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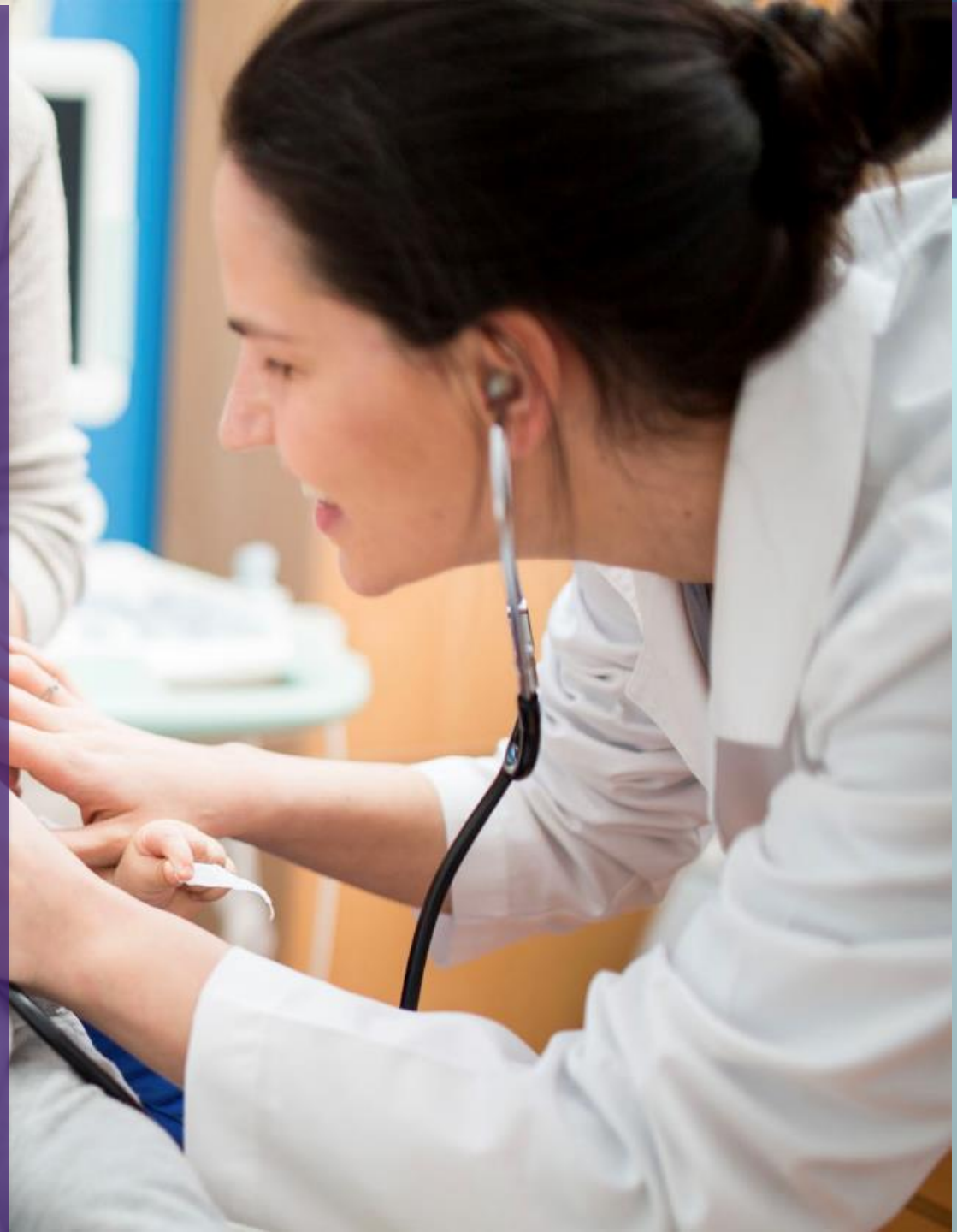
When to Use Amino Acid-Based Formula to Manage Cow Milk Allergy

Dr. Rosan Meyer & Dr. Carina Venter

April 30, 2019



Meet our speakers

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April 2019

Imperial College London

Disclosures

- Dr. Rosan Meyer:
  - Honorarium for today's webinar provided by Nutricia
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- Dr. Carina Venter:
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  - Consultant: Nestle

The opinions expressed by the speaker are independent of Nutricia North America

Learning Objectives

On completion, you should be able to:

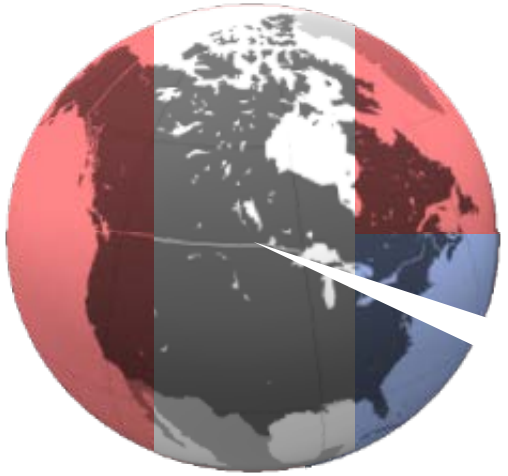
1. Discuss factors that can influence choice of hypoallergenic formula.

2. Explain what guidelines advise on choice of hypoallergenic formula.

3. Name at least four practical indicators to use amino acid-based formula first line to manage cow milk allergy.

Cow Milk Allergy (CMA) is not uncommon

- Global prevalence:
  - 1.9 - 4.9% of infants[1]
- North American prevalence:
  - ~2% of US infants[2,3]
  - Most common food allergen in infancy and early childhood[2]



1. Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. **2.** Gupta, et al. Pediatrics. 2011;128:e9-e17. **3.** Warren, et al. Annals of Allergy, Asthma & Immunology. 2018;121:S13.

Non-IgE-mediated allergies can involve CMA

- Eosinophilic esophagitis (EoE)
  - Cow milk = main EoE food trigger in US[1,2]
- Food protein-induced enterocolitis syndrome (FPIES)
  - Cow milk = main FPIES food trigger in US[3]
- Atopic dermatitis / Eczema
  - Increasing evidence of CMA in delayed-onset disorders, including chronic eczema[4]

1. Molina-Infante, et al. Expert Rev Gastroenterol Hepatol. 2017;11:115-23. **2.** Gonzalez-Cervera, et al. J Investig Allergol Clin Immunol. 2016;26:8-18. **3.** Nowak-Wegrzyn, et al. J Allergy Clin Immunol. 2017;139:1111-26.e4. **4.** du Toit, et al. Arch Dis Child Educ Pract Ed. 2010;95:134-44.

