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~~Got~~ Not Milk? What to Feed Infants and Children When Cow Milk is Not an Option

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Food Allergy University

December 10, 2021

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Disclosures

- Honorarium provided by Nutricia

The opinions reflected in this presentation are those of the speaker and independent of Nutricia North America

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Learning objectives

- Participants in this activity will learn to:
  - Identify appropriate formula selection for infants with food allergies and related conditions when breast milk is not possible
  - List appropriate milk substitutes for children one year of age and older with food allergies and related conditions
  - Demonstrate practical tips for formula adherence

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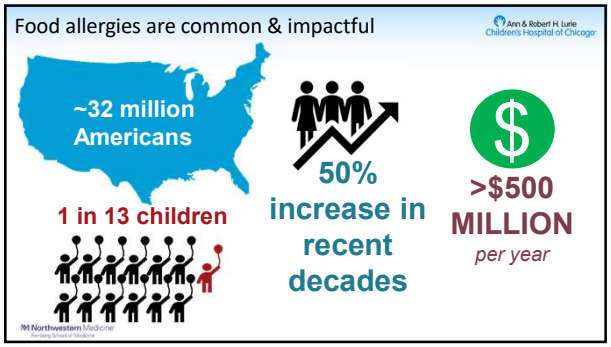

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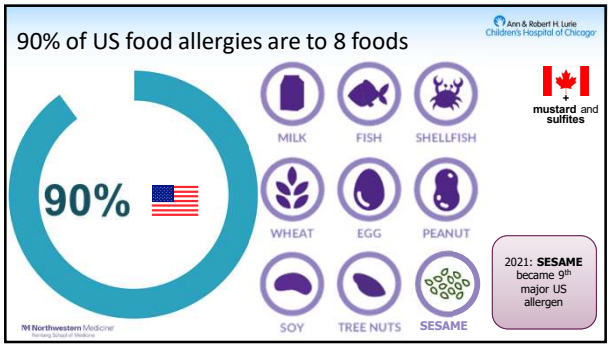

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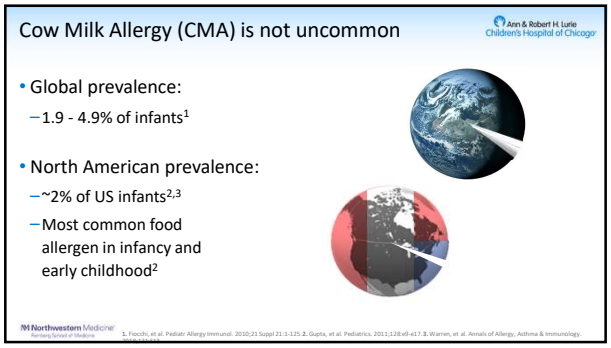

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Non-IgE-mediated allergies can involve CMA

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- 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]

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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. 2016;101:44-46.

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

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

• Systemic IgE-mediated reactions (anaphylaxis)
• IgE-mediated gastrointestinal reactions
• Oral allergy syndrome
• IgE-mediated respiratory reactions:
  ○ Asthma and rhinitis secondary to ingestion of milk
  ○ Asthma and rhinitis secondary to inhalation of milk
• IgE-mediated cutaneous reactions:
  ○ Acute urticaria or angioedema
  ○ Contact urticaria
• Atopic dermatitis
	• Atopic dermatitis
	• Gastroesophageal reflux (GER)
	• 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.

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Breast milk is the gold standard

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- 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 (e.g. calcium, vitamin D)[1]

Recommendations	Breast milk
DRACMA[1]	Encouraged, mother following strict CMP free diet + Ca supplementation
ESPGHAN[2]	Encouraged, mother following strict CMP free diet + Ca supplementation
AAP[3]	Encouraged, mother following strict CMP free diet + Ca supplementation

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1. Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. 2. Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. 3. American Academy of Pediatrics Committee on Nutrition. Pediatrics. 2000;106:346-9.

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When breast milk is not available...

- Initiate substitute formula:
  - Hypoallergenic OR soy (if tolerant) > 6 months of age[1,2]
  - No mammalian animal milks
  - No partially hydrolyzed formulas

Recommendations	Partially Hydrolyzed formulas
DRACMA[1]	Not recommended
NIAID US[3]	Not recommended
ESPGHAN[4]	Not recommended

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. Boyce, et al. J Allergy Clin Immunol.

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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.

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What about European formulas?

- Not regulated by FDA
  - Risk for using formulas not appropriately labeled
  - Stages of formula 0-6 months, 6-12 months
  - Mixing instructions differ/scoop sizes, labels not in English
  - Hypoallergenic may include partially or extensively hydrolyzed
  - Purchased outside distribution chain through third party vendors

DiMaggio, et al. J Pediatr Gastroenterol Nutr. 2019 Oct;69(4):480-486. doi: 10.1097/MPG.0000000000002395. PMID: 31107795.

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Infant formula act

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- Passed into law in 1980 section 201(z) and in Title 21 section 106.3 of the Code of Federal Regulations (CFR)
- Nutrient specifications include minimum amounts for 29 nutrients and maximum amounts for 9 of those nutrients
- Good manufacturing practices
- Recall procedures
- Formulas manufactured in US or abroad must meet standards to be sold in US

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Eeny meeny miny moe, which formula should we choose....

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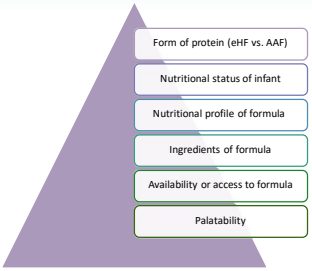

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AAF may be needed to manage CMA[1]

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- Trial an eHF first line for most patients
- Choose an AAF first line to manage CMA for these indicators:

2,3,5-7 **Severe gastrointestinal allergies**	2-5 **Anaphylaxis**
2-5 **Poor growth** especially with multiple food eliminations and/or GI tract/skin symptoms	2-5 **Symptoms not resolved on eHF**

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

RECOMMENDED READING: **When Should Infants with Cow's Milk Protein Allergy Use an Amino Acid Formula? A Practical Guide[1]**

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Symptoms not resolved on eHF[1-5]

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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**

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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.

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Poor growth[1-3] especially with multiple food eliminations and/or GI tract/skin symptoms

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First choices for CMA and related conditions when formula is needed[3]

Presentation or condition	NIAID US guidelines[6]	DRACMA international guidelines[7,8]	ESPGHAN European guidelines[4]	BSACI British guideline[5]	Additional international guidelines[1,2]
Poor growth	**Not specified**	**Not specified**	**eHF** **AAF** if accompanying "severe enteropathy"	**AAF**	**AAF**[5] "particularly… with" severe GI &/or skin presentations[4]

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1. Venter, et al. Clin Transl Allergy. 2013;3:23. 2. Ludman, et al. BMJ. 2013;347:f5424. 3. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. 4. Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. 5. Luyt, et al. Clin Exp Allergy. 2014;44. 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].

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Severe gastrointestinal (GI) allergies: Proctocolitis[1-5]

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First choices for CMA and related conditions when formula is needed[4]

Presentation or condition	NIAID US guidelines[6]	DRACMA international guidelines[5,7]	ESPGHAN European guidelines[1]	BSACI British guideline[8]	NASPGHAN & ESPGHAN[9]
Proctocolitis / Blood in stool	**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 unresponsive to management

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1. Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. 2. Venter, et al. Clin Transl Allergy. 2013;3:23. 3. Ludman, et al. BMJ. 2013;347:f5424. 4. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. 5. Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. 6. Boyce, et al. Nutr Res. 2011;31:61-75. 7. Motala, et al. http://www.worldallergy.org/professional/allergic_diseases_center/cows_milk_allergy_in_children/ [June 28, 2017]. 8. Luyt, et al. Clin Exp Allergy. 2014;44. 9. Rosen, et al. J Pediatr Gastroenterol Nutr. 2018;66:516-54.

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Severe GI allergies: Eosinophilic esophagitis[1-6]

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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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1. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99. 2. Fiocchi, et al. Pediatr Allergy Immunol. 2010;21Suppl 21:1-125. 3. Motala, et al. http://www.worldallergy.org/professional/allergic_diseases_center/cows_milk_allergy_in_children/ [June 28, 2017]. 4. Papadopoulou, et al. J Pediatr Gastroenterol Nutr. 2014;58:107-18. 5. Luyt, et al. Clin Exp Allergy. 2014;44:4. 6. Groetch, et al. J Allergy Clin Immunol Pract. 2017;5:312-24.e19. 7. Boyce, et al. Nutr Res. 2011;31:61-75.

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Severe GI Allergies: Food protein-induced enterocolitis syndrome[1-6]

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

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There are several factors to consider when weaning off breast milk or formula

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- Nutritional status of infant/child
- Volume of breast milk/formula
- Amount and variety of solid food eaten
- Availability or access to substitute formula

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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.

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Cow milk protein (CMP) in children one year of age and older

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CMP in our children...what is recommended?

USDA recommendations

- Only fortified soy beverage is considered dairy equivalent
- Small amounts plant-based milk (PBM) alternative in diet > 2 years of age
  - Recommended unsweetened
  - Not equivalent (less protein, not always fortified with calcium and vitamin D)

Dietary Guidelines for Americans 2020 - 2025

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The 2020 NASPGHAN Position Paper offers specific recommendations on the use of plant-based beverages[1]

Young child	• Hypoallergenic formulas, • Soy formula or • Soy, pea, possibly oat "milk", well-balanced diet
Older child	• Carefully planned diet, from plant/animal sources, may include nutritional supplementation
Consult RD	• Assess "milk" intake

– Consistent with guidance from ESPGHAN & DRACMA[2,3]

If child less than 2 years old, breast milk or substitute formula is recommended - DRACMA

When RD is involved, **NO** adverse impact on growth

Meyer et al. Clin Transl Allergy. 2014 Oct 3;4(1):31.
Meyer et al. Clin Transl Allergy. 2016 Jul 14;6:25.
Berry et al. Pediatr Allergy Immunol. 2015 Mar;26(2):133-8.

1. Meritt RJ, Fleet SE, Fill A, et al. NASPGHAN Position Paper: Plant-Based Milks. J Pediatr Gastroenterol Nutr. 2020. 2. Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9. 3. Fiocchi, et al. J Allergy Clin Immunol. 2010.

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DRACMA: CMP > 2 years old

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- Nutritionally adequate elimination diet can be provided by solid foods and liquids free of CMP unless the child has multiple food allergies (MFA).
- Avoid mammalian milks
- MFA or eosinophilic disorders: AAF may be considered to allow symptom improvement before an oral challenge with CMP is performed.
- Counseling by an RD experienced in pediatric nutrition is highly recommended to avoid hidden allergens.

