

Which elimination diet?

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Disclosure

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

- Research Grant (P.I., collaborator or consultant; pending and received grants) – ThermoFisher
- Speakers Bureau / Honoraria – Abbott, Danone Nutricia, Mead Johnson
- Consultant / advisory board – DBV Technologies

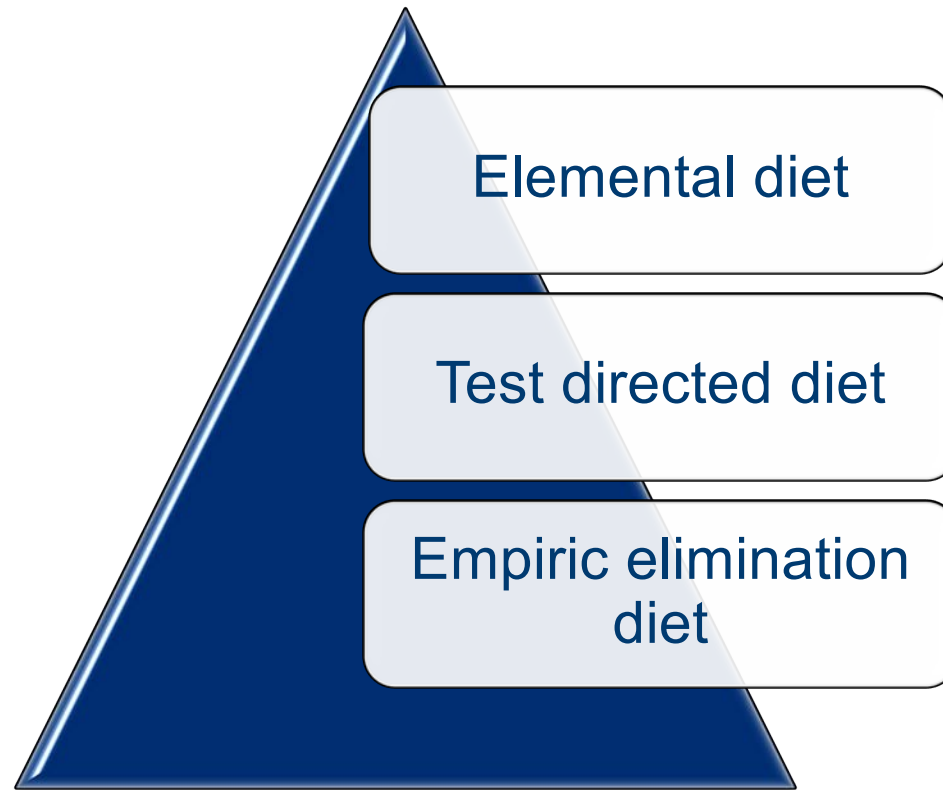
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Objectives

1. Review dietary approaches for the management of eosinophilic esophagitis (EoE)
2. Discuss the nutritional and growth implications of exclusion diets
3. Explore the nutrition conversation