Support breastfeeding in infants with CMA

- All current guidelines support breast milk as first line choice for the dietary management of CMA[1,3]
- Aim to follow WHO guidelines: 6 months exclusive breastfeeding; WHO suggests breastfeeding until 2 years of age
  - If maternal elimination is advised, needs to be supervised[1-3]
  - Not always needed (e.g. FPIES[2])
  - Consider vitamin and minerals (i.e. calcium, vitamin D)[1]

1. Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. **2.** Nowak-Wegrzyn, et al. J Allergy Clin Immunol. 2017;139:1111-26.e4. **3.** Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9.

When breast milk is not available….

INFANTS <1 yr

- ✓ Substitute formula:
  - Hypoallergenic OR
  - Soy (if tolerant) > 6 months of age[1,2]

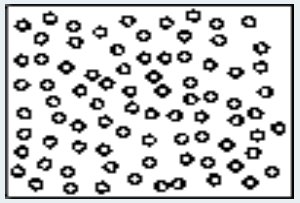
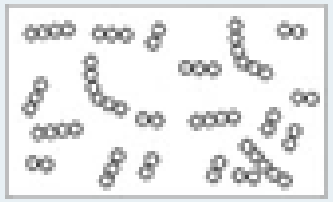
CHILDREN >1yr

- ✓ If ongoing allergy, continue with substitute formula until 2 years of age[1]
- ✓ After 2 years of age, assess nutritional status to inform use of either substitute milk or formula

1. Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. **2.** Nowak-Wegrzyn, et al. J Allergy Clin Immunol. 2017;139:1111-26.e4. **3.** Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9.

What factors can impact choice of hypoallergenic formula?

Defining the term “Hypoallergenic”

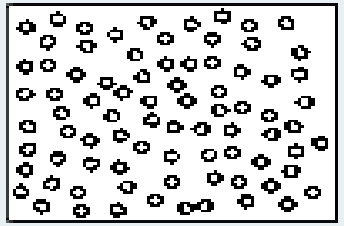
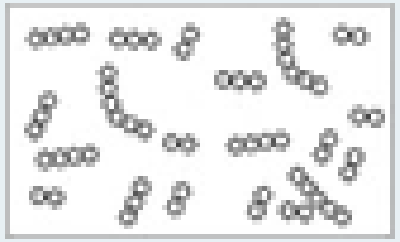
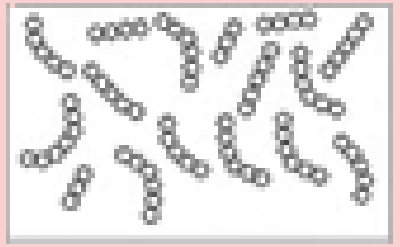
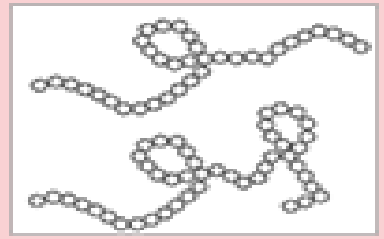
Formula type: (protein source)	**Amino acid- based (AAF)**	**Extensively hydrolyzed (eHF)**
Protein Source	100% free amino acids	Cow milk
Peptide size, kilodaltons	N/A (free AAs ~0.12[1]) 	Most <1.5[2] Up to 5% >3.5[3] 
Allergenicity	**Least**  **Most**	
Hypoallergenic?[2]	☑ **YES**	☑ **YES**

“Hypoallergenic”

- North America: ≥90% of patients with CMA tolerate (with 95% CI)[2]
- Europe: Formulas labeled “HA” are partially hydrolyzed and should not be used for CMA[4]
- North America & Europe: Extensively hydrolyzed/amino acid-based formulas are recommended for CMA[5]

1. https://www.seas.upenn.edu/~cis535/Fall2004/HW/GCB535HW6b.pdf. July 3, 2018. **2.** American Academy of Pediatrics Committee on Nutrition. Pediatrics. 2000;106:346-9. **3.** Lowe, et al. Expert Rev Clin Immunol. 2013;9:31-41. **4.** Bahna. Ann Allergy Asthma Immunol. 2008;101:453-9. **5.** Host, et al. Arch Dis Child. 1999;81:80–4.

Only 2 formula types are hypoallergenic

Formula type: (protein source)	**Amino acid- based (AAF)**	**Extensively hydrolyzed (eHF)**	**Partially hydrolyzed (pHF)**	**Regular** (Intact protein)
Protein source	100% free amino acids	Cow milk	Cow milk	Cow milk
Peptide size, kilodaltons	N/A (free AAs ~0.12[1]) 	Most <1.5[2] Up to 5% >3.5[3] 	Dairy: Most <5[3] and up to 18% >6[3] 	Dairy: 14-67[3] Soy: 20-225[4] 
Allergenicity	**Least** ←			→ **Most**
Hypoallergenic?[2]	☑ **YES**	☑ **YES**	☒ **NOT** HYPOALLERGENIC	☒ **NOT** HYPOALLERGENIC

1. https://www.seas.upenn.edu/~cis535/Fall2004/HW/GCB535HW6b.pdf. July 3, 2018. **2.** American Academy of Pediatrics Committee on Nutrition. Pediatrics. 2000;106:346-9. **3.** Lowe, et al. Expert Rev Clin Immunol. 2013;9:31-41. **4.** Hongsprabhas, et al. Joint ACS AGFD-ACS ICSCT Symposium; 2014.

There are a wide range of symptoms for IgE and non-IgE mediated CMA making formula selection difficult

IgE-Mediated[1]	Non-IgE-Mediated[1]

• Systemic IgE-mediated reactions (anaphylaxis)
• IgE-mediated gastrointestinal reactions
• Oral allergy syndrome
• IgE-mediated respiratory reactions:
  o Asthma and rhinitis secondary to ingestion of milk
  o Asthma and rhinitis secondary to inhalation of milk
• IgE-mediated cutaneous reactions:
  o Acute urticaria or angioedema
  o Contact urticaria
• Atopic dermatitis
	• Atopic dermatitis
	• Gastroesophageal reflux disease (GERD)
	• Eosinophilic esophagitis (EoE)
	• Cow's milk protein-induced enteropathy
	• Constipation
	• Severe irritability (colic)
	• Food protein-induced gastroenteritis
	• Food protein-induced enterocolitis syndrome (FPIES)
	• Food protein-induced proctocolitis
	• Non-IgE-mediated respiratory reactions
	• Heiner's Syndrome

1. Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125.

Quality of life may impact choice

- CMA symptoms + delayed diagnosis may affect family quality of life[1]
  - Food allergies impose significant burden on parents[2]
  - Delayed diagnosis: ~10 wks & 4 doctor visits in UK[2]
  - Parents want best / fast symptom resolution

Ideal: Identify children with CMA early to prevent delay in diagnosis and choose appropriate hypoallergenic formula if breast milk is not available[3]

1. Valentine, et al. Appetite. 2011;57:467-74. **2.** Lozinsky, et al. Children (Basel). 2015;2:317-29. **3.** Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99.