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

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Living the milk free life...

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- Extremely popular:
  - Increased awareness of CMP intolerance
  - Desire for vegan/plant-based dietary habits
- Vary widely in composition macronutrients & micronutrients
- Almost half (48%) of Americans have purchased both dairy- and plant-based milks over the past six months, according to an IPSOS survey of 2,006 adults commissioned by Dairy Management Inc.

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https://www.foodnavigator-usa.com/Article/2019/01/24/48-of-consumers-buy-dairy-and-plant-based-milks-reveals-IPSOS-survey Accessed November 23, 2021

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Plant-based beverages carry risks

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Per 1 cup[1]	Whole milk	Almond	Coconut	Oat	Pea	Soy	AAF
Calories	150	30-100	45-90	130	115	90	240
Protein (g)	8	1	0-1	4	8	6	7-8
Adjusted protein[2] (g)	8	0.16	-	2.9	4.8	4.8	7-8
Fat (g)	8	3	5	2.5	5	3.5	~11
CHO (g)	13	9-22	8-13	24	11	15	~25
Sugar (g)	12	7-20	0-9	19	10	9	2-12
Calcium (mg)	300	300-450	100-450	450	450	400	~280
Vitamin D (IU)	120	110	125	120	150	120	>190
Other risks	-	Common allergen	-	-	Soy content common	Common allergen	

Variations in products exist. Above represents average ranges.

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Based on: 1.Merritt RJ, Fleet SE, Fifi A, et al. NASPGHAN Position Paper: Plant-Based Milks [published online ahead of print, 2020 May 26]. *J Pediatr Gastroenterol Nutr*. 2. Mariamenatti CPF, Manzilla WS, Gioseffer A-K, Cerioli Foods World 2018;63:207-15.

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Protein content...quality or quantity?

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- Amino acid composition: adequate levels
  - Indispensable, dispensable and conditionally indispensable amino acids
- Protein digestibility:
  - Protein Digestibility Corrected Amino Acid Score (PDCAAS) - USDA
  - Digestible Indispensable Amino Acid Score (DIAAS) - FAO: based on ileal amino acid digestibility
- Amino acid bioavailability varies and is often not known.

DIAAS scores & PDCAA Scores for Foods

Food	DIAAS	PDCAAS
Milk protein concentrate	1.18	1.0
Soy protein isolate	0.94	1.0
Pea protein concentrate	0.822	0.979
Rice protein concentrate	0.371	0.419
Cooked rolled oats	0.542	0.670

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Hertzler S. Nutrients 2020, 12, 3704; doi:10.3390/nu12123704. Rutherfurd SM, et al. J Nutr. 2015 Feb;145(2):372-9. doi: 10.3945/jn.114.195438. Epub 2014 Nov 26. PMID: 25644383

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Tips for improving tolerance with AAF

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- ✓Serve chilled in covered sports or straw cup or bottle
- ✓Trial all flavors of AAF
- ✓Flavor AAF with allowed ingredients
- ✓Structured meals & locations for formula/foods
- ✓Make a smoothie with AAF with allowed ingredients

Flavoring AAFs

- ✓ Crystal Light™ powder: 1 tsp/8 fl oz formula
- ✓ Coffee flavoring syrups
- ✓ Vanilla/other flavoring extracts - juice (100%), fruit nectar
- ✓ 100 % cocoa powder (blend it in)
- ✓ Kool-Aid® powder + sugar to taste if needed, (particularly the citrus flavors helps mask the amino acid taste)
- ✓ Sweet Leaf® Sweet Drops®

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AAF smoothie recipes

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Smoothie recipe template

1) 4-8 fl oz (1/2 -1 cup) plant-based milk beverage
2) Add in allowed plant-based yogurt (~ 4-6 oz), (140-250 kcals, 1-6 gm protein)
3) Add ¼ - ½ cup of fresh/canned or frozen fruits (banana, berries, peach, mango, etc.) or vegetables (avocado, leafy greens: spinach, kale), cucumbers (seedless, skinless), tomatoes (seedless), carrots (cooked)
4) To sweeten add in a splash (1-4 tbsp) of juice (orange, pomegranate lemonade, apple, etc.), honey or agave syrup 2 tsp, allowed coffee flavored syrups (1 pump) cocoa powder, milk free syrups.
5) Add 3-4 scoops of AAF or ¼- ½ cup RTF AAF (1 scoop = ~40 kcals, 1.3 gm protein)
6) Extras: Chia/flaxseed oil (high in omega 3 fatty acids), allowed nut butters

Strawberry smoothie
4 scoops of AAF (strawberry flavored)
4 fl oz of allowed plant- based milk beverage
½ cup frozen strawberries

High kcal smoothie
4 scoops vanilla AAF
4 fl oz of allowed plant-based milk beverage
½ avocado
1 cup frozen pineapple
1 tbsp honey

Instructions:
1. Blend and enjoy!

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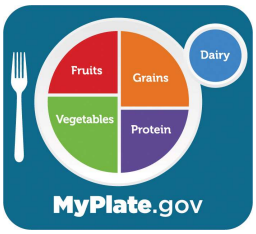
Making it work....

- Focusing on allowed foods vs. not allowed foods
  - What can be eaten rather than what is being excluded
  - Nutritionally appropriate alternatives
- ChooseMyPlate.gov
  - Lists of foods to fill common food groups
  - Meal proportions:
    - 1/2 vegetable, ¼ grain, ¼ protein
    - Allowed plant-based milk alternative or formula
    - Healthy fats, moderate added



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Practical Management of Infants with Cow Milk Allergy and the Role of the Intestinal Microbiota. Are We Doing Enough?

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University of Illinois at Chicago
Editor-in-Chief, Journal of Parenteral and Enteral Nutrition

Food Allergy University
December 10, 2021

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Disclosures

Dr. Kelly Tappenden received an honorarium provided by Nutricia for this presentation.

The above does not pose a conflict of interest for this presentation.

The opinions reflected in this presentation are those of the speaker and independent of Nutricia.

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Learning Objectives

- Explain the importance of the intestinal microbiota in early life and the development of the immune system;
- Explore the role of specific prebiotics and probiotics in the dietary management of infants with cow milk allergy;
- Discover tips for the practicing dietitian based on a growing body of evidence.

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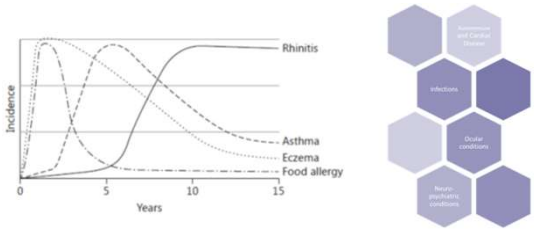
Atopy comorbidities vary by age through adulthood



Nutten. Ann Nutr Metab 2015;66(suppl1):8-16.

https://nationaleczema.org/research/eczema-facts/

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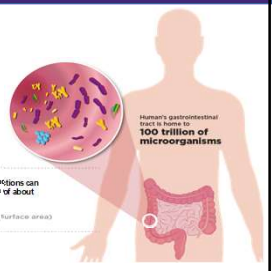
The intestinal microbiota

Gut microbiome and gut microbiota describe either the collective genomes of the microorganisms that resides in the gut, or the microorganisms themselves, respectively.

The gut hosts 70%[1] of the human body's immune cells



The gut contains more than **3 million microbial genes**[1]
(150 times more than human genes)

Host-microbiome interactions can occur on a surface area of about **30–40m²**
(20 times of the skin surface area)

Gut microbiota weighs up to **2 kg**[1]

Van de Wiele T et al. Nature Reviews Rheumatology, 12:398–411, 2016.

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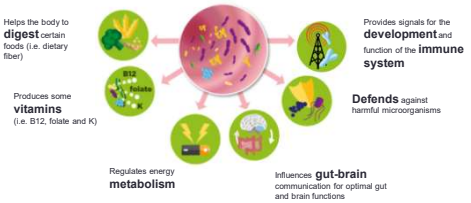
Why is intestinal microbiota important?



Helps the body to **digest** certain foods (i.e. dietary fiber)

Produces some **vitamins** (i.e. B12, folate and K)

Regulates energy **metabolism**

Provides signals for the **development** and function of the **immune system**

Defends against harmful microorganisms

Influences **gut-brain** communication for optimal gut and brain functions

Shamir R, et al. Essential Knowledge Briefing, Wiley, Chichester (2015).
Van de Wiele T et al. Nature Reviews Rheumatology, 12:398–411, 2016.

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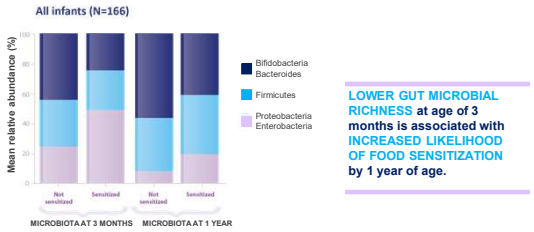
A HEALTHY GUT MICROBIOTA SUPPORTS ORAL TOLERANCE
Dysbiosis in infant gut microbiota precedes food sensitization



LOWER GUT MICROBIAL RICHNESS at age of 3 months is associated with INCREASED LIKELIHOOD OF FOOD SENSITIZATION by 1 year of age.

Azad et al., 2015. Clinical and Experimental Allergy.

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Dysbiosis precedes development of allergic phenotype

Age of dysbiosis	Phenotype	Age at diagnosis	Reference
1 month	Eczema	2 years	Abrahamsson et al., JACI 2012;129:434-440.
Day 7	Eczema	12 months	Ismail et al., PAI 2012:23:674-681.
1 week	Eczema	18 months	Wang et al., JACI 2008;121:129-134.
1 week/ 12 months	IgE, eos, rhinitis; NOT asthma, eczema	up to 6 years	Bisgaard et al., JACI 2011; 129:646-652.
3 weeks	Asthma		Vael et al., BMC Microbiol 2011;11:68.

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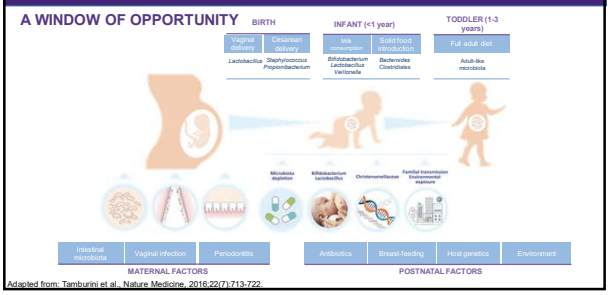
Early intestinal microbiota development



Adapted from: Tamburini et al., Nature Medicine, 2016;22(7):713-722.