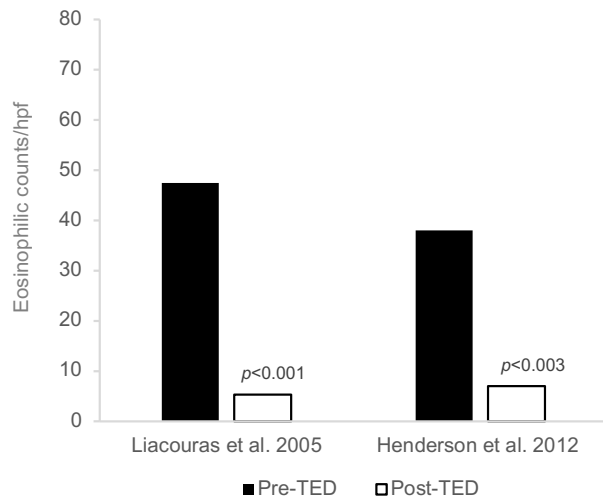


Dietary approaches for the management of EoE

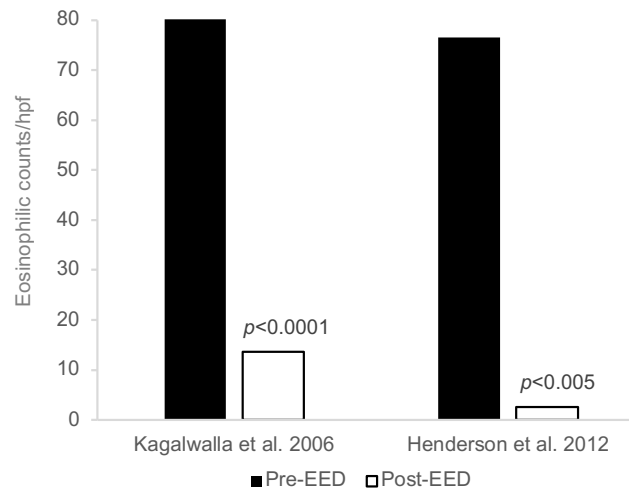
Elimination Diets

Eosinophil counts before and after intervention

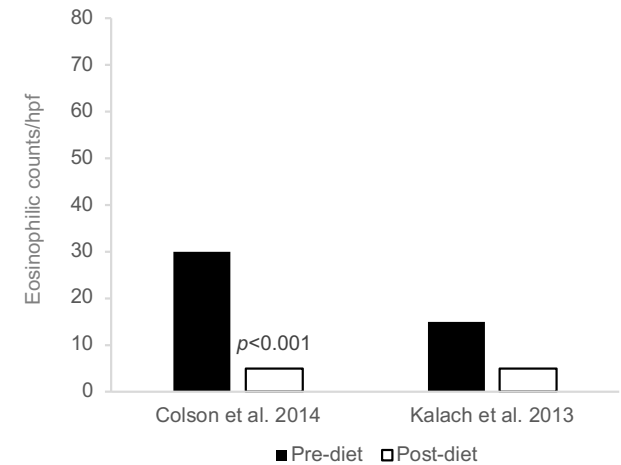
Targeted Elimination Diet



Empirical Elimination Diet

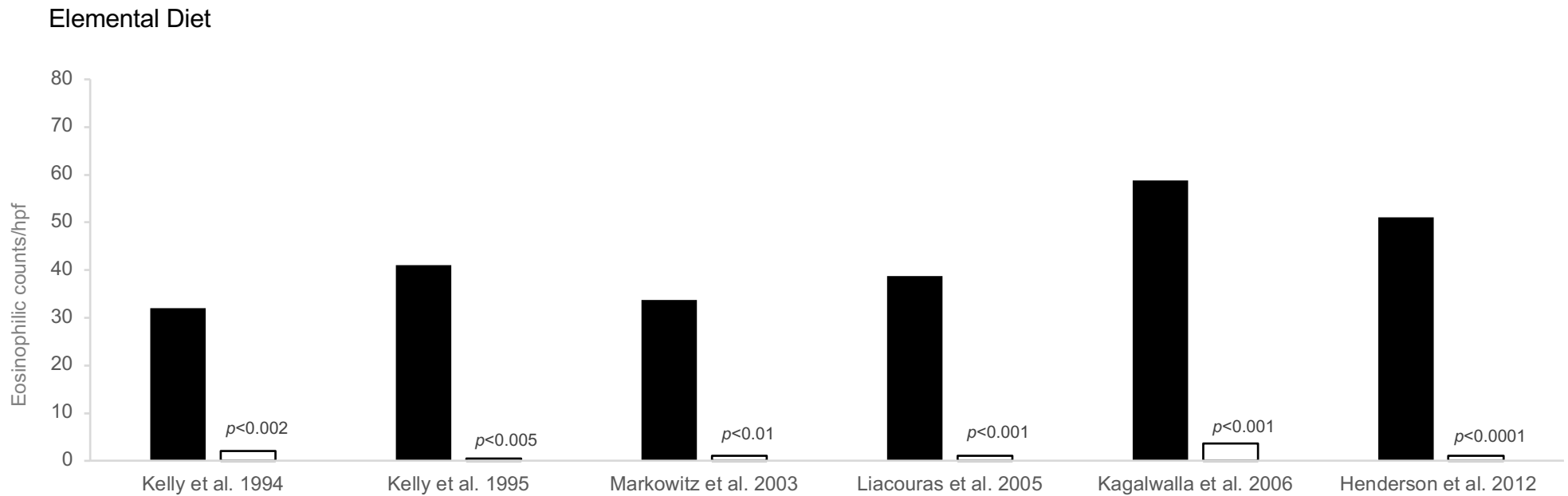


Combined Intervention
(Targeted Elimination Diet, Empirical Elimination Diet and Elemental Diet)