Factors may impact formula choice

Characteristic	Relevance
Nutrient profile	• To help patients meet individualized macro- and micronutrient needs
Synbiotic (probiotic + oligosaccharides**)**	• Helps balance gut microbiota dysbiosis seen in food allergy[1,2]
Probiotic - live beneficial bacteria	• Specific strains may help reduce future allergic manifestations / "march"[3,4] • Specific strains may help balance gut microbiota[1,2,5]
Nucleotides	• May improve early growth of formula-fed, SGA infants[6,7]
No soy oil	• Can help reduce unnecessary concern/confusion for families
No corn carbohydrate	• Can help reduce unnecessary concern/confusion for families
Kosher pareve	• For families who follow kosher dietary practices
Halal	• For families who follow halal dietary practices
Pediatric formulas	• Often indicated for food allergies beyond infancy[8,9]
• Flavors, pediatric	• Reduce flavor fatigue, support adherence
• Liquids, pediatric	• Safety, convenience, adherence, social normalcy, tube feeds

1. Candy, et al. Pediatr Res. 2018;83:677-86. **2.** Fox, et al. Clin Transl Allergy. 2019;9:5. **3.** Berni Canani, et al. J Allergy Clin Immunol. 2012;129:580-2, 2.e1-5. **4.** Berni Canani, et al. J Allergy Clin Immunol. 2017;139:1906-13.e4. **5.** Hol, et al. J Allergy Clin Immunol. 2008;121:1448-54. **6.** Singhal, et al. Pediatrics. 2010;126:e946-53. **7.** Cosgrove, et al. Arch Dis Child Fetal Neonatal Ed. 1996;74:F122-5. **8.** Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. **9.** Groetch, et al. J Allergy Clin Immunol Pract. 2017;5:312-24.e29.

Evidence may impact choice

- **Growth**
  - All infant formulas in US must have been demonstrated to support growth[1]
  - Limited data suggest height growth velocity may improve on AAF in children with food allergies who fail to fully improve on eHF[2-4]
- **Available research**

1. U.S. National Archives and Records Administration. 21CFR106.96. 2014. **2.** Isolauri, et al. J Pediatr. 1998;132:1004-9. **3.** Niggemann, et al. Pediatr Allergy Immunol. 2001;12:78-82. **4.** Hill, et al. Clin Exp Allergy. 2007;37:808-22.

To summarize influential factors:

1. Important to recognize CMA early and choose the appropriate hypoallergenic formula for fast symptom management

2. For the majority of children an eHF will be a suitable substitute formula, but in a subset of children with the more severe form of CMA an AAF will be required

3. Important to consider nutritional factors from substitute formulas to make the most appropriate choice for the individual patient

4. Hypoallergenic formula choice is best informed through well-designed clinical studies

What do guidelines advise on first choice of hypoallergenic formula to manage food allergies in infants?

High-level summary: inconsistency among guidelines can lead to confusion

	CMA	Breast-fed	Anaphyl-axis	Urticaria	Procto-colitis	MFA	AD	FG/ FTT	GER	EoE	FPIES
NIAID US[2]	NS	**Either**	NS	NS	NS	NS	NS	NS	NS	NS	**Either**
DRACMA[3,4]	**EHF***	NS	**AAF**	**EHF***	**EHF***	NS	**EHF***	NS	**EHF***	**AAF**	**AAF**
ESPGHAN European[5,6]	**EHF***	**Either**	**AAF**	**EHF**	**EHF***	**AAF**	NS	**EHF***	**EHF***	**AAF**	**EHF***
BSACI British[7]	**EHF***	**AAF**	**AAF**	**EHF**	**EHF***	**AAF**	**EHF***	**AAF**	**EHF***	**AAF**	**AAF**
***with exceptions for which AAF may be recommended first**			**GER**: NASPGHAN & ESPGHAN[8] **EoE**: AAAAI[9] **FPIES**: International Guidelines[10]						**EHF***	**AAF**	**Either**

1. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. **2.** Boyce, et al. Nutr Res. 2011;31:61-75. **3.** Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. **4.** Motala, et al. http://www.worldallergy.org/professional/allergic_diseases_center/cows_milk_allergy_in_children/ [June 28, 2017]. **5.** Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. **6.** Papadopoulou, et al. J Pediatr Gastroenterol Nutr. 2014;58:107-18. **7.** Luyt, et al. Clin Exp Allergy. 2014;44. **8.** Rosen, et al. J Pediatr Gastroenterol Nutr. 2018;66:516-54. **9.** Groetch, et al. J Allergy Clin Immunol Pract. 2017;5:312-24.e29. **10.** Nowak-Wegrzyn, et al. J Allergy Clin Immunol. 2017.

What are practical indicators – in guidelines and literature – for use of AAFs to manage CMA?

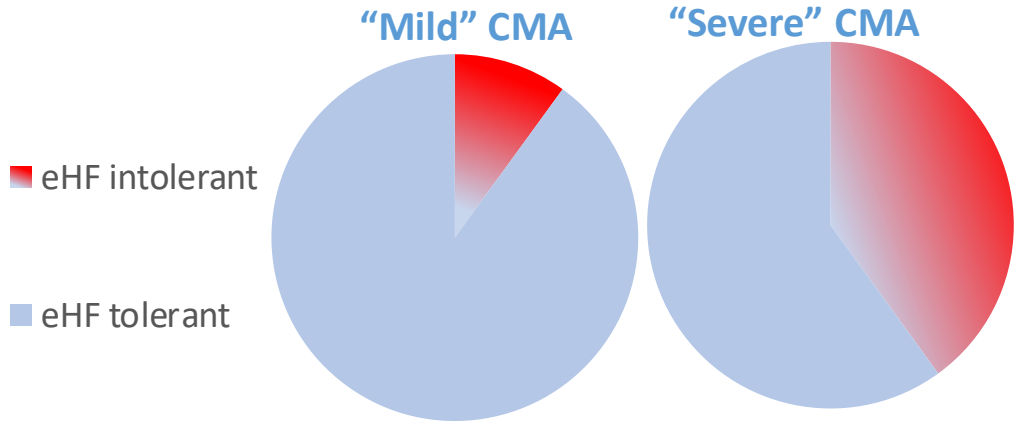
- ***Note***: Patients with food allergies may present with a combination of these indicators

Recommended reading:	Meyer R, Groetch M, Venter C. **When Should Infants with Cow's Milk Protein Allergy Use an Amino Acid Formula? A Practical Guide.** J Allergy Clin Immunol Pract. 2018;6:383-99.