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Factors disrupting microbial homeostasis during early life and development or protection against diseases

Disruptive factor	Study	Cohort characteristics	Outcomes
C-section	Sevelsted et al., 2015	1.9 million Danish term children, ages 0-15 years	Asthma, systemic connective tissues disorders, juvenile arthritis, IBDs, immune deficiencies and leukemia
	Huh et al., 2012	1,255 US children, age 3 years	Obesity, higher body-mass index and sum of skinfolds
	Eggesbø et al., 2003	2,803 Norwegian children, 0-2 years	Reactions to egg, fish or nuts, and a fourfold increase in egg allergy
Antibiotic treatment	Risnes et al., 2011 Hoskin-Parr et al., 2013	1,401 US children, ages 0-6 months 5,780 UK children, ages 0-2 years	Asthma and allergy Asthma and eczema
	Saari et al., 2015	12,062 Finnish children, ages 0-2 years	Overweight and obesity
	Schwartz et al. 2016	163,820 US children ages 2-18 years	Weight gain
	Kronman et al., 2012	9 million UK children	IBD development
Probiotics	Maldonado et al., 2012	215 Spanish children, ages 0-6 months	Reduction in gastrointestinal and upper respiratory tract infections
	Braegger et al., 2011	ESPGHAN Committee on Nutrition	Reduction in nonspecific gastrointestinal infections
Diet supplements	Zimmerman et al., 2010	Iron, 139 African children, ages 6-14 years	Intestinal inflammation, lower frequency of colic or irritability
Hygiene	Hesselmar et al., 2013	184 children, pacifier cleaning, ages 0-3 years	Lower risk of developing asthma, allergy and sensitization
Pets	Virtanen et al., 2014	3,143 Finnish children, ages 0-1 year	Reduction in risk of preclinical type I diabetes

Adapted from: Tamburini et al., Nature Medicine, 2016;22(7):713-722.

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HUMAN milk (HM) is best for infant health

44

HUMAN milk is best for infant health
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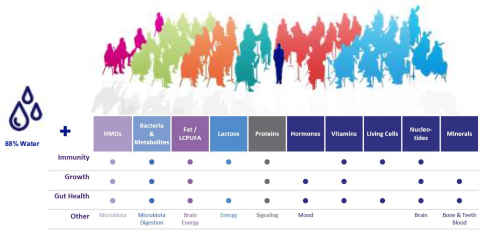
Human milk: a complex system with an orchestra of functions



Pereira et al., Nutrition. 2014;30(6):619-627.

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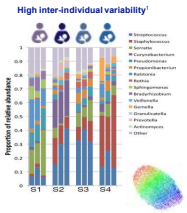
Bacteria composition of human milk is highly variable



HM contains 10^3-10^5 Colony Forming Units/ml bacteria, including Lactobacilli, Bifidobacterium and Staphylococcus.[1-3]

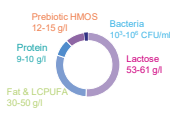
Lactic acid bacteria in human milk ≠ Vagina or skin of the mother.[2]

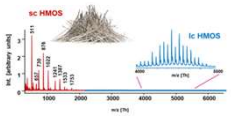
1. Hunt et al., Plos ONE: 2011; 21313. 2. Martin et al., J Pediatrics, 2003; 43(6):754-758. 3. Martin et al., Applied Env Microbiol, 2009;75(4):965-969.

47

PREBIOTIC HMOs: a key component of human milk

PREBIOTIC HMOs consist of different structures with >162 identified





1000s of structures
Stahl et al., *Analyt Biochem* 1994;223:218-226.

162 structures identified
Urashima et al., *Trends Glycosci Glycotechnol* 2018;30(172):51-65.

Key Milestones:
- Egge 1991 FABMS of HMOS
- Stahl 1991 MALDI-Mass Spec of OS
- Thurl 1991 LC of sc HMOS
- Stahl 1994 Mass Spec of sc & lc HMOS
- Thurl 1996 4 types of HMOS based on genes
- Thurl 2017 Systematic Rev on HMOS quantities
- Mank 2019 New LC Mass Spec of Key HMOS

HMOs = human milk oligosaccharides; LCPUFA = Long chain polyunsaturated fatty acids

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PREBIOTIC HMOs: a key component of human milk

HMOs have a multitude of functions

Prebiotic Effect: Growth and Activity of Beneficial Bacteria

- *Brand-Miller et al., J Pediatr 1998;133:95-98.*
- *György et al., Eur J Biochem. 1974;43:29.*
- *Robertfroid et al., Br J Nutr 2010; 104:S1-63.*

Brain Building Blocks

- Hart et al., *J Pediatr Psych* 2003;28:
- Wang et al., *Am J Clin Nut* 2003;78: 1024-1029.
- Stacey et al., *JACS* 2005
- Murrey et al *PNAS* 2006;103

Direct Effect on Immune Cells

- Eiwegger et al., *Pediatr Res* 2004;56:1-5.
- Bode et al., *Thromb Haem* 2004; 92:1402-10.
- Eiwegger et al., *PAI*, 2010; 21(6):1179-88.

Anti-Infective Effect as Receptor Analogues

- Boehm & Stahl, In: Mattila-Sandholm T(ed): *Funct Dairy Prod.*, 2002
- Newburg et al., *Glycobiology*, 2004, 14
- Coppa GV et al *Lancet* 1990

HMOs = human milk oligosaccharides

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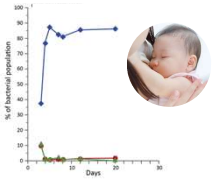
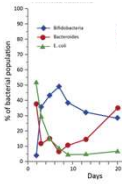
Microbiota: breast vs. bottle

HIGHER BIFIDOBACTERIA COUNT IN BABIES WHO BREASTFEED

Breastfeeding



Formula Feeding



Standard formula milk with no added prebiotics

Harmsen et al., J Pediatr Gastroenterol Nutr. 2000;30:61-67.

50

Synbiotics = prebiotic + probiotic

Can nutritional formulas be modified
- using a **SYNbiotic** approach -
to alter the intestinal microbiota and
improve clinical outcomes in children?

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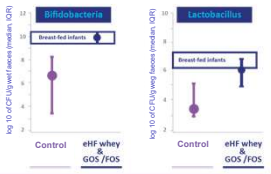
Prebiotics and Bifidogenic gut colonization

scGOS & lcFOS

- 6 clinical trials
- With a specific mixture of short-chain galacto-oligosaccharides (scGOS) and long chain fructo-oligosaccharides (lcFOS)
- In a ratio 9:1 in infant milk formulas
- Showed consistent positive effects on stool consistency and stool frequency

Reviewed in Scholtens et al., World Gastroenterol 2014

EFFECT ON GUT MICROFLORA (TERM INFANTS AFTER 28 DAYS FORMULA FEEDING)



Moro et al., J Ped Gastroenterology & Nutrition 2002

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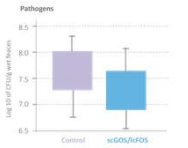
scGOS/lcFOS supports intestinal microbiota by discouraging the growth of potential pathogens

Target population
Preterm

Conclusions
Supplementation of a preterm formula with scGOS/lcFOS sign decreases the sum of pathogens. Also the sum of pathogens as % of total bacterial count was lower than control.

Study design
25 preterm infants
- 0.0g scGOS/lcFOS [Control] (n=15)
- 1.0 g/100ml scGOS/lcFOS (n=12)



scGOS/lcFOS sign reduces the number of clinically relevant pathogens in stools of preterm infants

Knol, J. et al. (2005). Acta Paediatrica;94 (Suppl 449):31–33.

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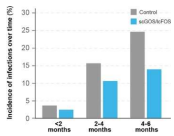
scGOS/lcFOS reduces infections during the first 6 months of life

Target population
Healthy infants

Conclusions
0.8 g/100ml scGOS/lcFOS reduced the number of infectious episodes during the first 6 months of life.

Study design
Randomized, double blind, controlled study; Healthy, term infants with parental history of atopic eczema, allergic rhinitis, or asthma:
- 0.0 g scGOS/lcFOS [Control] (n=104)
- 0.8 g/100ml scGOS/lcFOS (n=102)



scGOS/lcFOS results in lower incidence of infections over time

Arslanoglu, et al. J Nutr 2007;137:2420-2424.

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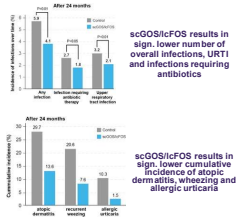
scGOS/lcFOS reduces infections and incidence of allergic manifestations during the first 2 years of life

Target population
Healthy infants

Conclusions
Early nutritional intervention with 0.8 g/100ml scGOS/lcFOS is effective in priming the infant's immune system, providing substantial protection against both allergy and infection.

Study design
Randomized, double blind, controlled study; Healthy, term infants with parental history of atopic eczema, allergic rhinitis, or asthma; for 2 years:

- 0.0 g scGOS/lcFOS [Control] (n=68)
- 0.8 g/100ml scGOS/lcFOS (n=66)



scGOS/lcFOS results in sign. lower number of overall infections, URTI and infections requiring antibiotics

scGOS/lcFOS results in sign. lower cumulative incidence of atopic dermatitis, wheezing and allergic urticaria

Arslanoglu, et al. J Nutr 2008;138:1091-1095.

URTI = upper respiratory tract infections

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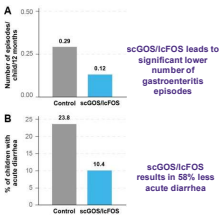
scGOS/lcFOS reduces intestinal infections

Target population
Healthy infants

Conclusions
These data show that scGOS/lcFOS 0.4 g/100 ml reduced intestinal infections in healthy infants during the first year of age.

Study design
A prospective, randomized, controlled, open trial.
Healthy infants aged between 15 and 120 days were enrolled in two intervention groups; formula feeding for 12 months

- 0.0 g scGOS/lcFOS [Control] (n=105)
- 0.4 g/ 100mL scGOS/lcFOS (n=96)



scGOS/lcFOS leads to significant lower number of gastroenteritis episodes

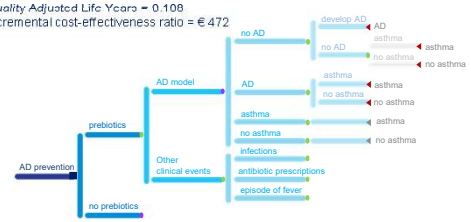
scGOS/lcFOS results in 58% less acute diarrhea

Bruzzese, et al. Clinical Nutrition 2009;28:156-161.