Elemental Diets

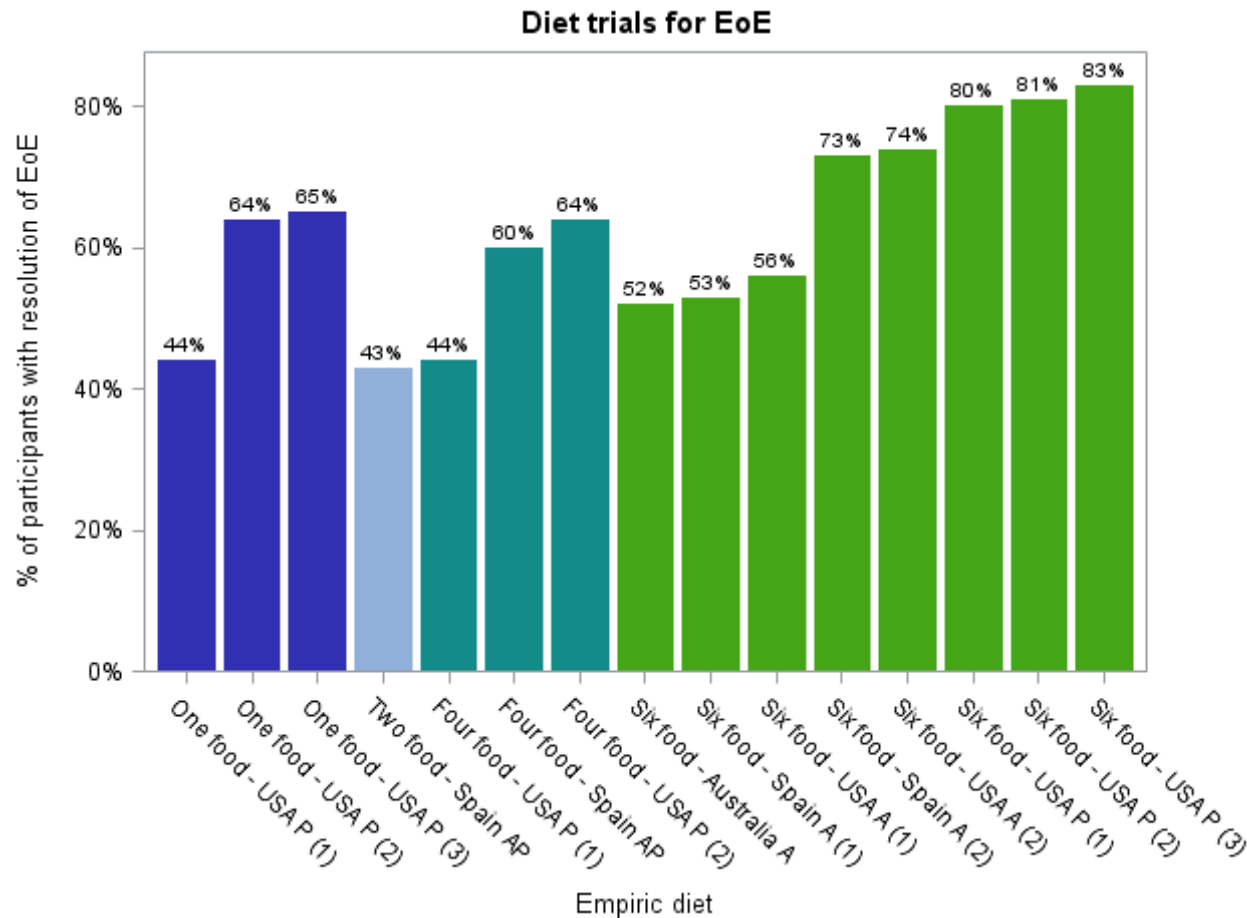
Eosinophil counts before and after intervention



What percentage of children are likely to improve on a one food exclusion diet?

1. 40 – 60%
2. >80%
3. < 10%
4. 10 – 25%
5. > 90%

Efficacy of Diets in Adults vs. Children



Why is the Data so Confusing?

	Molina-Infante 2017 Spain Adults	Molina-Infante 2014 Spain Adults	Lucendo 2012	Kagalwalla 2017 USA Pediatric	CEGIR study 2019
Milk	All dairy products (either goat's or sheep's milk can cross-react with cow's milk)	Mammalian milk	Milk	Milk	Milk
Egg	Egg	Egg	Egg	Egg	Egg
Wheat	All gluten-containing grains (cross-reactive with wheat, including barley, rye, and oats)	Wheat/gluten-containing grains	Cereals (wheat, rice, corn)	Wheat	Wheat
Soy	Legumes, including soy, lentils, chickpeas, peas, beans, and peanuts	Soy/legumes	Legumes/peanuts, and soy	Soy	Soy
Nuts	All kind of nuts	NA	Nuts	NA	NA
Seafood	Fish and seafood	NA	Fish/seafood	NA	NA
Other allergens?	Food allergens known to cause oral allergy syndrome symptoms were avoided already by patients before enrollment	No mention	No mention	No mention	NA
May contain	Patients were also advised to avoid processed foods because of the high likelihood of containing wheat or milk traces, including processed meats (eg, sausages and hamburgers), soups, sauces, pizza, mashed potato, and instant rice	No mention	No mention	No mention	NA

Cianferoni et al. 2019

Foods Triggering EoE

Causative foods From six food avoidance diets				Causative foods four food avoidance diets	Causative foods From elemental diets
USA				USA	USA
Adult ^{43,68}		Pediatric ^{34,59,115}		Pediatric ⁷⁰	Pediatric ^{42,75}
Wheat (60%)	Milk (44%)	Milk (65%)	Milk (74%)	Milk (85%)	Cow milk (70%)
Milk (50%)	Egg (44%)	Egg (40%)	Wheat (26%)	Egg (35%)	Soy protein (40%)
Soy (10%)	Wheat (22%)	Wheat (37%)	Eggs (17%)	Wheat (33%)	Wheat (20%)
Nuts (10%)	Shellfish (11%)	Soy (38%)	Soy (10%)	Soy (19%)	Peanut (20%)
Egg (5%)	Nuts (11%)		Peanut (6%)		Egg (10%)
					Beef (10%)
					Chicken (9%)
Spain ³⁷ —adult				Spain ⁵³ —adult	Spain ⁶⁰ —pediatric
Milk (62%)		Milk (64%)		Milk (50%)	Legumes (n = 1)
Wheat (29%)		Wheat (28%)		Egg (36%)	
Egg (26%)		Egg (21%)		Wheat (31%)	
Legumes (24%)		Legumes (7%)		Legumes (18%)	
Fish/Seafood (19%)					
Nuts (17%)					
Australia ⁶⁹ —adult				Netherlands ¹¹⁶ —adult	
Wheat/gluten (43%)				Milk:	
Milk (39%)				n = 3 (17.6%) based on	
Egg (35%)				histology; n = 2 (11.8%)	
				based on symptoms	
				Successive introduction of	
				egg, nuts and/or seeds and	
				wheat n = 3 (17.6%) based	
				on endoscopy	
				Unable to identify food	
				n = 3 (17.6%)	