When symptoms persist on an eHF[1-5]

Rationale & substantiation:

- Intolerance to eHF can occur:
  - Up to 10% of infants with mild CMA[4,6]
  - Up to 30% of infants with non-IgE-mediated CMA[7]
  - Trend toward higher eHF “failure” with non-IgE-mediated CMA[1]



- International guidelines recommend if symptoms don't completely resolve within ~2-4 weeks on an eHF, trial an AAF[4,8]

1. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. **2.** Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. **3.** Motala, et al. http://www.worldallergy.org/professional/allergic_diseases_center/cows_milk_allergy_in_children/ [June 28, 2017]. **4.** Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. **5.** Luyt, et al. Clin Exp Allergy. 2014;44. **6.** Hill, et al. Clin Exp Allergy. 2007;37:808-22. **7.** Latcham, et al. J Pediatr. 2003;143:39-47. **8.** Venter, et al. Clin Transl Allergy. 2013;3:23.

When symptoms persist on an eHF[1-5]

First choices for CMA and related conditions when formula is needed[1]

Presentation or condition	NIAID US guidelines[6]	DRACMA international guidelines[2,3]	ESPGHAN European guidelines[4]	BSACI British guideline[5]
Cow milk protein-induced enteropathy	**Not specified**	**EHF** or **AAF** AAF "*equally reasonable*" when AAF cost is low	**EHF** or **AAF** if faltering growth + "*severe enteropathy*"	**EHF** severe: **AAF**

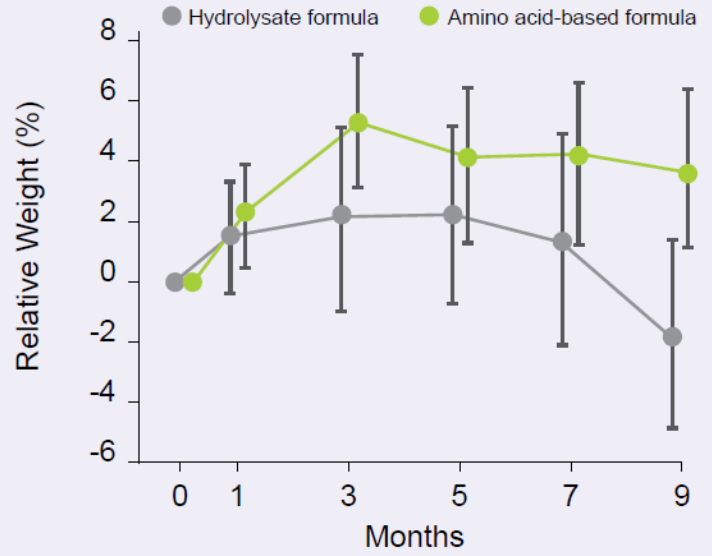
1. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. **2.** Luyt, et al. Clin Exp Allergy. 2014;44. **3.** Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. **4.** Motala, et al. http://www.worldallergy.org/professional/allergic_diseases_center/cows_milk_allergy_in_children/ [June 28, 2017]. **5.** Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. **6.** Boyce, et al. Nutr Res. 2011;31:61-75.

Growth faltering / Failure to thrive[1,2]

Rationale & substantiation:

- Isolauri et al[1]:
  - Similar energy intake, but length increase was higher (p=0.006) in the AAF group
- Niggeman et al[2]:
  - Similar energy intake, but significantly better height growth in children on the AAF

Length of infants with atopic dermatitis and cow milk allergy in those fed eHF versus AAF



Adapted from Isolauri et al 1995[1]

1. Isolauri, et al. J Pediatr. 1995;127:550-7. **2.** Niggeman, et al. Pediatr Allergy Immunol, 2001;12:78–82.

Growth faltering / Failure to thrive[1-5]

First choices for CMA and related conditions when formula is needed[1]

Presentation or condition	NIAID US guidelines[6]	DRACMA international guidelines[7,8]	ESPGHAN European guidelines[2]	BSACI British guideline[3]	Additional international guidelines[4,5]
Growth faltering / Failure to thrive	**Not specified**	**Not specified**	**EHF** **AAF** if accompanying *"severe enteropathy"*	**AAF**	**AAF**[5] *"particularly… with"* severe GI &/or skin presentations[4]

1. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. **2.** Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. **3.** Luyt, et al. Clin Exp Allergy. 2014;44. **4.** Venter, et al. Clin Transl Allergy. 2013;3:23. **5.** Ludman, et al. BMJ. 2013;347:f5424. **6.** Boyce, et al. Nutr Res. 2011;31:61-75. **7.** Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. **8.** Motala, et al. http://www.worldallergy.org/professional/allergic_diseases_center/cows_milk_allergy_in_children/ [June 28, 2017].

Studies investigating growth of infants and children with food allergies on AAF[1]

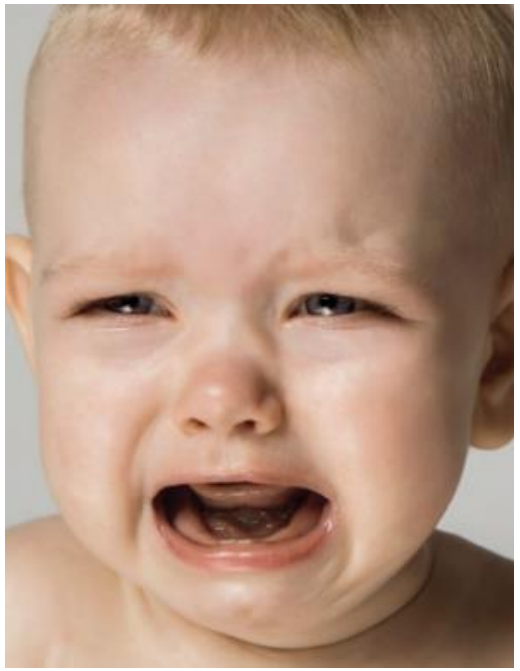
First author	Type of Study	Patient Characteristics	Outcome on Growth
Niggemann et al[2]	Randomized **eHF vs. AAF**	CMA + eczema as 1° symptom Infants	**Height-for-age was significantly higher (p = 0.04) in infants on AAF**
Hill et al[3]	Prospective All put on AAF	Suspected non-IgE CMA Infants + children	All infants with growth failure at baseline (4/18) achieved normal growth with AAF
Sicherer et al[4]	Non-randomized All put on AAF	IgE CMA Infants + children	No significant effect on growth at 4-mo visit (18/31), 8/31 had previously been on eHF
Borschel et al[5]	Non-randomized All on AAF	Chronic diarrhea + allergic and/or digestive disorder Infants + children	Significant increases in weight-for-age and height-for-age in all children. Greater impact on growth in younger subjects.
Isolauri et al[6]	Randomized **eHF vs. AAF**	CMA + eczema Infants	**Significant increases in weight- (p= 0.09) & length-for-age (p=0.006) in AAF group vs. eHF group**
McLeish et al[7]	Randomized **eHF vs. AAF**	Suspected non-IgE CMA + persistent diarrhea Infants + children	Both groups were undernourished at beginning of the study, but at 24 months there were no statistical differences in growth between the 2 groups.
Vanderhoof et al[8]	Prospective All on AAF	CMA + failed eHF + weight loss Children	Significant increase in weight (+0.433 z-score) at wk 12. Length increased over this period (NS).
Berni Canani et al[9]	Randomized **eHF vs. AAF** (+HC)	CMA Infants + children	**No differences in length, weight, head circumference between three groups after 12 months**

1. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. **2.** Niggemann, et al. Pediatr Allergy Immunol. 2001;12:78-82. **3.** Hill, et al. J Allergy Clin Immunol. 1995;96:386-94. **4.** Sicherer, et al. J Pediatr. 2001;138:688-93. **5.** Borschel, et al. BMC Pediatr. 2014;14:136. **6.** Isolauri, et al. J Pediatr. 1995;127:550-7. **7.** McLeish, et al. Arch Dis Child. 1995;73:211-5. **8.** Vanderhoof, et al. J Pediatr Gastroenterol Nutr. 2016;63:531-3. **9.** Berni Canani, et al. J Pediatr Gastroenterol Nutr. 2017;64:632-8.

Symptoms while breastfeeding[1-4]

Rationale and substantiation:

- Host et al. 1988:[1]
  - Only 1 prospective study
  - 0.5% presented while on breast milk only (out of 2.2%)
- Some infants with CMA can react to residual β-lactoglobulin transferring to breast milk[2]
  - Breast milk: 0.9-150ug/l (median 4.2ug/l)[3,4]
  - EHFs: 0.84 -14.5ug/l[3.4]
- However limited evidence available to substantiate this as first line formula if breast milk not available[5]



Breast milk is the preferred nutrition for infants with CMA[5] - Infant should continue taking breast milk while, if advised, mom avoids dairy under medical supervision[6-8]

1. Host, et al. Acta Paediatr Scand. 1988;77:663-70. **2.** Host, et al. Allergy. 2004; 59: 45–52. **3**. Makinen-Kiljunen, et al. Clin Exp Allergy. 1993;23:287–91. **4.** Rosendal, et al. J Dairy Sci. 2000;83:2200–10. **5.** Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. **6**. Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. **7.** Ludman, et al. BMJ. 2013;347:f5424. **8.** Venter, et al. Clin Transl Allergy. 2013;3:23.

Symptoms while breastfeeding[1-6]

First choices for CMA and related conditions when formula is needed[1]

Presentation or condition	NIAID US guidelines[2]	DRACMA international guidelines[7]	ESPGHAN European guidelines[3]	BSACI guidelines[4]
Breast-feeding with ongoing symptoms (already on maternal elimination diet) or requiring formula, e.g. to supplement	**EHF** or **AAF** *"Prior to initiating an oral food challenge… until the allergic* [sic] *food is identified"*	**Not specified**	**EHF** or **AAF** *"In breast-fed infants with severe symptoms …it is common practice in many countries to use AAF for diagnostic elimination…"*	**AAF** if symptoms when exclusively breastfed

- Limited data suggest an AAF can be used first line if formula is needed to supplement or replace breast milk because intolerance to eHF may occur[3,5,6,8]

1. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. **2.** Boyce, et al. Nutr Res. 2011;31:61-75. **3.** Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. **4.** Luyt, et al. Clin Exp Allergy. 2014;44. **5.** Ludman, et al. BMJ. 2013;347:f5424. **6.** Venter, et al. Clin Transl Allergy. 2013;3:23. **7.** Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. Hill, et al. Clin Exp Allergy. 2007;37:808-22. **8.** de Boissieu, et al. J Pediatr. 1997;131:744-7. 9. Host, et al. Allergy. 2004;59 Suppl 78:45-52.

Carina Venter, PhD, RD

Children's Hospital Colorado
Here, it's different.

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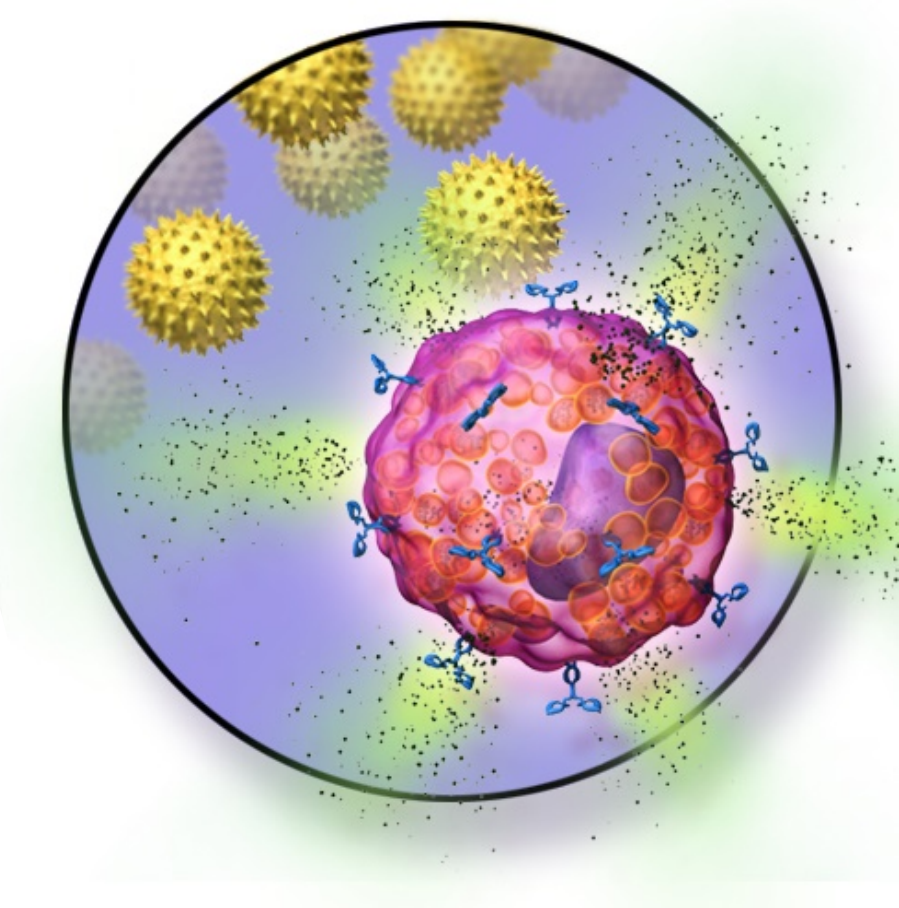
University of Colorado Denver School of Medicine | Children's Hospital Colorado

Anaphylaxis[1-5]

Rationale and substantiation:

- Frequency of potentially life-threatening anaphylaxis in patients with CMA varies from 0.8% to 9%[2]

- Case reports of anaphylactic reactions to eHFs exist[6,7]



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1. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. **2.** Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. **3.** Motala, et al. http://www.worldallergy.org/professional/allergic_diseases_center/cows_milk_allergy_in_children/ [June 28, 2017]. **4.** Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. **5.** Luyt, et al. Clin Exp Allergy. 2014;44. **6.** Sotto, et al. Arch Pediatr. 1999;6:1279-85. **7.** Businco, et al. Ann Allergy. 1989;62:333-5.