56

USE of formula with scGOS/lcFOS prebiotics result in positive short- and long-term health economic benefits

- Prebiotic cost = €51
- Quality Adjusted Life Years = 0.108
- Incremental cost-effectiveness ratio = € 472



Lenoir-Wijnkoop et al., Eur J Health Econ 2012;13:101–110.

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Amino acid-based formula (AAF) with specific synbiotics aims to eliminate allergens for active management of cow milk allergy

maximal allergen elimination

- Hypoallergenic formula
- Protein source: 100% amino acids
- 0-12 months of age

helps to address underlying gut dysbiosis

- **scFOS / lcFOS** (9:1 ratio)
- 0.63g / 100 ml
- no GOS, to avoid cow milk protein contamination

- ***Bifidobacterium breve* M-16V**
- 10^8 *CFU*/g powder
- processed in a milk-free environment

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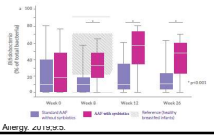
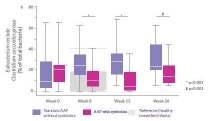
AAF + specific synbiotic blend promotes sustained bifidobacteria growth and reduces *Eubacterium / Clostridia*, similar to breastfed infants

***Bifidobacterium* species in fecal microbiota**



***E. rectale / C. coccoides* cluster in fecal microbiota**



Fox, et al. Clin Transl Allergy. 2019;9:5.

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Recent meta-analysis of AAF + specific synbiotic blend

Lead Author (Date)	Population and Type of Study	Male	Mean Age (Months)	Amount of Formula Consumed/Day (mL) Mean ± SD	n AAF-Syn	n AAF	Intervention Duration	Timepoint Outcomes Measured
Harvey (2018) [30] Full paper	Infants with IgE-mediated CMPA aged 0–36 months. One arm DBPCFC and 7 day feeding period	63%	37.3, range 3.3–46.9	Not reported	30	30	7 days	7 days
	Full-term healthy infants aged 3–16 months. RCT §	67%	10.6, range 3–16	AAF-Syn: 349 ± 127 §, AAF: 331 ± 124 §	30	36	16 weeks	2, 4, 8, 12 & 16 weeks
Berks (2015) [29] Full paper	Infants with IgE or non-IgE mediated CMPA aged 0–9 months, RCT	62%	4.5, range 0.6–8.9	Not reported. Intake was reported as comparable in both groups	34	36	16 weeks	4 & 16 weeks
Candy (2018) [32] A96KN study, full paper	Infants with non-IgE mediated CMPA aged 0–13 months, RCT Included breast-fed healthy reference group (not randomised)	73%	6, range 1.2–12.8	Week 8 AAF-Syn 672 ± 17%; AAF 639 ± 232	35	36	8 weeks	4 & 8 weeks
Fox (2019) [33]* A96KN study, full paper	Infants with non-IgE mediated CMPA aged 0–13 months. 26-week follow-up of Candy (2018)	73%	6, range 1.2–12.8	Week 8 AAF-Syn 672 ± 17%; AAF 639 ± 232	35	36	8 weeks	8, 12 & 26 weeks
Wopereis (2019) [41]† A96KN study, full paper	Infants with non-IgE mediated CMPA aged 0–13 months Gene-sequencing analysis from Candy (2018) and Fox (2019).	73%	6, range 1.2–12.8	Week 8 AAF-Syn 672 ± 17%; AAF 639 ± 232	35	36	8 weeks	8, 12 & 26 weeks
Chatchatee (2019) [31] PRESTO study ‡, conference abstract	Infants with confirmed IgE mediated CMPA aged 0–13 months, RCT	72%	9.36, SD 2.33	At 12 months: AAF-Syn: 347 ± 162, AAF: 330 ± 308	80	89	12 months	12 months
Wopereis (2020) [34] PRESTO study ‡, conference abstract	Infants with confirmed IgE mediated CMPA aged 0–13 months, RCT							

CMPA, cow's milk protein allergy; RCT, randomised controlled trial; DBPCFC, double blind placebo-controlled crossover food challenge; AAF-Syn, amino acid formula with synbiotics (Nocuate Syneo®, Nutricia); AAF (control), amino acid formula (Nocuate LGG®, Nutricia); * original RCT Candy 2018 [32] was for 8 weeks, Fox (2019) [33] and Wopereis (2019) [41] were published after original RCT; † Chatchatee (2019) [31] and Wopereis (2020) [34] report different outcomes from same study; ‡ Converted from reported oz (AF: 11.9 ± 4.3 oz; d AAF-Syn: 11.2 ± 4.2 oz; d AAF).; § Included in table for completeness, but outside scope of review as subjects were not required to have CMPA.

Sorensen et al., Nutrients. 2021;13:935-954.

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Meta-analyses reveal consumption of AAF + specific synbiotic blend enhance microbiota community

- Increased percentages of fecal bifidobacterial species with AAF with synbiotics

- Lower percentages of adult-like *Eubacterium rectale* and *Clostridium coccoides* species with AAF with synbiotics

Sorensen et al., Nutrients, 2021;13:935-954.

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Multiple studies demonstrate consumption of AAF + specific synbiotic blend improve clinical outcomes

- Compared to AAF, significantly fewer infants fed AAF with synbiotics had infections*
- Overall medication* use, including antibacterials and anti-infectives, was lower among infants fed AAF with synbiotics.
- Significantly fewer infants had hospital admissions (arising from infections) with AAF with synbiotics compared to AAF (8.8% vs. 20.2%, p = 0.036; 56% reduction), leading to potential cost savings† per infant of £164.05–£338.77.

*Exploratory findings, from component studies (not powered to test these outcomes), were the results of safety evaluations. Exploratory findings do not intend to offer final and conclusive results, and further research is needed to confirm the findings. † Cost savings based on UK hospital admission costs. Costs may vary in the US.

Sorensen et al., Nutrients, 2021;13:935-954.

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Conclusion

Nutritional strategies employing
PRObiotics + PREbiotic fiber

– hence SYNbiotics –

are important for addressing dysbiosis of the developing intestinal microbiota and stimulating critical development of the immune system in early life.

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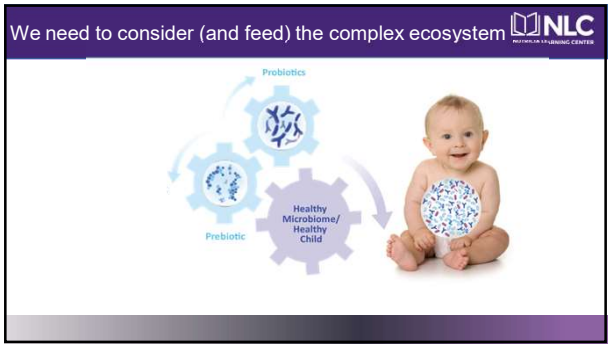

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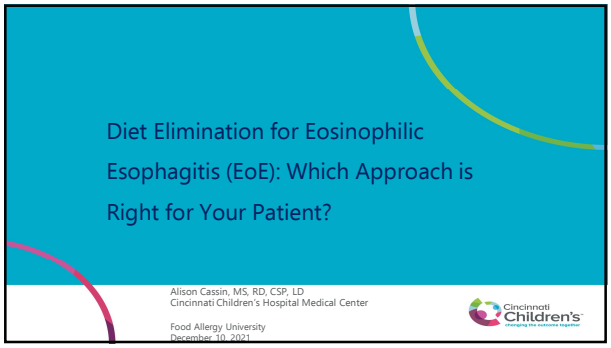

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Objectives

- Describe and compare different types of dietary management options used for EoE
- Discuss patient factors and how they align with different dietary management options
- Identify common nutrient deficiencies associated with elimination diets and discuss strategies for replacement and supplementation

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Eosinophilic Esophagitis (EoE)

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

Dellon, et al. Gastroenterology 2018;155:1022-33.e10.

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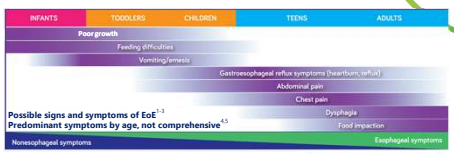
Signs & symptoms of EoE vary by age



- **Infants and toddlers**: FTT, reflux, irritability, vomiting
- **School age**: Abdominal pain, reflux
- **Adolescents/Adults**: Dysphagia and food impaction, reflux

UNUSUAL EATING BEHAVIORS: Slow eating, lots of fluid with meals,[1] and preference for pureed textures are seen in children[2]

1. Noel RJ, et al. NEJM 351:9, 2004. 2. Spergel, et al. Allergy. 2020. 3. Furuta, et al. Gastroenterology. 2007;133:1342-63. 4. Dellon, et al. Am J Gastroenterol. 2013;108:679-92. 5. Dohlen, et al. Pract Gastroenterol. 2018;42:40-51. Illustration courtesy of Nutricia Medical and Scientific Affairs, North America.

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Role of the RD in recognizing symptoms

EoE symptoms can be non-specific

Esophageal dysfunction may not be apparent

Not sufficient to ask "Do you have trouble swallowing?"

- Prolonged mealtimes
- Excessive fluids with meals
- Texture avoidance - meats, breads, potato, rice, "dough"

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Diagnosing and Monitoring EoE

Medical History
(Symptoms of Esophageal Dysfunction)

⇩

Esophagogastroduodenoscopy
(EGD)
Biopsy

⇩

Pathology
≥ 15 eos/HPF from esophageal biopsy

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Natural history

- EoE is chronic
- Therapy prevents long-term complications
  - Fibrosis – scar tissue
  - Stricture formation
  - Narrow caliper esophagus
- Swallowing difficulties

Photo by Rundel, licensed under CC BY 2.0

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Medical therapy

- Swallowed corticosteroids
  - Asthma preparations
    - Fluticasone inhaler
    - Budesonide mixed with carrier
- Immunomodulators
- Proton pump inhibitors
- Dilation

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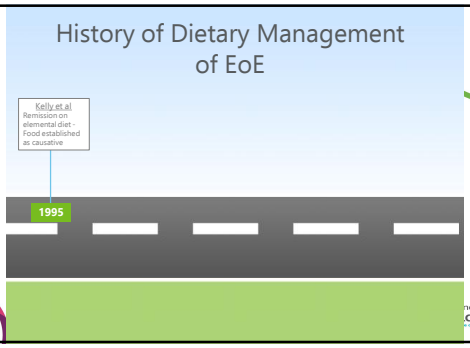
History of Dietary Management of EoE



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Elemental Diet

- Complete removal of ALL dietary antigens
= All Food
- ***Replace*** food with amino acid-based formula

Efficacy
Peds: 90%
Adults: 94%

Markowitz et al. *Am J Gastroenterol*. 2003 Apr;98(4):777-82.
Arias et al. Gastroenterology 2014;146:1639–1648

