

# Evidence Based Approach to Cow's Milk Protein Intolerance

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# Disclosures

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- No financial disclosures
- I will not discuss off-label use and/or investigational use in my presentation

# Objectives

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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

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K.M. is a 12-week old male

Hematochezia and reflux symptoms

- Arching
- Spit ups
- Fussiness

Formula fed- (standard cow's milk formula)

- 2-3 oz every 2-3 hours

Otherwise healthy, growing and developing appropriately

Normal exam

# Case #1

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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

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T.C. is a 4 month-old female

Presented to ED in hypovolemic shock 2<sup>o</sup> 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

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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

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CMPI is the leading cause of food allergy in infants and young children

- Casein:  $\alpha$ s1-,  $\alpha$ s2-,  $\beta$ - and  $\kappa$ -casein
- Whey:  $\alpha$ -lactalbumin,  $\beta$ -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)



# How Common?

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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



# 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

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

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

# IgE- vs. Non-IgE Mediated

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

# Diagnostic Challenge

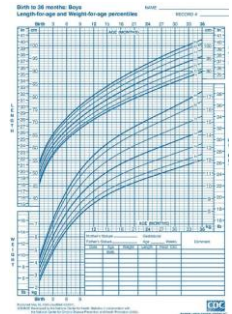
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Challenge remains in making the correct diagnosis while assuring optimal growth and development

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



# Approach in Clinical Practice

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## Thorough History and Physical Exam

- Can usually be enough to suspect CMPI
- $\pm$  laboratory tests

***Confirmation of CMPI should be based on eliminating CMP with subsequent resolution of symptoms that recur after reintroduction***



# Role for Allergy Testing?

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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

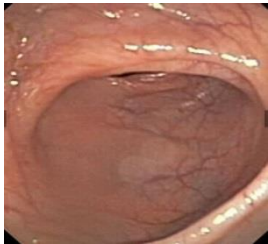
- No current agreement on standardization and preparation/ application of antigen as well as subjectivity to interpretation
- ***Cannot be recommended at present time***

# Is there a Role for Endoscopy?

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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

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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

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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?

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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)*



# Diagnostic Elimination of CMP

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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

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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

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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**



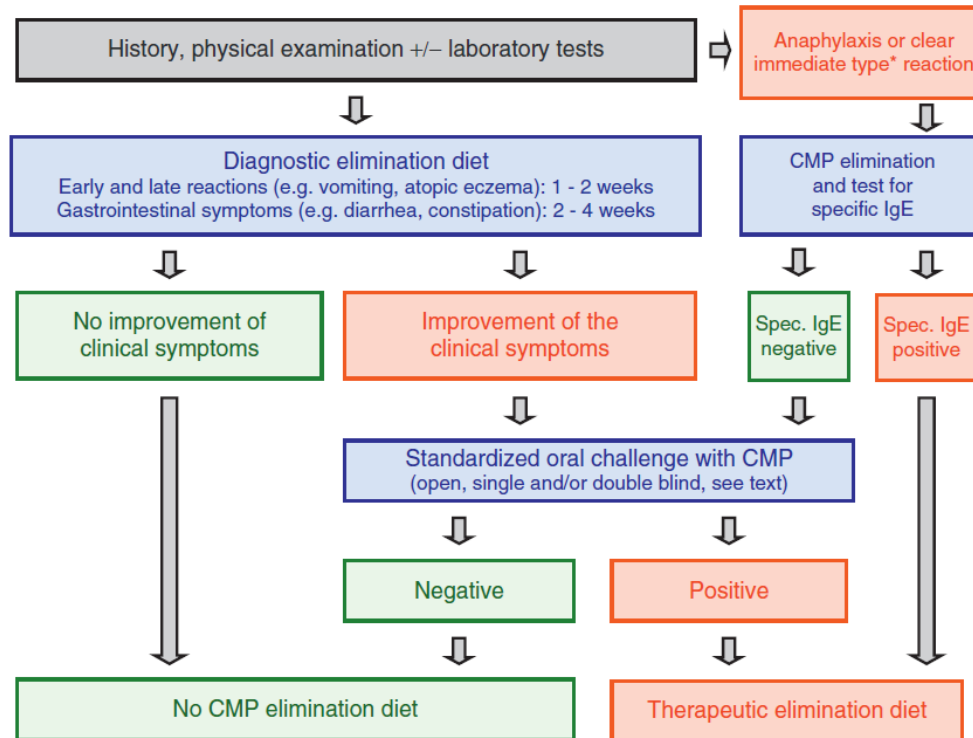
# Open Food Challenge

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## 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***

# ESPGHAN Algorithm for CMPI



**FIGURE 1.** Algorithm for infants and children with symptoms suggestive of cow's-milk protein allergy (CMPA). eHF: extensively hydrolyzed formula based on cow's-milk protein, AAF: amino acid-based formula. See text for definition of clear immediate-type reactions.

# What Should I Do in My Clinical Practice?

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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?

