  ◦ Complementary foods should also be free of CMP

Therapeutic formula for at least 6 months or until 9-12 months of age

Formula choice based on:
  ◦ Residual allergic potential
  ◦ Cost
  ◦ Availability
  ◦ Infant acceptance
Therapeutic Formula

**Extensively Hydrolyzed Formula (eHF)**
- Oligopeptides with molecular weight of $< 3,000$ Daltons
- $> 90\%$ of infants tolerate eHF

**Amino Acid Formula (AAF)**
- Protein in the form of free amino acids and no peptides
- $< 10\%$ of children with CMPI will require AAF
- Can be first line in extremely sick infants (severe enteropathy, hypoproteinemia, faltering growth, high risk for anaphylaxis)

Koletzko, 2012; Lifschitz, 2015
Unsuitable Formulas

Partially hydrolyzed formula based on CMP or other mammalian protein are not recommended
- Oligopeptides > 5,000 Daltons

Avoid industrial juices labeled as “milk” are unsuitable to meet the infants nutritional needs due to low energy and protein composition
- Almond
- Coconut
- Cashew
- Hazelnut
Elimination diet in cow’s milk allergy: risk for impaired growth in young children

100 infants with atopic dermatitis and challenge proven CMPI

Evaluated for growth during therapeutic elimination diet

Conclusion:

- Mean length z-score and weight-for-length decreased compared to healthy matched controls
- Need close dietary counseling and close follow up
Amino acid based formula in cow’s milk allergy: long-term effects on body growth and protein metabolism. A randomized trial

65 infants age 5-12 months with CMPI
Compared AAF vs. eHF vs. Healthy Controls
Baseline (0), 3, 6, and 12 months later

Conclusion
- Long-term treatment with AAF is safe and allows adequate body growth in CMPI children
Tolerance to CMP

Rapid Resolution of Milk Protein Intolerance in Infancy

Evaluate the timing of acquisition of tolerance in CMPI

Prospective, cohort study enrolled infants <4 months with +heme stools who were transitioned to AAF
- 16 infants that developed –heme stools for 2 consecutive months were re-challenged
- Tolerance achieved at a mean of 6.7 ± 1.0 months old
- All achieved tolerance by 10 months

Conclusion
- May be reasonable to challenge earlier
Tolerance to CMP

Formula Selection for Management of Children with Cow’s Milk Allergy Influences the Rate of Acquisition of Tolerance: A Prospective Multicenter Study

N= 260
- Food challenge done after 12 months to assess tolerance

<p>| Table. Baseline main demographic and clinical characteristics of the study population |
|-----------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Group 1 EHCF</th>
<th>Group 2 EHCF + LGG</th>
<th>Group 3 RHF</th>
<th>Group 4 SF</th>
<th>Group 5 AAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>55</td>
<td>71</td>
<td>46</td>
<td>55</td>
<td>33</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>41 (74.5)</td>
<td>38 (53.5)</td>
<td>28 (60.9)</td>
<td>37 (67.3)</td>
<td>23 (69.7)</td>
</tr>
<tr>
<td>Age, m (95% CI)</td>
<td>5.03 (4.20-5.86)</td>
<td>5.73 (4.83-6.62)</td>
<td>6.65 (5.53-7.76)</td>
<td>6.45 (5.45-7.45)</td>
<td>5.93 (4.57-7.30)</td>
</tr>
<tr>
<td>Weight, kg (95% CI)</td>
<td>6.47 (6.00-6.95)</td>
<td>6.66 (6.14-7.18)</td>
<td>6.97 (6.36-7.58)</td>
<td>6.96 (6.41-7.51)</td>
<td>6.04 (5.31-6.78)</td>
</tr>
<tr>
<td>Breastfeeding ≥2 months, n (%)</td>
<td>41 (74.5)</td>
<td>54 (76.1)</td>
<td>38 (82.6)</td>
<td>38 (69.1)</td>
<td>24 (72.7)</td>
</tr>
<tr>
<td>IgE-mediated CMA, n (%)</td>
<td>24 (43.6)</td>
<td>27 (38)</td>
<td>23 (50)</td>
<td>23 (41.8)</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms, n (%)</td>
<td>35 (63.6)</td>
<td>51 (71.8)</td>
<td>30 (65.2)</td>
<td>31 (56.4)</td>
<td>25 (75.8)</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>23 (41.8)</td>
<td>27 (38)</td>
<td>17 (37)</td>
<td>18 (32.7)</td>
<td>10 (30.3)</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
<td>18 (32.7)</td>
<td>24 (33.8)</td>
<td>13 (28.3)</td>
<td>13 (23.6)</td>
<td>19 (57.6)</td>
</tr>
<tr>
<td>Cutaneous symptoms, n (%)</td>
<td>25 (45.5)</td>
<td>29 (40.8)</td>
<td>17 (37)</td>
<td>27 (49.1)</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>Atopic dermatitis, n (%)</td>
<td>21 (38.2)</td>
<td>26 (36.6)</td>
<td>15 (32.6)</td>
<td>21 (38.2)</td>
<td>9 (27.3)</td>
</tr>
<tr>
<td>Urticaria, n (%)</td>
<td>6 (10.9)</td>
<td>6 (8.5)</td>
<td>5 (10.9)</td>
<td>8 (14.5)</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td>Respiratory symptoms, n (%)</td>
<td>6 (10.9)</td>
<td>7 (9.9)</td>
<td>6 (13)</td>
<td>7 (12.7)</td>
<td>3 (9.1)</td>
</tr>
</tbody>
</table>
Results