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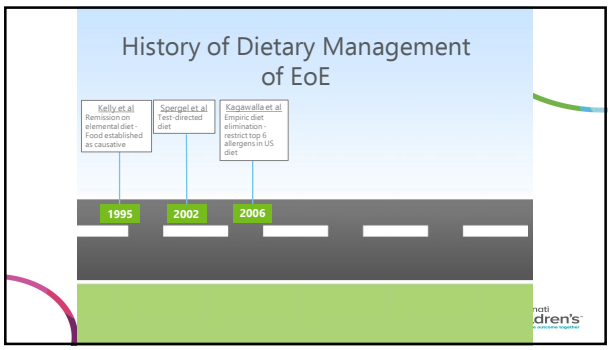

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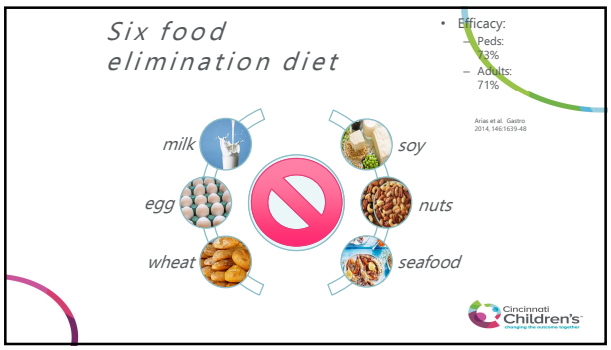

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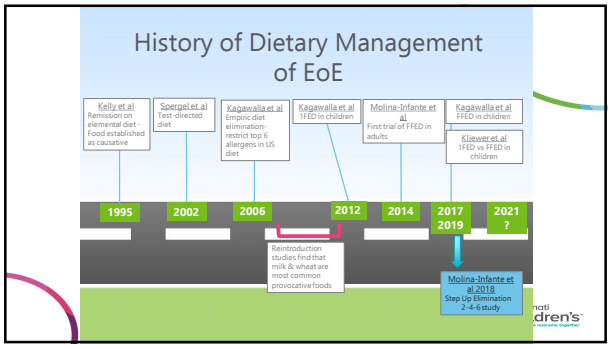

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Diet Elimination - What is Our Goal?

Symptomatic and histologic remission

But, other factors to consider

- Efficiency
  - Management duration
  - Number of endoscopies
- Nutritional implications
- Quality of life
- Uncertain nature of empiric elimination

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Step-down approach

- Current standard practice
- Eliminate all major allergens simultaneously
  - Usually a SFED/FFED
- Confirm EoE remission with endoscopy

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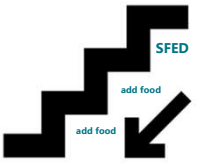
Step-down approach

- If EoE in remission, reintroduce single food groups
- Each period of food introduction is followed by EGD
- Continue trials until maintenance diet achieved



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Advantages of step-down approach

- High rate of efficacy- 72% remission (Arias et al 2014 meta-analysis)
- Achieves remission in 6-12 weeks
- For most patients, provides a clear path for reintroduction
- Initial elimination is extensive, but subsequent reintroductions to rebuild diet are encouraging for patients

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Advantages of step-down approach

- Despite restricting multiple foods, elimination diet ***may not*** impair growth
  - Short-term elimination diet did not worsen weight-for-height z-scores in children (Colson et al 2014)
  - Children who were underweight before diet actually gained weight during elimination diet (Liacouras 2005)
  - In adults, SFED did not cause weight changes (Lucendo 2013)

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Limitations of step-down approach

- Potential for impaired nutrition without diet counseling
- Quality of Life (QoL)
  - Diet elimination associated with *lower* QoL (Menard-Gardner 2013)
    - Meal enjoyment, restriction
  - Diet elimination associated with *improved* QoL (Gonsalves 2012)
    - overall score + symptom improvement

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Limitations of step-down approach

- Prolonged avoidance can lead to hypersensitivity in IgE-sensitized patients (Barni et al 2004)
- Requires several endoscopies
  - if done with SFED, could require 7 endoscopies
  - If each reintroduction trial lasts 3 months, total duration = 21 months

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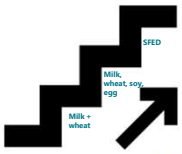
Step-up approach

- Start with minimal elimination
  - milk +/- wheat
- Non responders step up to more restricted diets
  - Remove soy and egg

If still not responsive
- Remove nuts, seafood



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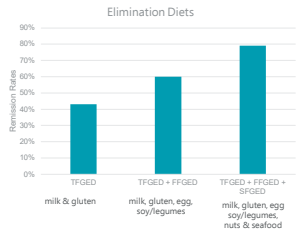
2-4-6 study



TFGED = Two food group elimination diet
FFGED = Four food group elimination diet
SFGED = Six food group elimination diet

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Advantages of step-up approach

- Quickly identifies responders to less restricted diets
- For those who achieve remission early
  - Fewer endoscopies
  - Less dietary restriction = lower nutritional risk

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Limitations of step-up approach

For non-responders:

- Prolonged inflammation may exacerbate complications of EoE
  - Feeding disorders in children (Mukkada 2010)
  - Longer disease duration → lower QoL in adults (Van Rhijn 2014)
  - Duration of untreated EoE correlates with stricture formation (Schoepfer 2013)

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Challenges for non-responders

- Stepping up to next diet elimination requires re-inventing the individual's diet for a second or third time

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Limitations of step-up approach

- Psychologically challenging
- High drop out rates in 2-4-6 study
  - 26% from 2FGED to 4FGED
  - 30% from 4FGED to 6FGED
- 6FGED not effective for ~25% of patients-
  - Further delays inflammation

2FGED = Two food group elimination diet
4FGED = Four food group elimination diet
6FGED = Six food group elimination diet

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Step-down elimination?

- Parents unsure of what food may be the trigger
- Can control diet of the young child
- Want to complete process before child enters kindergarten
- Effort to resolve inflammation quickly to prevent feeding disorders

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Step-up elimination?

- Adult with busy lifestyle and frequent travel.
- Wants to try milk and wheat elimination to "see how it goes"
- Familiar with diet - friends and colleagues have followed vegan and GF diets
- If milk/wheat not effective then will consider further elimination vs. medical therapies

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Key takeaways

Step-Down Approach

Efficacious, quick resolution of inflammation

Diet progressively expands = rewarding for patients

More EGDs = long duration

Risk of hypersensitivity

Step-Up Approach

Efficient for responders to early elimination

Prolonged inflammation for non-responders= delay in treating symptoms

Multiple diet changes

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Shared decision making

Where is the patient in the continuum of their disease?

- Newly diagnosed and enthusiastic about diet management?
- Prolonged disease due to delayed diagnosis or failed medical therapies? Delayed intervention d/t pandemic?
- Do they know what their "max" elimination is?
- Severity of symptoms requiring quick relief?
- What is their emotional tolerance for uncertainty/potential protracted management?

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Allergy-restricted diets are potentially low in:

- Protein
- Fat and essential fatty acids, omega-3s
- Calcium and vitamin D
- Zinc, copper, selenium, iodine

- But deficiencies are difficult to predict…

Meyer et al 2018, Berry et al 2015, Christie et al 2002

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Diet adequacy depends on:

- Type of milk substitute
- Formula use
- Degree of enrichment & fortification of grain-based foods
- Supplementation use
- Fruit and vegetable intake
- Fat and protein sources

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Case study

- 5 YO with EoE, has been on a SFED for 18 months
- Follow up delayed due to pandemic
- Scope further delayed - accidental exposures to avoided foods since starting school
- Weight gain is adequate, but linear growth plateauing
- Most meals are home-cooked, eats a few allergen-free convenience foods
- 500 mg daily calcium supplement recommend by PCP
- Occasional calcium carbonate antacid

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Typical intake

Breakfast	Corn cereal 8 fl oz plant-based milk Fruit
Snack	Vegan yogurt GF granola 4-6 fl oz plant-based milk
Lunch	Ham roll up on corn tortilla Apple slices 8 fl oz plant-based milk
Snack	Carrot sticks GF pretzels
Dinner	Rice pasta with tomato sauce Steamed vegetable 8 fl oz plant-based milk

GF = gluten free

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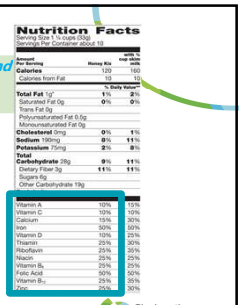
Type of cereal?

Breakfast	Corn cereal- ***store brand***



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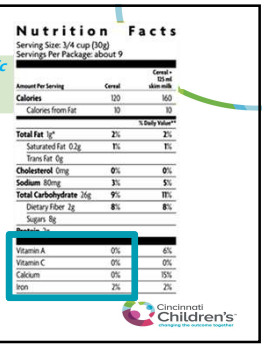
Type of cereal?

Breakfast	Corn cereal- ***organic***



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Should individuals on elimination diets just take a multivitamin?

"Can't hurt… right??"

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It depends…

- Vitamin D deficiency is common
  - All MVI contain vitamin D
- But MVI also contain vitamin A,
  - Which may not be necessary (lead to over supplementation)
- 2008 FITS study: many young children exceed UL for vitamin A when taking MVI
- Exceed UL for zinc w/ fortified cereal intake

Butte NF et al J Am Diet Assoc. 2010
Meyer et al. 2015

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Type of "milk"?

Breakfast	Corn cereal 8 fl oz ***coconut*** milk
Snack	8 fl oz plant-based milk
Lunch	8 fl oz plant-based milk
Snack	
Dinner	8 fl oz plant-based milk

Nutrition Facts
Serving Size 1 Cup (240mL)
Servings Per Container 8
Amount Per Serving
Calories 50 Calories from Fat 30
% Daily Value*
Total Fat 3g 5%
Saturated Fat 1g 6%
Trans Fat 0g
Polyunsaturated Fat 0g
Monounsaturated Fat 1g
Cholesterol 0mg 0%
Sodium 170mg 7%
Total Carbohydrate 5g 2%
Dietary Fiber 0g 0%
Protein <1g
Vitamin C 0%
Calcium 45% Iron 2%
Vitamin D 50% • Vitamin E 50%
Riboflavin 30% • Vitamin B12 50%

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Type of "milk"?