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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

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## **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)

# Unsuitable Formulas

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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

# Growth and Nutrition

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## **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

# Growth and Nutrition

## Amino acid based formula in cow's milk allergy: long-term effects on body growth and protein metabolism. A randomized trial

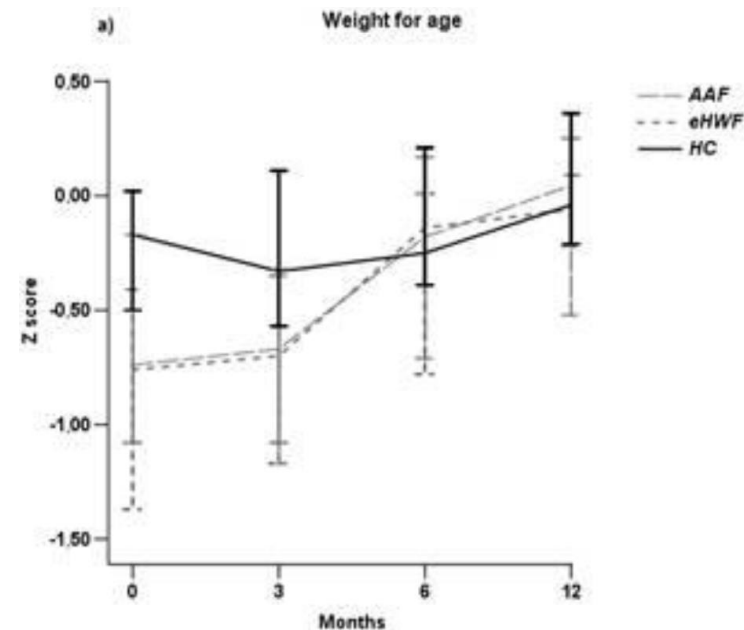
65 infants age 5-12 months with CMPI

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

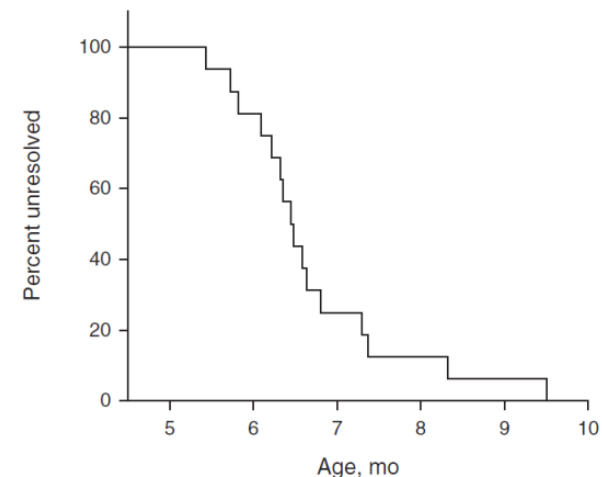
Evaluate the timing of acquisition of tolerance in CMPI

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  $6.7 \pm 1.0$  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

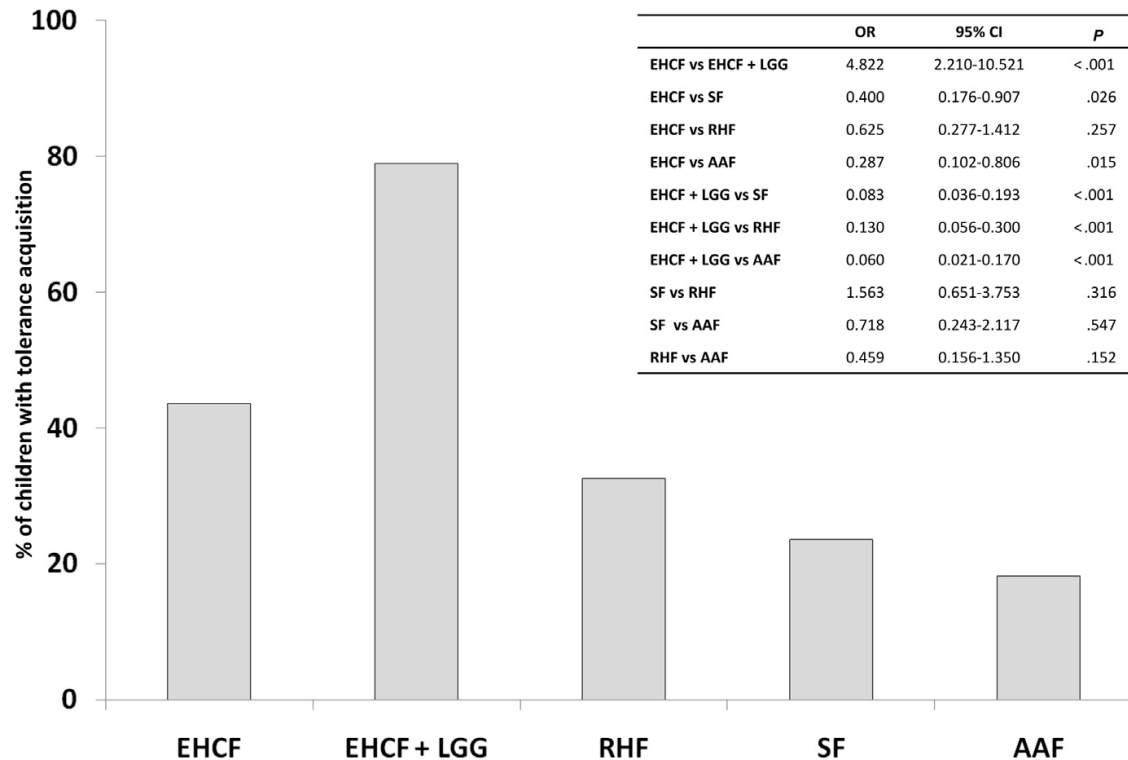
**Table.** Baseline main demographic and clinical characteristics of the study population