Anaphylaxis[1-5]

First choices for CMA and related conditions when formula is needed[1]

Presentation or condition	NIAID US guidelines[6]	DRACMA international guidelines[2,3]	ESPGHAN European guidelines[4]	BSACI British guideline[5]
Anaphylaxis	**Not specified**	**AAF**	**AAF**	**AAF**

- International consensus guidelines recommend AAF first for anaphylaxis to cow milk[2,3]
  - Hospital-based challenge to eHF can be considered if feasible[1]

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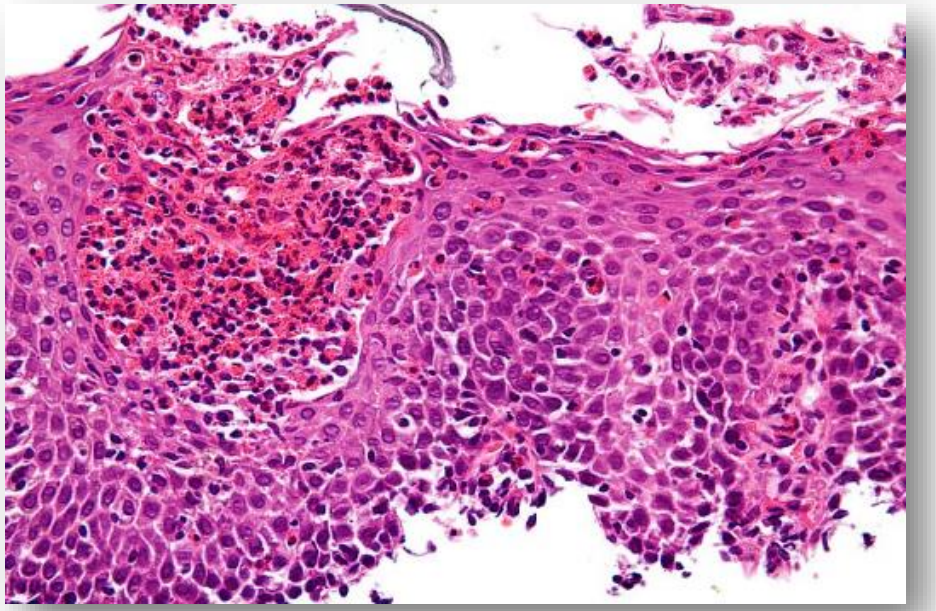
Eosinophilic esophagitis (EoE)[1-6]

Rationale and substantiation:

- Cow milk is the main food implicated in triggering EoE[7,8]
- 90-98% of EoE patients achieved histologic remission and symptom resolution using AAF[1,9]

EoE: "a chronic, local immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation."[10]



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Eosinophilic esophagitis (EoE)[1-6]

First choices for CMA and related conditions when formula is needed[1]

Presentation or condition	NIAID US guidelines[7]	DRACMA international guidelines[2,3]	ESPGHAN European guidelines[4]	BSACI British guideline[5]	AAAAI US guidelines[6]
Eosinophilic Esophagitis (EoE)	**Not specified** - evidence for AAF reviewed	**AAF**	**AAF**	**AAF**	**AAF**

- US & international guidelines recommend AAF first-line[2-6]

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Studies using AAF for management of EoE[1]

First author	Subjects on AAF, no. and ages	Remission / Response		Notes
Kelly et al[2]	10 with GERD Median 34.3 mo	80% total symptom resolution 20% partial resolution	8 / 10 2 / 10	Median counts of eosinophils/high-powered field (eos/hpf) decreased significantly from 41 (15-100) to 0.5 (0-22) (p = 0.005) after AAF trial
Liacouras et al[3]	164 Median 8.1 ± 4.3 y	**97.6%**	160 / 164	Of 160 who improved, eosinophil counts improved from 38 ± 10.3 eos/hpf pre-diet to 1.1 ± 0.5 eos/hpf post-diet
Kagalwalla et al[4]	25 Mean 6.4 y	**88%** (≤10 eos/hpf)	22 / 25	Pre-diet peak of 58.8 ± 31.9 eos/hpf decreased to post-diet peak of 3.7 ± 6.5 eos/hpf (p < 0.001)
Spergel et al[5]	151	**>95%** (<15 eos/hpf)	>143 / 151	Response based on maximal eosinophil count in most severely affected esophageal biopsy specimen
Rizo Pascual et al[6]	3	100%	3 / 3	Remission defined as <10 eos/hpf
Henderson et al[7]	49 Median 5.6 y	**96%** (<15 eos/hpf)	47 / 49	Median eosinophil counts decreased from 51 (28-90) eos/hpf pre-diet to 1 (0-3.5) eos/hpf post-diet
Markowitz et al[8]	51 Median 8.3 ± 3.1 y	**96%**	49 / 51	Median eosinophil counts decreased from 33.7 eos/hpf pre-diet to 1.0 eos/hpf post-diet (p < 0.01)

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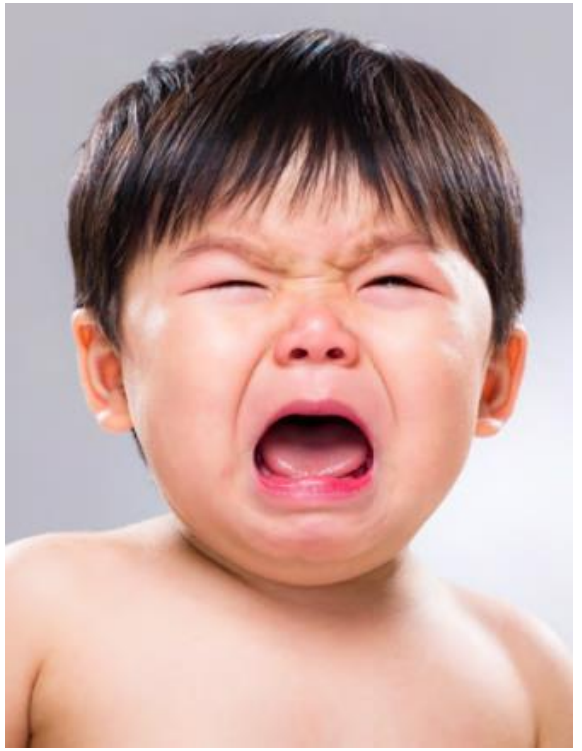
“Severe” or “complex” GI symptoms[1-7]