Breakfast	Corn cereal 8
Snack	8
Lunch	8
Snack	
Dinner	8 fl oz plant-based milk

Calcium
Coconut milk= 1800 mg
Supplement= 500 mg
Total= 2300 mg
(RDA = 1000 mg/day
UL= 2000 mg/day)

Nutrition Facts
Serving Size 1 Cup (240mL)
Servings Per Container 8
Riboflavin 30% • Vitamin B12 50%

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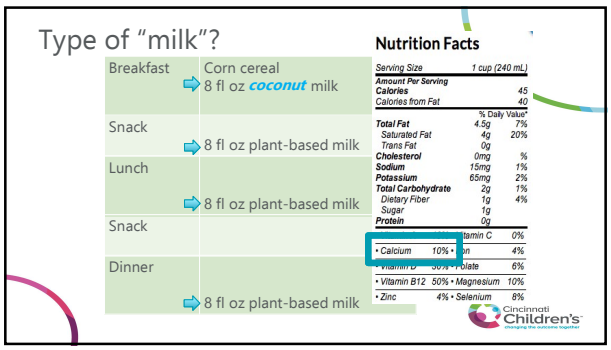

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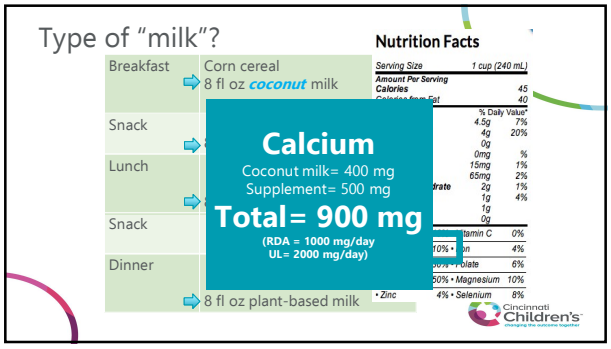

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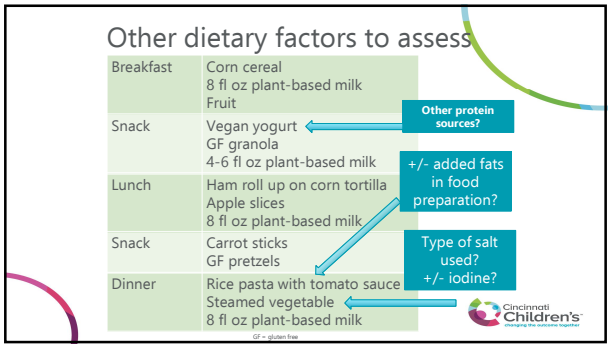

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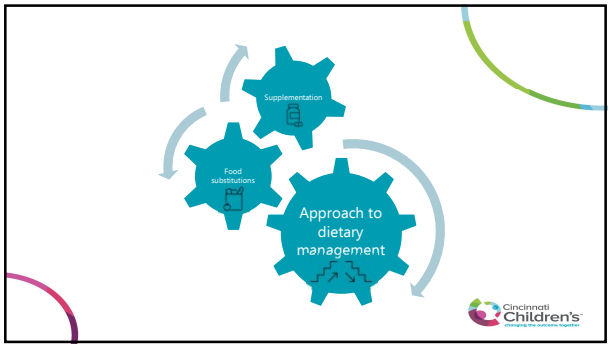

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Resources

AAAAI Work Group Report

Dietary Therapy and Nutrition Management of Eosinophilic Esophagitis: A Work Group Report of the American Academy of Allergy, Asthma, and Immunology

INDANA International Network for Diet and Nutrition in Allergy

NLC NUTRICIA LEARNING CENTER

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st joseph home

You are what you DON'T eat:
Using nutrition-focused physical exam (NFPE) to identify nutrient deficits in children on allergy-restricted diets

Sarah Vermilyea
MS, RD, CSP, LD, CNSC
St Joseph Home of Cincinnati

Food Allergy University: December 10, 2021

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Disclosures

Honorarium provided by Nutricia

The opinions reflected in this presentation are those of the speaker and independent of Nutricia North America

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Learning Objectives

Participants in this activity will learn to:

- Distinguish signs of macro- and micronutrient deficiencies specific to children receiving allergy-restricted diets
- Describe barriers and challenges to performing nutrition-focused physical exam (NFPE)
- Apply the targeted NFPE process to a real world scenario

Photo by Brett Jordan on Unsplash

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Nutrition Focused Physical Exam (NFPE)

- Hands-on assessment
- Specific to nutrition-related components
- Domain of the Nutrition Care Process*
- Does not replace exam of other medical professionals

Photo by Markus Spiske on Unsplash

*The Nutrition Care Process is a systematic method to providing nutrition care developed by the Academy of Nutrition and Dietetics.

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Logistics

Facility
- Time
- Equipment
- Documentation
- Follow up
- Multidisciplinary coordination

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Logistics

Photo by Brett Jordan on Unsplash

Personal
- Training
- Experience
- Expectations

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Comprehensive vs. Focused Exam

Comprehensive

Focused

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Focused Exam for Allergy-Restricted Diets

Some Potential Deficiencies

- Calories
- Protein
- Essential fatty acids
- Calcium
- Vitamin D
- B vitamins
- Iodine
- Zinc
- Copper
- Selenium

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Focused Exam for Allergy-Restricted Diets

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Excess/Toxicities

- Calcium
- Vitamin A

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Essential Fatty Acids (EFA)

EFA Deficiency Sign	Exam
Hair: easy to pluck	Gently tug hair at roots
Skin: waxy, oily, crusty especially scalp/lips/nose; extremely dry	Look at skin on face; look at and feel skin on arms or legs
Signs can also be caused by: over processed hair; nasal drainage; hypothyroidism; uremia; ichthyosis; allergies; aging; poor skin hygiene; excessive vitamin A; deficiencies of vitamin A, riboflavin, zinc, B6, biotin	

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Essential Fatty Acid (EFA) - Follow up

Follow up
- If findings make sense
  - Increase EFA intake
  - Consider obtaining a **serum essential fatty acid profile**
- If findings don't make sense
  - Ask more questions
  - Consider alternate causes of concerning exam findings

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Protein

Protein Deficiency Sign	Exam
Hair: severe loss, color change (overall or at a certain hair length), easily plucked	Look at scalp and hair, gently tug hair at roots, ask questions
Skin: color loss, dark cheeks, lack of fat underneath, slow wound healing	Look at face, gently pinch skin on any area except hands and elbows; similar to feeling for triceps skinfold; look at all exposed/exposable skin; ask questions
Parotid gland: enlarged	Palpate jaw line below ears
Nails: vertical or horizontal indentation running across all fingernails, soft scooped appearance	Look at and palpate fingernails
Edema: bilateral, "moon" face	Gently press on lowest section of body, whether legs if sitting or standing, feet or lower back if laying down for long time period, look at face and palpate for fat stores/muscle mass/fluid
Muscles: decreased mass and density	Palpate muscles* and compare to past assessments *temple, clavicle, deltoid, scapular area, quads, knees, calves
Demeanor: listlessness	Observe demeanor; Ask questions

Signs can also be caused by: deficiencies of iron, zinc, biotin, manganese, selenium, copper, calcium, calories, EFA, B vitamins, vitamin C, hydration; aging; chemotherapy; radiation to head; stress; endocrine disorders; medications; overprocessing of hair; bulimia; mumps; salivary duct stones; portal cirrhosis; Sjogren's syndrome; severe illness; immunosuppressive therapy; diabetes; lupus; Raynaud's disease; hypothyroidism; severe arterial disease; poor skin care; steroids

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Protein - Follow up

Follow up
- If findings make sense
  - Increase protein intake
- If findings don't make sense
  - Ask more questions
  - Consider alternate causes of concerning exam findings

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Calcium (deficiency)

Calcium Deficiency Sign	Exam
Muscles: twitches or cramps	Look at muscles; Ask questions
Bone: demineralization	Read x ray and DXA imaging results
Signs can also be caused by: altered levels of hydration, magnesium, zinc, phosphorus; vitamins B6, D, and A	

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Calcium (toxicity)

Calcium TOXICITY Sign	Exam
Bone: pain	Ask questions
Neuro: headaches, fatigue, lethargy, memory problems, irritability, depression	Observe demeanor; Ask questions
GI: nausea, constipation, anorexia	Ask questions
Muscles: pain, weakness, cramps	Look at muscles; Ask questions
Signs can also be caused by: altered intake of vitamin D, phosphorus, potassium, vitamin C, iron, chloride, sodium, magnesium, B vitamins; fractures; arthritis; cancer; diabetes	

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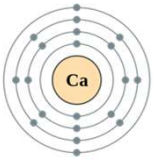
Calcium - Follow up

Follow up

- If findings make sense
  - Alter calcium intake
  - Consider obtaining **serum calcium** level
- If findings don't make sense
  - Ask more questions
  - Consider alternate causes of concerning exam findings



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Vitamin D

Vitamin D Deficiency Sign	Exam
Gums: red, puffy	Look at gums
Teeth: holes, chips, dark spots	Look at teeth
Bone: demineralization, tenderness, pain, epiphyseal enlargement	Read x-ray and DXA imaging results, ask questions; look at and touch wrists, knees, legs, forehead
Muscles: weakness, twitches, cramps, pain	Have patient push against your hand; Look at and palpate muscles; Ask questions
Signs can also be caused by: deficiencies of vitamin C, niacin, folate, zinc, vitamin D, vitamin B6, fluoride, calcium, phosphorus, potassium, iron, magnesium, chloride, sodium, biotin, zinc; dehydration; genetics; smoking; pregnancy; diabetes; medications; poor oral hygiene; fibromyalgia; fractures; arthritis; cancer; toxicity: vitamin A	

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Vitamin D - Follow up

Follow up
- If findings make sense
  - Increase vitamin D intake
  - Consider obtaining **25-hydroxyvitamin D** level
- If findings don't make sense
  - Ask more questions
  - Consider alternate causes of concerning exam findings

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Zinc

Zinc Deficiency Sign	Exam
Hair: severe loss	Look at scalp; Ask questions
Gums: red, puffy	Look at gums
Taste: loss or change	Look at tongue; Ask questions
Nails: indentation running horizontally across all nails	Look at fingernails
Skin: slow wound healing; red and itchy; waxy, oily, crusty especially scalp/lips/nose; severe diaper rash	Look at all exposed/exposable skin; Ask questions
Neuromuscular: seizures, memory impairment, behavioral disturbances	Observe demeanor; Ask questions of patient and caregivers
Signs can also be caused by: aging; stress; endocrine disorders; medications; poor oral hygiene; pregnancy; diabetes; smoking; genetics; excessive vitamin A intake; deficiencies of vitamins D, C, A, niacin, folate, A, riboflavin, B6, biotin, EFA; SARS-CoV-2 disease illness; chemotherapy; immunosuppressive therapy; poor skin care; steroids; dermatitis; nasal drainage	

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Zinc - Follow up

Follow up

- If findings make sense
  - Increase zinc intake
  - Consider obtaining **serum zinc** level
- If findings don't make sense
  - Ask more questions
  - Consider alternate causes of concerning exam findings