#1
MILK

10

#1
MILK

Which Dietary Treatment?

Dietary Treatment	Advantages	Disadvantages
Elemental diet	<ul style="list-style-type: none"> • Highly effective/rapid response • No testing • Easy instructions • Low risk of dietary errors 	<ul style="list-style-type: none"> • Social isolation • Expense • Poor adherence • Not a long term solution • Extended time normalize diet
Empiric elimination	<ul style="list-style-type: none"> • Removal of specific foods • No testing • More rapid normalization of diet 	<ul style="list-style-type: none"> • Variability in response • Risk of accidental ingestion of eliminated allergens • High need for dietary education
Skin Testing-directed diets	<ul style="list-style-type: none"> • Removal of specific foods based on testing • More rapid normalization of diet 	<ul style="list-style-type: none"> • High variability in response • Risk of accidental ingestion of eliminated allergens • High need for dietary education • Lack of standardized testing protocols

Groetch M, et al. *J Allergy Clin Immunol Pract.* 2013;1(4):323-31.
 Arias A, et al. *Gastroenterology.* 2014;146(7):1639-48.

Allergens don't exist in isolation. Eating more or less of an allergen, comes with nutritional consequences which could have immunomodulatory effects



THE MIGHTY PEANUT



Nutrition Facts

Serving Size 77 g

Amount Per Serving

Calories 130 Calories from Fat 79

% Daily Value*

Total Fat 8.8g **13%**

Saturated Fat 2.6g **13%**

Trans Fat 0.0g

Cholesterol 0mg **0%**

Sodium 69mg **3%**

Potassium 109mg **3%**

Total Carbohydrates 9.9g **3%**

Dietary Fiber 1.8g **7%**

Sugars 4.8g

Protein 4.9g

Vitamin A 2%

Vitamin C 4%

Calcium 7%

Iron 11%

The most likely nutrient deficiency in an individual excluding milk and seafood is:

1. Magnesium
2. Omega-3 fatty acid
3. Iodine
4. Zinc
5. Fat

These Foods Come at a Nutritional Cost

TABLE 4 Nutrients in major food allergens and appropriate substitutes on 6-food elimination diet

Food	Nutrients	Substitutions
Milk	Protein, calcium, phosphorus, vitamin D, riboflavin, pantothenic acid, vitamin B12. Iodine	Meats, legumes, whole grains, nuts, fortified foods and enriched beverages (dairy, soy, tree nut-free), fortified orange juice
Wheat	Iron, niacin, riboflavin, thiamin, folate, fibre	Fortified foods, fruits, vegetables, other fortified grains (barley, oat, corn, rice, rye). Alternative grains such as buckwheat, quinoa, millet, teff, amaranth
Egg	Protein, choline, vitamin A, riboflavin, pantothenic acid, biotin, selenium.	Meats, legumes, whole grains (gluten-free) or enriched gluten-free grains
Soy	Protein, thiamin, riboflavin, B6 folate, calcium, phosphorus, magnesium, iron, zinc.	Meats, other legumes, enriched beverages (as above)
Peanuts/tree nuts	Protein, selenium, zinc, manganese, magnesium, niacin, phosphorus, vitamin E, B6, alpha linolenic acid, and linoleic acid	Meats, seeds, seed butters, legumes, vegetable oils
Fish/shellfish	Protein, iodine, zinc, phosphorus, selenium, niacin Fatty fish: vitamin A, vitamin D, omega-3 fatty acids	Meats, legumes, seeds, vegetable oils (canola/flax), enriched beverages as above