- No definition of what “severe” or “complex” is

Rationale and substantiation:

- Children with non-IgE-mediated allergy with GI symptoms seem more likely to react to eHFs[1,8] - though limited data

- In vitro studies suggest certain AAFs do not elicit pro-inflammatory immune responses[9,10]



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“Severe” or “complex” GI symptoms[1-7]

First choices for CMA and related conditions when formula is needed[1]

Presentation or condition	NIAID US guidelines[8]	DRACMA international guidelines[2,3]	ESPGHAN European guidelines[4]	BSACI British guideline[5]	NASPGHAN & ESPGHAN[6]
Gastroesophageal reflux	Not specified	EHF or AAF “equally reasonable” when AAF cost is low	EHF or AAF if “severe enteropathy” + faltering growth	EHF or AAF in “severe… enteropathies”	EHF or AAF if “severe symptoms”
Enteropathy					International guidelines[7,9]
Proctocolitis / Blood in stool					EHF or AAF if unresponsive to management

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Food protein-induced enterocolitis syndrome (FPIES)[1-6]

Rationale and substantiation:

- FPIES involves GI symptoms that can be severe and lead to hypotensive shock[3]
- Cow milk and soy are the most common FPIES triggers in the US with co-reactivity of up to ~40%[3]
- No clear data on best formula to use first for FPIES[1]
  - Some children with FPIES exclusively tolerate AAFs[3]

FPIES: "a non-IgE cell-mediated food allergy"
with low awareness[3]

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Food protein-induced enterocolitis syndrome (FPIES)[1-6]

First choices for CMA and related conditions when formula is needed[1]

Presentation or condition	NIAID US guidelines[2]	International FPIES guidelines[3]	ESPGHAN European guidelines[4]	BSACI British guideline[5]	DRACMA international guidelines[6]
Food protein-induced enterocolitis syndrome (FPIES)	**EHF** or **AAF**	**EHF** or **AAF**	**EHF** or **AAF** if *"severe enteropathy"* + faltering growth	**AAF**	**AAF**

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Multiple food allergies (MFA)[1-4]

Rationale and substantiation:

- Approximately 1 in 3 children with CMA may develop allergies to other foods[2,5] - MFA
- Children with MFA tend to have more severe food allergies[1]
- Risk of poor growth increases as more allergenic foods are avoided[6-8]
  - Limited data: height growth velocity may improve on AAF in children who fail to fully improve on eHF[5,9,10]

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Multiple food allergies (MFA)[1-4]

First choices for CMA and related conditions when formula is needed[1]

Presentation or condition	NIAID US guidelines[5]	DRACMA international guidelines[6]	ESPGHAN European guidelines[2]	BSACI British guideline[3]
Multiple food allergies	**Not specified**	**Not specified**	**AAF**	**AAF**

- Limited data: Infants with MFA may be at higher risk of reacting to eHF[2,4,7]

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Studies using AAF for management of multiple food allergies[1]

First author	Type of Study	Patient Characteristics	Number of foods eliminated
Hill et al[2]	Prospective	Children with suspected delayed CMPA that stabilized on AAF	All children were referred with delayed reactions but 7/18 had positive SPT/specific IgE to a combination of milk, egg, and nuts (although many had not been exposed). Adverse delayed reactions were reported: rice, wheat and chicken.
Isolauri et al[3]	Randomized, controlled	Eczema and CMPA	No intake of wheat, barley, rye, oats for 68% in the eHF group and 65% in the AAF group, as well as restrictions on various fruits and vegetables in 31% of children in the eHF group and 26% in the AAF group.
Sicherer et al[4]	Prospective, non-randomized study	Blinded oral food challenge to AAF	29/31 children in this study had > 1 food allergy. 14/31 had ≥3 food allergies all tolerated an AAF.
Sampson et al[5]	Prospective, DBPCFC to cow's milk, AAF and EHF.	IgE mediated CMPA	Multiple food allergies From this cohort 2 reacted to an eHF

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Severe atopic dermatitis (AD)[1-5]

Rationale and substantiation:

- Association exists between infant eczema and food allergy[5,6]
  - Up to 90% of patients with CMA develop skin symptoms[2]
- Some data imply that combined skin and gut symptoms may require more attention in choice of hypoallergenic formula[1]
- A subgroup of infants with AD may need AAF[5,7]

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Studies comparing eHF to AAF in atopic dermatitis[1]

First author	Type of study	Number of subjects	Patient characteristics	Outcomes on AD
Niggemann et al[2]	Randomized	31 eHF 42 AAF	Median age 5.7 mo Confirmed CMA, mixed IgE and non-IgE	No statistical difference in SCORAD (SCORing Atopic Dermatitis) between groups either 3 or 6 mo after starting formula
Isolauri et al[3]	Randomized	22 eHF 23 AAF	Median age 6 mo Confirmed CMA, mixed IgE and non-IgE	No statistical difference in SCORAD at baseline or in improvements between groups
Kaczmarksi et al[4]	Prospective	67 eHF (45 eHF) (22 eHF → AAF)	Mean age 11.34 ± 8.52 mo Confirmed CMA, non-specified	22 of 67 patients had intolerance reactions to eHF 21/22 improved on AAF No significant differences in SCORAD among any groups
Leung et al[5]	Randomized crossover	15	Median age 1.4 y 5/15 SPT + to CM 10/15 SPT + to egg and/or soy	Consumed CM or soy formula during active phase, AAF during placebo phase. Median changes for SCORAD and symptoms not significantly different between phases.

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Severe atopic dermatitis (AD)[1-5]

First choices for CMA and related conditions when formula is needed[1]

Presentation or condition	NIAID US guidelines[6]	DRACMA guidelines[2,3]	ESPGHAN European guidelines[7]	BSACI[4]
Atopic eczema/ atopic dermatitis (AD)	**Not specified**	**EHF** or **AAF** *"equally reasonable"* when AAF cost is low	**Not specified** **AAF:** *"In breast-fed infants with severe symptoms…it is common practice…to use AAF…in these extremely sick exclusively breast-fed infants."* **OR** *"If multiple food allergies are suspected in highly atopic children…AAF may be considered to allow symptom improvement…"*	**EHF** or **AAF** in *"severe"* presentations[4,5] *"particularly in association with faltering growth"*[5]

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How accessible are amino acid-based formulas?