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Iodine

Iodine Deficiency Sign	Exam
Thyroid: enlarged	Gently palpate front of neck
Signs can also be caused by: hypo- or hyperthyroidism; malignancy; cysts; inflammation	

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Iodine - Follow up

Follow up

- If findings make sense
  - Increase iodine intake
  - Consider obtaining **serum iodine**
- If findings don't make sense
  - Ask more questions
  - Consider alternate causes of concerning
  - exam findings

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B vitamins

B Vitamin Deficiency Signs	Exam
Hair: severe loss	Look at scalp; Ask questions
Skin: waxy, oily, crusty; red and itchy; scaly patches; color loss; hyper- or yellow pigmentation; flushing	Look at skin on all exposed/exposable skin
Muscles: twitches or cramps; weakness; tenderness; pain	Look at muscles; Ask questions
Teeth: holes, chips, dark spots	Look at teeth
Nails: vertical nail ridges	Look at fingernails
Eyes: pale conjunctiva, skin redness/fissures, eye weakness	Look at corners of eyes, gently pull down lower eyelid to see the lining of the lower eyelid, watch eyes move (looking for weakness or shaking)
Mouth: soreness/burning; red swollen skin **Tongue:** sore/swollen/magenta/smooth/beefy/pale	Look at corners of mouth, lips, tongue
Body: edema/moon face	Gently press on lowest section of body; look at face and palpate for fat stores/muscle mass/fluid
GI: anorexia, flatulence, diarrhea	Ask questions
Neuro: inability to concentrate, fatigue, depression, peripheral neuropathy, irritability	Observe demeanor; Ask questions

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B vitamins - Follow up

Follow up

- If findings make sense
  - Increase intake
  - Specific B vitamin testing available
- If findings don't make sense
  - Ask more questions
  - Consider alternate causes of concerning exam findings

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Vitamin A (toxicity)

Vitamin A TOXICITY Sign:	Exam:
Hair: loss	Look at scalp; ask questions
Neuro: headache	Ask questions
Mouth: redness, scars, swelling or fissures	Look at corners of mouth
Gums: swollen, spongy, bleeds easily, redness, retracted	Look at gums
Nails: brittle, soft, dry, weak or thin, split easily	Look at fingernails
Skin: waxy, oily, crusty especially scalp/lips/nose; extremely dry	Look at skin on face; look at and feel skin on arms or legs
Bone: demineralization	Read x ray and DXA imaging results

Signs can also caused by: deficiency of vitamins A, B, C, D, and B, calcium, phosphorus, iron, zinc, magnesium, essential fatty acids; malnutrition; poor oral hygiene; genetics; smoking; pregnancy; diabetes; medications; dry skin; dehydration; herpes; selenium toxicity; metabolic bone disorder; thyroid disorder; systemic amyloidosis; aging; nasal drainage

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Vitamin A - Follow up

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Follow up
- If findings make sense
  - Decrease intake
  - Consider obtaining **serum vitamin A (retinol)**
- If findings don't make sense
  - Ask more questions
  - Consider alternate causes of concerning exam findings

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Back to: Alison's Case Study

5 year old with eosinophilic esophagitis (EoE) has been on a six food elimination diet (SFED) for 18 months

Supplements: 500 mg calcium supplement
Meds: occasional calcium carbonate for reflux
Milk: recently accepting a milk substitute
Weight: adequate gain
Height: plateauing
Meals: most are home-cooked

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Planning a Focused NFPE

Nutrients of concern based on his diet history
- Protein
- Fat
- Calcium (excess)
- Trace minerals
- B vitamins
- Iodine

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Planning a Focused NFPE

Focused exam	Areas of concern
Head	hair, skin, eyes, tongue, gums, teeth, taste, thyroid gland, parotid gland, neuro
Arms/Torso	Skin, muscles, fingernails, GI symptoms, bones
Legs	Skin, muscles, bone

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NFPE Findings

NFPE findings	Likely nutrients of concern	Follow up plan
Bone: pain		
Skin: waxy/crusty around nose and forehead		
Skin: extremely dry		
Muscles: decreased mass and density		
No concerns noted regarding thyroid, hair, taste, gums, mouth, teeth, nails, neuro, GI, parotid gland, fluid accumulation		

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Nutrients of Concern

NFPE findings	Likely nutrients of concern	Follow up plan
Bone: pain	Deficiency: vitamin D Toxicity: calcium	
Skin: waxy/crusty around nose and forehead	Deficiency: zinc, essential fatty acids (EFA), or B vitamins Toxicity: vitamin A	
Skin: extremely dry	Deficiency: EFA	
Muscles: decreased mass and density	Deficiency: protein	

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Nutrients of Concern

NFPE findings	Likely nutrients of concern	Follow up plan
Bone: pain	Deficiency: vitamin D Toxicity: calcium	
Skin: waxy/crusty around nose and forehead	Deficiency: zinc, essential fatty acids (EFA), or B vitamins Toxicity: vitamin A	
Skin: extremely dry	Deficiency: EFA	
Muscles: decreased mass and density	Deficiency: protein	
No concerns noted regarding thyroid, hair, taste, gums, mouth, teeth, nails, neuro, GI, parotid gland, fluid accumulation		

Photo by Tim Mossholder on Unsplash

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Follow up Plan

NFPE findings	Likely nutrients of concern	Follow up plan
Bone: pain	Deficiency: vitamin D Toxicity: calcium	• 25 hydroxyvitamin D level • Serum calcium level • Discontinue calcium supplement • Depending on lab value: supplement vitamin D
Skin: waxy/crusty around nose and forehead	Deficiency: zinc, essential fatty acids (EFA), or B vitamins Toxicity: vitamin A	• Increase EFA intake • Consider increase of zinc, B vitamin food sources • Readdress if child is taking ANY supplement containing vitamin A
Skin: extremely dry	Deficiency: EFA	• Increase EFA intake • Consider serum EFA profile
Muscles: decreased mass and density	Deficiency: protein	• Increase protein intake • Reassess for adequate fat stores and growth
No concerns noted regarding thyroid, hair, taste, gums, mouth, teeth, nails, neuro, GI, parotid gland, fluid accumulation		

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- Litchford MD. Nutrition Focused Physical Assessment: Making Clinical Connections. CASE Software & books; 2013.
- Wittenbrook W, Corkins KG, eds. Nutrition-Focused Physical Exam. In: *Academy of Nutrition and Dietetics Pocket Guide to Children with Special Health Care and Nutritional Needs*. 2nd ed. Academy of Nutrition and Dietetics; 2021:33-51.

Additional Resource

- DeTall C, ed. The Practitioner's Guide to Nutrition-Focused Physical Exam of Infants, Children, and Adolescents. ASPEN; 2019.

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Food Oral Immunotherapy (OIT): An Approach to Managing IgE-mediated Food Allergies

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University of Cincinnati College of Medicine

Food Allergy University
December 10, 2021

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Disclosures

- Honorarium provided by Nutricia
- Personal fees - Aimmune
- The material presented does discuss the off-label use of grocery-store bought peanut.

The opinions reflected in this presentation are those of the speaker and independent of Nutricia North America

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Objectives

- Explain the procedure and application of OIT in clinical practice
- Illustrate the mechanism behind desensitization
- Summarize the benefits, risks and alternatives of OIT
- Determine the role of the dietitian in OIT

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Outline

- Food Allergy History and Case
- OIT Basics
- Dietitian Role

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Food allergy history: 1980s to now

1980s
"Allergies to food?
You believe in that?"

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Food allergy epidemic

Food allergy incidence and prevalence increased

Today: 5-8% prevalence

1980s: 1% prevalence

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Food allergy anxiety

High anxiety

Food allergy anxiety increased

- Accidental ingestions common
- Constant vigilance and carrying of medications at all times
- Limitations of social activities, group bonding
- Fear of life-threatening reactions

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Peanut avoidance is difficult

- Peanut is **ubiquitous** in the US food industry.
- Food sharing between children in daycare and school settings.
- Cross-contamination of foods and utensils.
- Incorrect ingredient information in restaurants and on product labels.
- Mistakes in label reading.

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Peanut avoidance is difficult

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Social media exacerbates anxiety

Ohio Teen's Death From Peanut Allergy Inspires Parents To Take Action

Allison's dream of becoming an educator inspired the Allison Rose Foundation to teach others about the dangers of food allergies.

Milwaukee teen dies weeks after allergic reaction to peanut butter cookie

POSTED 12:55 PM, NOVEMBER 28, 2014, BY FOX6 NEWS, UPDATED AT 05:04PM, NOVEMBER 28, 2014

WEBMD HEALTH NEWS

Alabama Boy's Death Worries Food Allergy Parents

By Jennifer Clayton

College student dies after severe allergic reaction to peanut butter

Fatal Food-Induced Anaphylaxis

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Annual incidence of fatal food anaphylaxis is on par with death by lightning

Annual Incidence	Cause
~1 in 10	Emergency room attendance due to injury
~1 in 100	Death from any cause (Europe or US)
~1 in 1,500	Death due to an accident (Europe or US)
~1 in 10,000	Death due to murder (US)
~1 in 100,000	Death due to fire Death due to murder (Europe)
~1 in 1 to 8 million	**Death due to lightning** **Death due to food anaphylaxis**

Turner et al. *J Allergy Clin Immunol Pract.* 2017.

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Perception versus reality

Perception of fatality risk for guardian/person with food allergies

- High
- Possibility of fatal anaphylaxis can cause significant anxiety and restriction of daily activities, negatively impacting quality of life

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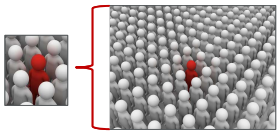
Perception versus reality

Reality of fatality risk for population with food allergies

- Very low (likely < 1 in 1-10 million)
- Adding little to overall mortality risk



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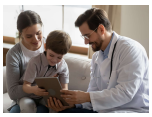
Food allergy history: 1980s to now

Food allergy incidence increased



Food allergy anxiety increased

1980s

"Allergies to food? You believe in that?"

Now

Food Allergies are real. Rare to die or have morbidity, but anxiety is high for families.

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Management options for food allergy

Avoidance and Epinephrine

"You have food allergies. Avoid eating that food. Here is an EpiPen® for emergency use. Schedule to see me next year."

EpiPen is a registered trademark of Mylan Inc., a Viatris Company.

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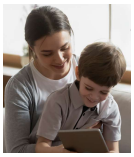
Patient: Martin



A 6 y.o. boy, Martin, presents to Allergy Clinic at Cincinnati Children's with a history of peanut allergy.

The family asks whether OIT is a possibility for Martin.