Nutritional Inadequacy in Children with EoE

TABLE 3. Nutritional assessments based on food diaries and laboratory testing

Mean intake (standard deviation)			
	GERD (N = 15)	EoE (N = 33)	P
Total, kcal · kg ⁻¹ · day ⁻¹	78 (25)	76 (19)	0.77
Protein, g · kg ⁻¹ · day ⁻¹	2.79 (1.0)	2.59 (0.9)	0.48
Carbohydrate, g · kg ⁻¹ · day ⁻¹	10.9 (3.7)	10.8 (3.1)	0.94
Fat, g · kg ⁻¹ · day ⁻¹	2.8 (1.0)	2.6 (0.9)	0.44
Vitamin D, IU/day	73* (73)	112* (128)	0.19
Calcium, mg/day	786 (441)	606† (266)	0.16
Iron, mg/day	9.8 (6.5)	10.9 (5.4)	0.54
Mean serum laboratory values (standard deviation)			
	GERD	EoE	P
Ferritin, ng/mL	25.0 (15.4)	34.0 (29.9)	0.06
Prealbumin, mg/dL	20.8 (4.0)	19.7 (3.7)	0.19
PTH, pg/mL	41.5 (23.5)	36.6 (17.2)	0.28
Vitamin D, ng/mL	30.4 (10.4)	30.3 (8.8)	0.98

EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease; PTH = parathyroid hormone. Normal values: ferritin >20 ng/mL; prealbumin >18 mg/dL; PTH: 11.5–78.4 pg/mL, Vitamin D >30 ng/mL.

*Below the recommended daily intake of 600 IU/day.

†Below the recommended daily intake of 700–1000 mg/day.

If a child still has symptoms, particularly feeding issues..

Taking more foods are likely to resolve the feeding issues

1. True
2. False

Symptoms vs. Eosinophil resolution

Elemental diet - children

Markowitz et al, AJG, 2003

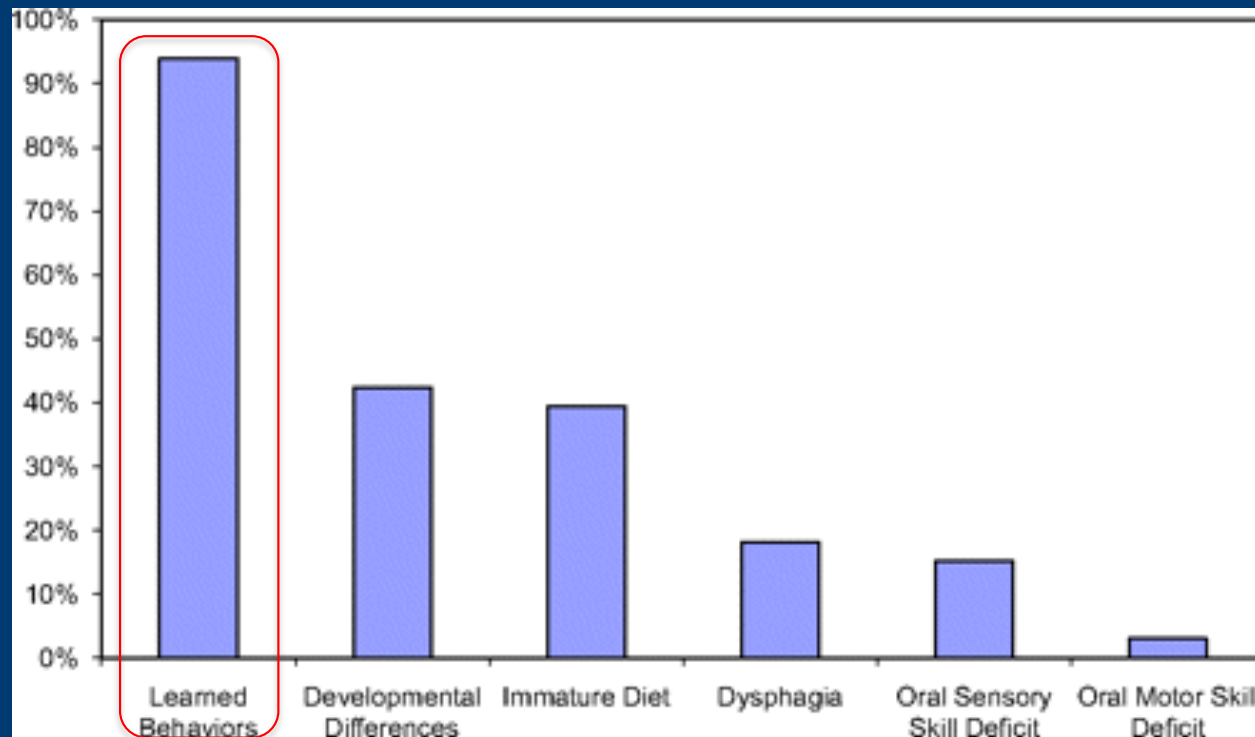
- 51 children with EoE
- Commercial formula (free AAs, corn syrup solids, and medium chain triglycerides); patients also allowed either grapes or apples; 4 week rx period

	Pre-diet	Post-diet	P
Eos/hpf	34 ± 10	1 ± 0.6	< 0.01
Abdominal pain	40	2	< 0.01
Vomiting	36	1	< 0.01
Heartburn	27	2	< 0.01
Waterbrash	11	1	< 0.01

- Average time to improvement: 9 days



Feeding Behavior in Children with EoE



Mukkada 2010; Furuta 2018

It can work both ways

1FED vs 4FED?