- Rate of tolerance was significantly higher in groups EHCF (43.6%) and EHCF+LGG (78.9%)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHCF vs EHCF + LGG</td>
<td>4.822</td>
<td>2.210-10.521</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EHCF vs SF</td>
<td>0.400</td>
<td>0.176-0.907</td>
<td>.026</td>
</tr>
<tr>
<td>EHCF vs RHF</td>
<td>0.625</td>
<td>0.277-1.412</td>
<td>.257</td>
</tr>
<tr>
<td>EHCF vs AAF</td>
<td>0.287</td>
<td>0.102-0.806</td>
<td>.015</td>
</tr>
<tr>
<td>EHCF + LGG vs SF</td>
<td>0.083</td>
<td>0.036-0.193</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EHCF + LGG vs RHF</td>
<td>0.130</td>
<td>0.056-0.300</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EHCF + LGG vs AAF</td>
<td>0.060</td>
<td>0.021-0.170</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SF vs RHF</td>
<td>1.563</td>
<td>0.651-3.753</td>
<td>.316</td>
</tr>
<tr>
<td>SF vs AAF</td>
<td>0.718</td>
<td>0.243-2.117</td>
<td>.547</td>
</tr>
<tr>
<td>RHF vs AAF</td>
<td>0.459</td>
<td>0.156-1.350</td>
<td>.152</td>
</tr>
</tbody>
</table>
Conclusion

- EHCF accelerates tolerance acquisition in children with CMPI that is augmented by LGG

- Exposure to CMP residues helps achieve oral tolerance earlier
  - Small peptides are absent in AAF
Retrospective study of 348 infants in NICU receiving TPN

CMPI based on feeding intolerance that resolved with change of formula to eHF or AAF

Results

5% fulfilled diagnostic criteria for CMPI

- Predictor: multiple courses of TPN vs. single course (p<0.001)
- 11 of 14 diagnosed with late-onset NEC (22 days)
- 4 of 11 with subsequent “NEC-like” recurrence
  - Resolved with change of formula to eHF or AAF
Manuscript of Cow’s-Milk Protein Intolerance in Preterm Infants

*Jonathan Cordova, †Sudhir Sriram, ‡Tiffany Patton, §Hillary Jericho, †Ranjana Gokhale, †Dana Weinstein, and †Timothy Sentongo

Hypothesis
- Disruption of the neonatal commensal intestinal flora with antibiotic use may play a role in sensitization to cow’s milk protein

Conclusion
- Need for multiple courses of TPN due to persistent feeding intolerance after recovery from NEC or recurrence of “NEC-like” illness may be manifestations of CMPI in preterm infants
- NEC and/or antibiotic use in the preterm infant may be a “sensitizing event”

Cordova, 2016; Nagler, 2014
Take Home Points

Cow’s Milk Protein Intolerance is seen in upwards of 2-3% of infants

Diagnosis is *clinical* in a majority of cases

Elimination of Cow’s Milk Protein is the first step followed by a confirmatory oral challenge if symptoms resolve

Extensively hydrolyzed formula is first line therapeutic formula

- Consider AAF trial if severely ill or concern for ongoing reaction
- Addition of LGG can help gain oral tolerance faster
Resources

GIKids.org
  ◦ http://www.gikids.org/content/103/en/cows-milk-protein-intolerance

Support Groups
  ◦ http://cowsmilkproteinallergysupport.webs.com/
THANK YOU!
References