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

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

### Results

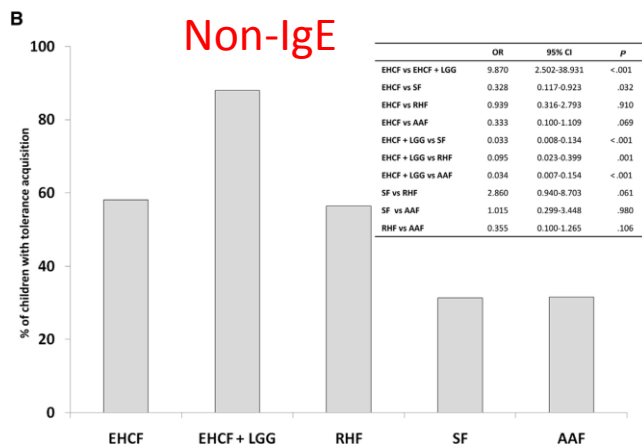
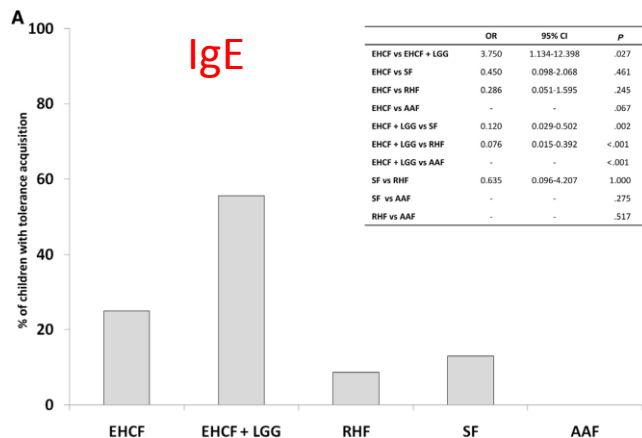
- Rate of tolerance was significantly higher in groups EHCF (43.6%) and EHCF+LGG (78.9%)



	OR	95% CI	P
EHCF vs EHCF + LGG	4.822	2.210-10.521	<.001
EHCF vs SF	0.400	0.176-0.907	.026
EHCF vs RHF	0.625	0.277-1.412	.257
EHCF vs AAF	0.287	0.102-0.806	.015
EHCF + LGG vs SF	0.083	0.036-0.193	<.001
EHCF + LGG vs RHF	0.130	0.056-0.300	<.001
EHCF + LGG vs AAF	0.060	0.021-0.170	<.001
SF vs RHF	1.563	0.651-3.753	.316
SF vs AAF	0.718	0.243-2.117	.547
RHF vs AAF	0.459	0.156-1.350	.152



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



### 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

# Manifestations of Cow's-Milk Protein Intolerance in Preterm Infants

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

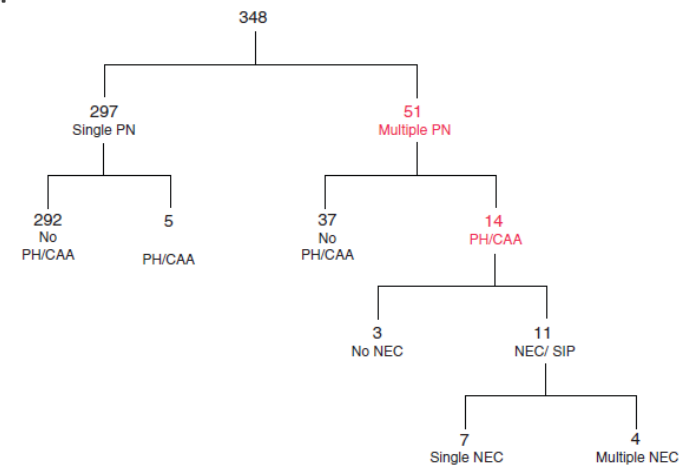
Retrospective study of 348 infants in NICU receiving TPN

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



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## 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”

# Take Home Points

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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

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## GIKids.org

- <http://www.gikids.org/content/103/en/cows-milk-protein-intolerance>

## Support Groups

- <http://cowsmilkproteinallergysupport.webs.com/>

THANK YOU!

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