First reported RCT for dietary therapy

- Children (6 to 17 yrs) with EoE were randomized to 1FED (n=38) and 4FED (n=25) over 10 sites
- Primary endpoint: PEESS v2.0
 - Change in total symptom score was greater in 4FED (-25.0 points) compared with 1FED (-14.3 points) (p=0.04).
- Histologic response (<15 eos/hpf)
 - 4FED 41% vs 1FED 44% (p=1.0)
- QoL improved in 1FED > 4FED

Kliewer, Rothenberg et al, DDW, 2019

But that is why a nutritional consultation is so important!

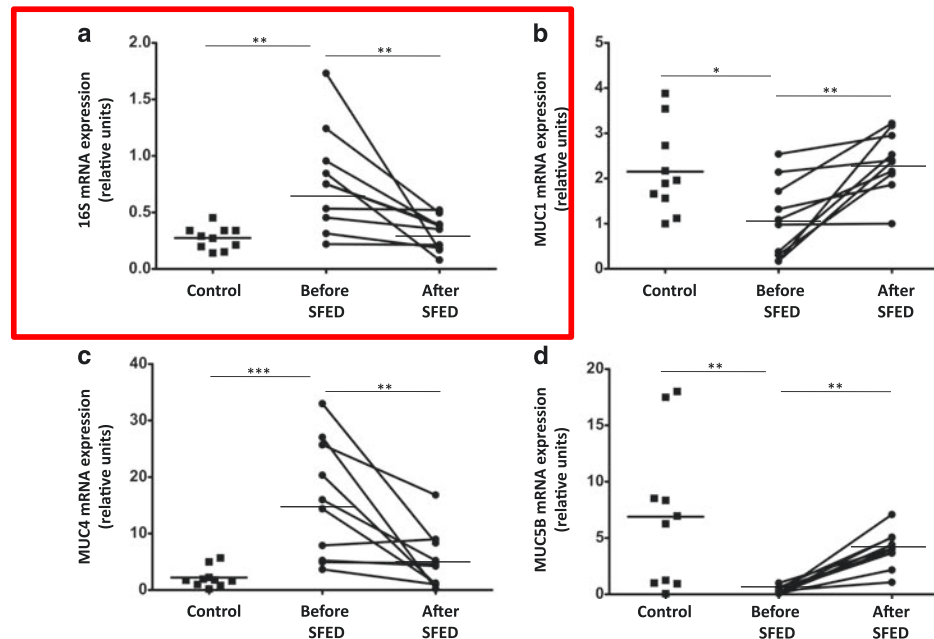
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Egg	Protein, choline, vitamin A, riboflavin, pantothenic acid, biotin, selenium.	Meats, legumes, whole grains (gluten-free) or enriched gluten-free grains
Soy	Protein, thiamin, riboflavin, B6 folate, calcium, phosphorus, magnesium, iron, zinc.	Meats, other legumes, enriched beverages (as above)
Peanuts/tree nuts	Protein, selenium, zinc, manganese, magnesium, niacin, phosphorus, vitamin E, B6, alpha linolenic acid, and linoleic acid	Meats, seeds, seed butters, legumes, vegetable oils
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Foods/Nutrients and EoE...

Positive (reduced counts)	Negative (increased counts)
Rice/Pasta	Phosphorous
Iron	Vitamin B12
Fiber	Meat
Soy	Sunflower Oil
Magnesium	Stir Fry Oil
Vegetables	Added Fat/Total Fat
Yogurt/Buttermilk	

EoE – Changes in microbial load before and after six food exclusion diet



- Esophageal TLR-dependent signaling pathways in EoE support the potential implication of microbiota and the innate immune system in the pathogenesis of this disease.

Fig. 2 Bacterial load and mucin expression in the esophagus of EoE patients. a Total microbiota load (determined as 16s gene expression) and b–d mRNA expression (in relative units) of Muc1, Muc4, and Muc5B mucins were determined in esophagus biopsies from patients before and after six-food elimination diet (SFED) treatment, and healthy controls. Paired *t*-test compared EoE patients before and after SFED, while EoE patients (both before and after SFED) were compared with the control population by non-paired *t*-test. Horizontal bars indicate mean values (**p* < 0.05; ***p* < 0.01; ****p* < 0.001)