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Patient: Martin

Why family is asking:

- **Anxiety is disabling**. Martin is fearful of eating at school and restaurants.
- Mom and dad are both fearful of accidents and have **limited activities** as a result.
- Parents **surf the internet** researching **peanut allergy deaths.**
- The smell of peanut butter causes Martin **anxiety-induced reactions.**

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Patient: Martin

Martin's Medical History

- Hives as a baby with first exposure. No reactions since.
- Peanut IgE >100
- No asthma
- Infant eczema. Now resolved.

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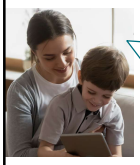
Questions about Peanut OIT



- **What is OIT?**
- What are the risks and benefits of OIT?
- Will OIT cure his allergy?
- Is Martin a candidate for OIT?

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What is OIT?

OIT is a treatment approach in which a patient with food allergies consumes gradually increasing quantities of specific food allergens with the goal of inducing desensitization (i.e., temporary hypo-responsiveness).[1,2]

[1]Wood RA. J Investig Allergol Clin Immunol (2017)
[2]Gernez, Y and A Nowak-Wegrzyn. JACI Pract (2017)

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Defining Terminology

Important concepts of OIT

- Sensitization
- Clinical allergy
- Tolerance
- Desensitization
- Sustained unresponsiveness

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Sensitization

- Evidence of IgE either by skin testing or in vitro IgE
- This is not food sensitivity

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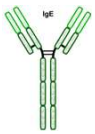
Clinical allergy



- Presence of a clinical reaction history consistent with an IgE-mediated reaction (e.g. hives) and IgE sensitization

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Tolerance

- Normal, physiologic response to ingested food antigens resulting in the ability to ingest food without symptoms **despite prolonged periods of avoidance** or irregular intake.

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Desensitization

- A **temporary** state of antigen hyporesponsiveness
- Depends on **regular antigen exposure**
- When dosing is interrupted, the protective effect of desensitization is lost

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Sustained Unresponsiveness (SU)

- A state of unresponsiveness despite food avoidance in an individual who has food allergies and has been desensitized
- SU may represent a state of potential oral tolerance, but there is no agreement on the exact period of food avoidance to indicate a state of permanent oral tolerance.

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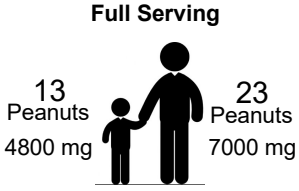
Peanut protein: accounting



United States Department of Agriculture. USDA National Nutrient Database for Standard Reference, (2002).

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Three phases of OIT

Desensitization

3. Maintenance: Home dosing at maintenance **target dose** (≥300-2000 mg)

2. Build-up: Daily dosing with observed dose increases every 2 weeks over 6-9 months.

1. Escalation: Initial dose escalation day (0.1 → 7.2 mg).

Baseline
Clinical history, screening +/- Baseline oral food challenge.

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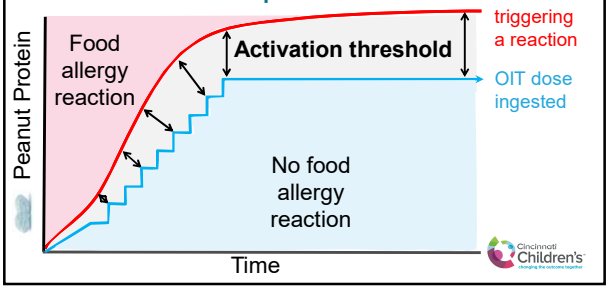
OIT process



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Peanut used in OIT

- Grocery store-bought peanut protein
  - –PB2® or peanut butter or peanuts
- Palforzia®
  - –FDA-approved peanut powder
  - –Approved for patients who are 4-17 years old
  - –Pharmaceutical grade
  - –$4,000 - 10,000 a year

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PB2 is a registered trademark of PB2 Foods, Inc.
Palforzia is a registered trademark of Aimmune Therapeutics, Inc.

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OIT is a way of life

Home Dosing Do's

- ✓Give dose every day
- ✓Give dose at the same time every day with a meal
- ✓Carry epinephrine (adrenaline) autoinjector at all times

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OIT is a way of life

Home Dosing Do NOTs

- × Do not feed your child any of the allergy food in their diet
- × Do not take dose on the day of your child's visit
- × Do not give the dose 2 hours before or 2 hours after taking other medications
- × Do not give the dose if you think your child is sick
- × **Do not give the dose 1 hour before your child goes to sleep**
- × **Do not allow your child to have vigorous activity that would cause sweating or increase in heartbeat, exercise, or take a hot bath for 30 minutes before and 2 hours after the daily dose.**

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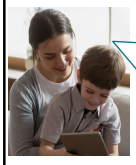
Questions about peanut OIT



- What is OIT?
- **What are the benefits and risks of OIT?**
- Will OIT cure his allergy?
- Is Martin a candidate for OIT?

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What are the benefits of OIT?

There are **3 main benefits of OIT**.

1) **Risk mitigation:** Peanut OIT is very effective at desensitizing patients to peanut.
2) **Reduce food restrictions:** OIT may allow us to add the triggering food into his diet.
3) **Improve mental and psychosocial health:** OIT may improve your family's quality of life and food-related anxiety.

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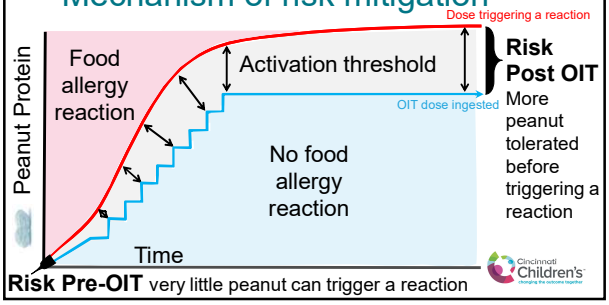
Mechanism of risk mitigation



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What are the risks of OIT?

Adverse reactions are very common during OIT (45-100% of patients) and range from mild to severe (anaphylaxis). Reactions are **generally mild**.

Adverse reactions requiring epinephrine **can occur over the course of OIT** (0-36% of patients treated with epinephrine). Most reactions are during the build up phase and are mild.

Eosinophilic esophagitis (EoE) has been reported (2-3%) as an adverse event of OIT.

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What is the risk of an adverse event (AE) during OIT?

Extrinsic factors that increase risk for AEs during OIT

- Anxiety
- Exercise (< 2 hour after dose)
- Infection
- Allergen exposure
- Menstruation

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What is the risk of an adverse event (AE) during OIT?

A percentage of patients are unable to tolerate therapy due to AEs

- Chronic abdominal pain is the most common symptom leading to discontinuation.
- Eosinophilic esophagitis (EoE) has been reported in several studies (true incidence of EoE in peanut OIT is currently unclear).

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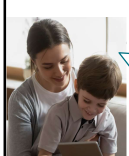
Questions about Peanut OIT



- What is OIT?
- What are the risks and benefits of OIT?
- **Will OIT cure his allergy?**
- Is Martin a candidate for OIT?

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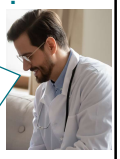
Will OIT Cure his Allergy?

- OIT is a new therapy whose long-term outcomes are still being investigated. **It is too early to know whether peanut OIT can induce long-term tolerance**.
- Several studies have used sustained unresponsiveness as a surrogate for permanent tolerance. From these studies, permanent tolerance is unlikely for most people who undergo OIT.



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Will OIT Cure his Allergy?

Expect Martin to be on **lifelong therapy to maintain desensitization and protection**

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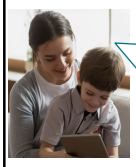
Questions about Peanut OIT



- What is OIT?
- What are the risks and benefits of OIT?
- Will OIT cure his allergy?
- **Is Martin a candidate for OIT?**

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OIT Candidates

At Cincinnati Children's:

- ✓9 months to 18 years with confirmed peanut allergy
- ✓Convincing history of an IgE-mediated reaction with levels of sensitization consistent with high probability of reaction OR
- ✓Allergy clinic in-office allergic food challenge to the food

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Exclusions

- This is an elective procedure
  - × Poor adherence or healthcare literacy
  - × Unstable asthma or other comorbid condition that is considered by the treating allergists to be contraindicated
- **High specific IgE is not exclusionary**

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Therapy	Relative Benefit	Relative Risk
Avoidance	Fewer reactions Less daily commitment	Unexpected and can be severe reactions Fear of death
OIT • Not a cure • Elective • **Lifetime commitment with significant impact on the patient family**	Risk mitigation Less anxiety, improved social restrictions Improved QoL	More frequent reactions Daily and lifetime commitment Rare EoE

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For more information or to refer a patient, contact Christa Mills
(513) 636-9227
christa.mills@cchmc.org

Cincinnati Children's Food Allergy Program website
https://www.cincinnatichildrens.org/service/a/allergy-immunology/programs/food-allergy

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Food Oral Immunotherapy (OIT): The Role of the Dietitian

Alison Cassin, MS, RD, CSP, LD
Cincinnati Children's Hospital Medical Center

Food Allergy University
December 10, 2021

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Disclosures

- Honorarium provided by Nutricia

The opinions reflected in this presentation are those of the speaker and independent of Nutricia North America

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Evolving Role of RD in Food Allergy

Historically:
- What to avoid?
  - Causal food allergens
- What to eat?
  - Food substitutions
  - General healthful diet
  - Quality of life and social situations

Today:
- What to eat?
  - Causal food allergens!?!
    - Early introduction
    - Oral immunotherapy

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The RD has an Important Role in OIT

- **Protein equivalency calculations**
  - Nutrition database experience
  - Food label interpretation
  - Culinary applications

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Alternative Whole Food Sources

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Promoting OIT success

She really doesn't like the taste of peanuts. It's a fight every time...

(Mother of 8-year-old desensitized to peanut)

Leroux et al. JACI In Practice, 2020.

- Brainstorming alternatives for those with flavor/texture aversion

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What About Packaged Foods?

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High Calorie and Lack Significant Protein

~2 g peanut protein	Bamba (17 g)	Peanut butter (10 g)	Peanuts (8 g)	Peanut-flavored Cereal
Kcal	93	59	45	550
Sugar, g	0.4	0.65	0.38	45
Salt, mg	68	48	1	649
Fat, g	6.1	4.95	3.94	7.5

Based on: Venter & Groetch. *J Allergy Clin Immunol Pract.* 2016.

Bamba is manufactured by the Ossm® corporation.

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Nutritional Outcomes of OIT

- Unintended weight gain?
  - Frequent consumption of a high calorie food (nuts)

  Versus
  - Changes in dietary patterns, allowing higher intake of packaged snack foods

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