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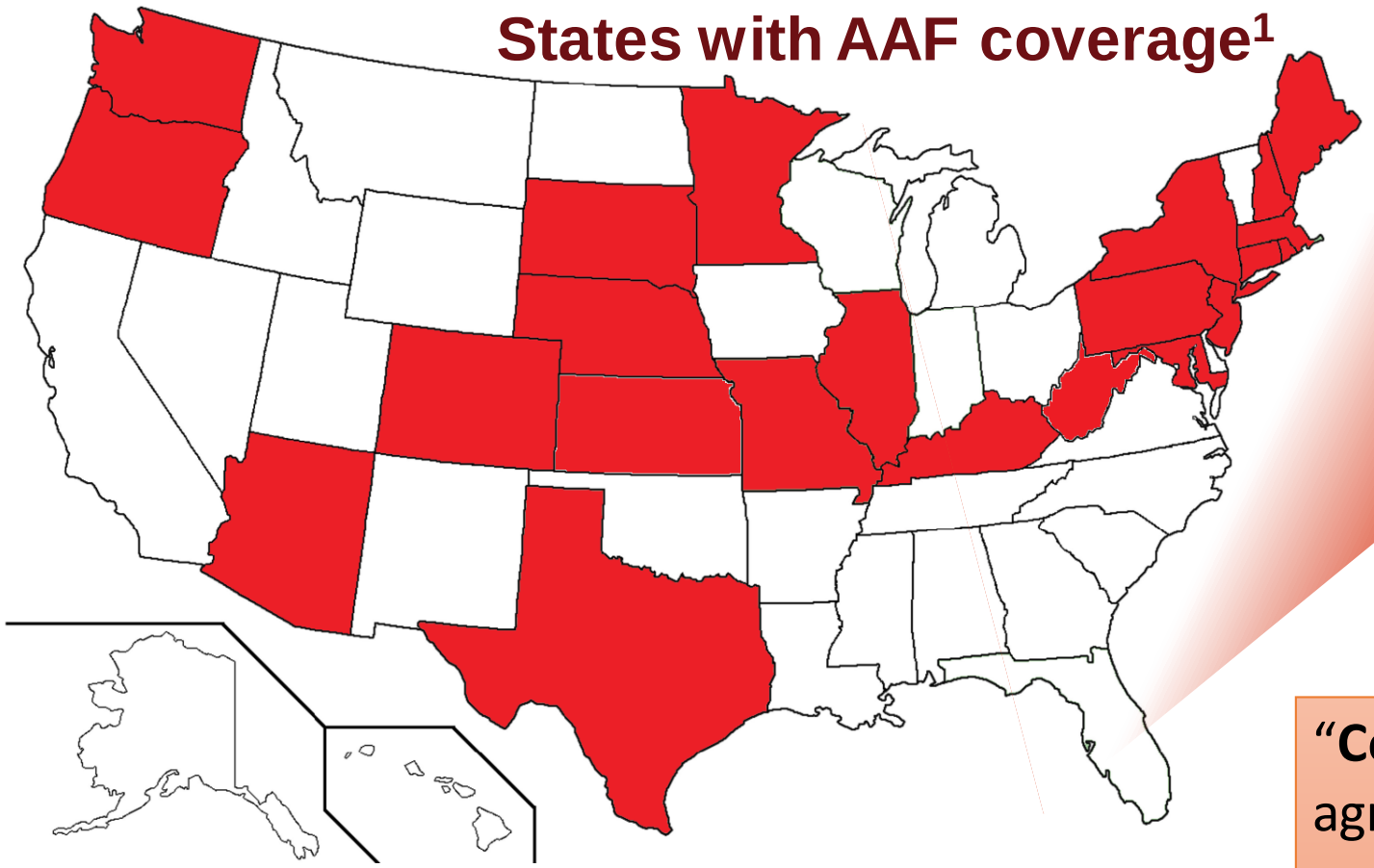
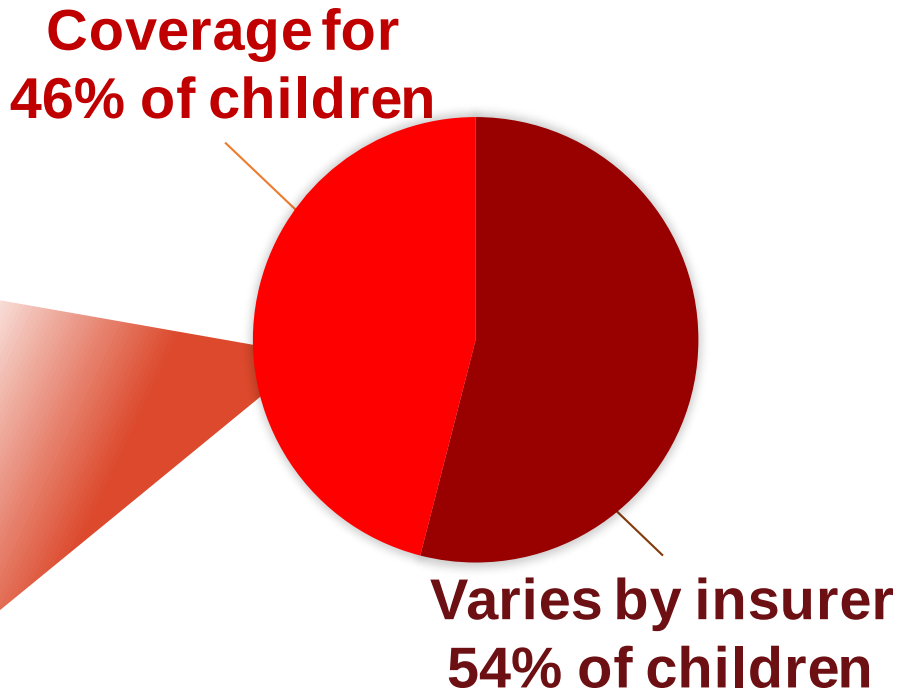
Amino acid-based formulas are medical foods and should be used under medical supervision.

AAF may be as accessible as eHF

1. AAF coverage in 22 states





"**Coverage**" = Mandate or insurance agreement to cover AAFs for certain conditions and ages. Self-funded insurance plans are exempt.

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1. http://childrensmagicus.org/coverage-states/

AAF may be as accessible as eHF

2. **AAF pharmacy & store access increasing**

3. **AAF are WIC* eligible**

4. **Coverage & cost assistance** programs offered by some AAF manufacturers

5. **Online costs vary** - costs of eHFs[1] and AAFs[2] are sometimes comparable

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1. Manufacturer online prices, powder & 8 oz liquid, July 2018. **2.** Durban, et al. Pract Gastroenterol. 2018;42:40-51.
*WIC is a registered service mark of the U.S. Department of Agriculture for USDA's Special Supplemental Nutrition Program for Women, Infants and Children.

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Thank you!

Nutricia North America would like to thank **Marion Groetch, MS, RD, CDN**, Senior Dietitian at Jaffe Food Allergy Institute, Mount Sinai School of Medicine, New York, NY for her expertise in the development of this presentation.

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