Diet Quality

Even nutrients don't exist in isolation

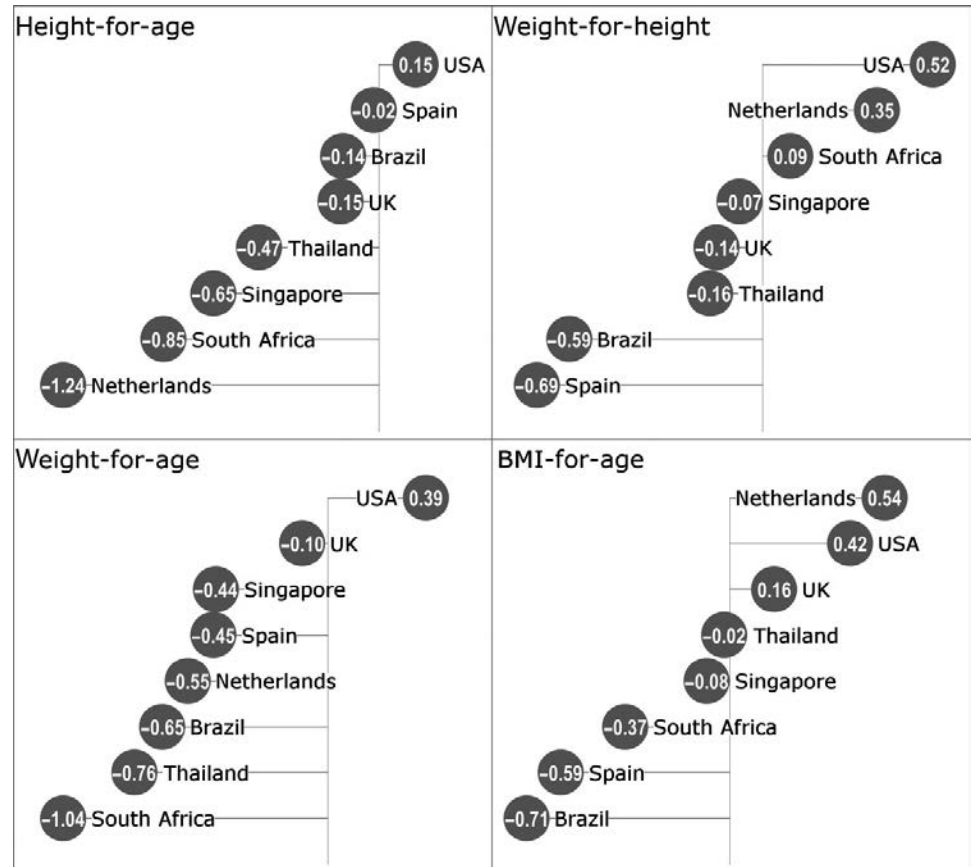
	Participant 1		Participant 3	
	Baseline	Six-Food Elimination Diet	Baseline	Six-Food Elimination Diet
Deficiencies	Fiber - 65% Calcium - 74% Magnesium - 64% Iron - 50% Selenium - 33% Iodine - 31% Vitamin K - 21%	Energy - 72% Carbohydrate - 62% Fiber - 51% Omega 3 - 75% Calcium - 54% Iron - 66% Iodine - 27% Vitamin K - 37%	Carbohydrate - 81% Fiber - 61% Omega 3 - 61% Calcium - 85% Selenium - 75% Thiamin - 24%	Energy - 73% Carbohydrate - 65% Fiber - 76% Selenium - 39% Iodine - 25% Vitamin K - 81% Riboflavin - 54% Folic acid - 82%
Excess	Fat - 139% Saturates - 175%	Sugar - 136%		Sugar - 125%
Fruit & Vegetables	Low	Moderate	Moderate	Moderate
Convenience Foods	High	Low	High	High
Processed Meat	High	Low	Moderate	Moderate
Alcohol	Moderate	Moderate	High	Moderate

Hunter and Venter presented EAACI 2018

Growth in Children with Food Allergies

12 International Centers

Children with food allergies are underweight, normal weight and overweight...and growth is often impaired



Growth and EoE – Mainly Elemental Formulas

Study	Growth Outcome
Kelly et al. 1995	'Poor weight gain had resolved'
Al-Hussaini et al. 2013	Corrected growth after 2 months of therapy
Liacouras et al. 2005	'No significant weight loss', 'or alteration of growth parameters (height, weight, head circumference)' in those on dietary therapy, however reported that n=5 patients considered to have failure to thrive had a significant increase in weight after receiving amino acid-based formula (AAF)
Kagalwalla et al. 2005	The children with failure to thrive on AAF (n=14) mean weight gain was 1.03kg (range 0.1-2.1kg), and of children identified with failure to thrive on the EED (n=5), mean weight gain was 1.32kg (range 0.9-2kg), after six weeks of intervention
Colson et al. 2014	(n=59) diet height and weight gains were significant after 5 months, but weight-for-height z-scores did not change

Getting Practical



The Basics of Elimination

- 1 Food label terminology
- 2 Hidden allergens in foods
- 3 Suitable replacement of foods
- 4 Ensuring nutritional adequacy



The Dietary Consultation Should Include:

TABLE 6 Allergen-free diet education

Targets	All caregivers (parents, babysitters, grandparents etc.) Patients (if mature enough)
Modalities	Focus on what children can eat (vs what they cannot). Give appropriate resources for additional information
Written Resources	Allergen-free sample menus Lists of allergen-free foods Food allergy cookbooks Online resources Food Allergy Research and
Online resources	Food Allergy Research and Education (FARE) The American Partnership for Eosinophilic Disorders (www.apfed.org)
Other	Acknowledge impact on family life Referrals for psychological counselling if patients experience ongoing sadness or anger regarding their treatment plan

Elemental Diet

Can I only have formula?

- The following treats may be eaten for social reasons but they do not provide any nutrition
 - Candy (patients must read product labels each and every time)
 - Dum Dum Lollipops (artificial flavors only)
 - Rock Candy
 - Charms Cotton Candy
 - Smarties Brand Candies (Sugar-based not milk-chocolate version)
 - Smarties Brand Candy Canes
 - Fun Dip
 - Pixie Sticks



Big kids vs. monkeys

Vanilla Almond Coconut Almond Walnut

1g protein and 90 kcal

Chocolate
Single-Serve

Important textures



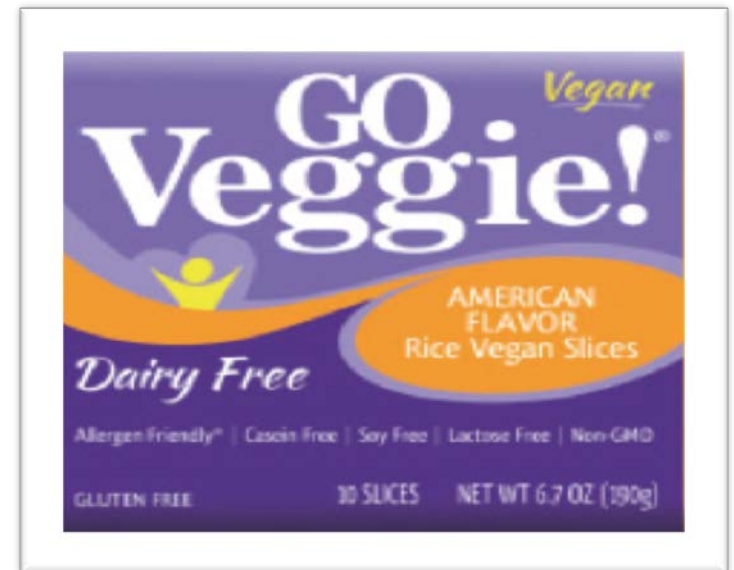
Bringing a bit or normality



“What’s more is that it’s a terrific solution if you are concerned about peanut allergies. I was thrilled to find this product when Celia was a baby, so I had a peanut-free alternative to offer her without worrying about allergies.”



On the wild (teenage side)



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Give advice focused on meals/snacks

Monitoring is a Must

Close monitoring is required in patients following extensive dietary elimination

- Periodic repeat endoscopy is necessary to determine effectiveness of food elimination and to determine implicated food triggers
- Periodic dietary assessment to ensure adequate nutrition intake (3-day food diary)
- Follow-up nutrition laboratory tests as indicated
- Periodic reassessment of growth- both height and length/weight
- Periodic reassessment of feeding skills and food acceptance

2-4-6?

Which elimination diet?

1. Milk
2. Milk and Wheat (2 food)
3. Milk, Wheat, Soy, Egg (4 food)
4. Milk, Wheat, Soy, Egg, Seafood, Nuts (6 food)
5. Depends on age
6. Depends on age and country

Less restrictive options? 2-4-6!

Molina-Infante et al

- N=124 from 13 Spanish and 1 Italian centers
 - “TFGED” (dairy; gluten cereals) x 6 wks
 - “FFGED” (+ egg; legume) x 6 wks
 - “SFGED” (+ nuts; seafood) x 6 wks
- Results:
 - 43% response (<15 eos/hpf) for TFGED
 - 60% response for FFGED
 - 79% response with SFGED
- Could reduce EGDs and time by 20-30%

JACI, 2017

What do mothers want?

Helps me to protect my child and keep them healthy

And when she says well actually she's getting enough from her fruit, she's getting enough from her veg, actually that's okay...I get reassurance."

Teaches me to be an expert

"It was really nice to say get information from her about the chocolate factories...which has then helped [child] with his, his nut allergy."

Provides me with hints and tips to provide some sort of normality

"I sort of think you've got to manage it, you know, for the children to have a proper, a rounded life...it's a sort of balancing act all the time and um, it's about being realistic isn't it?"

Helps to promote my child's independence

"...they give you that little biscuit, and this was just at the age where she wanted to challenge me with things..."

Advocates and helping me fight my child's corner

Provides me with emotional support

"I found, I think one thing [the dietitian] really sort of made me think was „don't stress about it" which I thought was really good because...He's just stopped eating everything other than what he wants to eat which is very minimal, so I, and I think that's nice with [the dietitian] saying „just try a little bit of that, try a little bit of this, don't force it"...and so, now I'm just thinking don't worry about it." (Lucy, son age 7)

J Allergy Clin Immunol Pract. 2017 Mar - Apr;5(2):312-324.e29. doi: 10.1016/j.jaip.2016.12.026.

FULL-TEXT ARTICLE

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

Groetch M¹, Venter C², Skypala I³, Vlieg-Boerstra B⁴, Grimshaw K⁵, Durban R⁶, Cassin A⁷, Henry M⁸, Kliwer K², Kabbash L⁹, Atkins D¹⁰, Nowak-Węgrzyn A¹¹, Holbreich M¹², Chehade M¹³; Eosinophilic Gastrointestinal Disorders Committee of the American Academy of Allergy, Asthma and Immunology.



THANK YOU!



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