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Efficacy of Amino Acid-based diet on Histologic Remission and Restoring Esophageal Mucosal Integrity in Adult Patients with Eosinophilic Esophagitis (EoE)

Dr. Marijn Warners
June 23, 2016



Webinar Presenter:





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Case: help, my food gets stuck



Details:

- ♂ 38 years old
- Symptoms:
 - Acute obstruction after eating chicken
 - Dysphagia for solids
 - Unable to swallow saliva
- Background:
 - Repetitive food impactions
 - Allergic rhinitis



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Case: help, my food gets stuck



Additional findings:

- Clinical Symptoms
 - Dysphagia
 - Food impaction
- Endoscopy
 - Concentric rings
 - Edema
 - Food impaction
- Biopsies
 - Pronounced eosinophilia
 - Eosinophilic micro abscesses



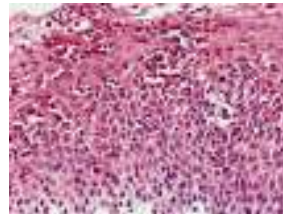
Differential Diagnosis: Eosinophilic Esophagitis

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Eosinophilic Esophagitis (EoE)

Diagnosis based on consensus criteria^{1,2}:

- Esophageal dysfunction
- Eosinophilia: ≥ 15 eosinophils / High Power Field (HPF)
- PPI trial failure
- Exclusion of other causes: Crohn's disease, GERD, infections



1) Liacouras et al. J Allergy Clin Immunol. 2011. 2) Dellon et al. Am J Gastroenterol. 2013



Epidemiology of EoE

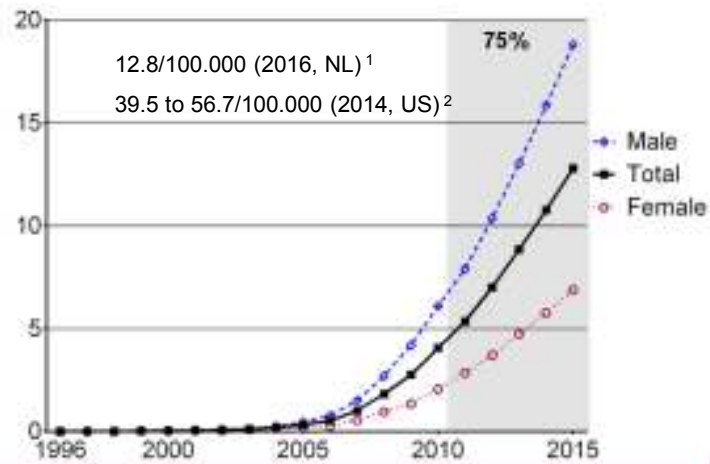
- First cases of EoE described in 1960-1970's:
 - Multiple esophageal rings, but no compelling evidence of GERD
- Initial description of EoE as a distinct entity by:
 - Atwood 1993¹
 - Straumann 1994²
- New disease
 - Awareness
 - Accelerating incidence and prevalence
- Case reports from USA, Europe, Australia, New Zealand, China, Korea

1) Atwood et al. Digestive Diseases and Sciences. 1993. 2) Straumann et al. Schweiz Med Wochenschr. 1994.



Prevalence of EoE

Per 100 000 / year



1) van Rhijn et al. Neurogastroenterol Motil. 2012, and unpublished data Warners et al, 2) Dellon et al. Clin Gastroenterol Hepatol. 2014.



Endoscopic Signs



Edema



Rings



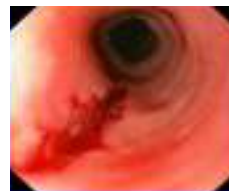
Exudates



Furrows



Stricture



Crepe paper esophagus

1) Hirano et al. Gut. 2013



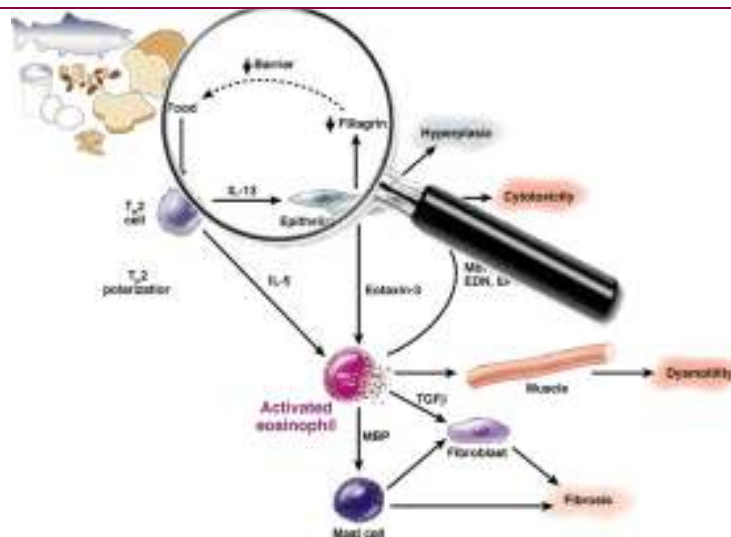
EoE Pathogenesis

- Immune mediated chronic allergic disease of the esophagus
- Genetic component
 - Five susceptibility loci have been identified ¹
 - Familial clustering of EoE ²
- High prevalence of other atopic diseases and mutual suspected loci ³
- Role of (food) allergens
 - Remission after elemental diet ⁴
 - Seasonal variation ³

1) Rothenberg et al. 2010. Nat Genet. 2) Alexander et al. J Allergy Clin Immunol. 2014. 3) Sleiman et al. Best Pract Res Clin Gastroenterol. 2015. 4) Kelly et al. 1995. Gastroenterol.



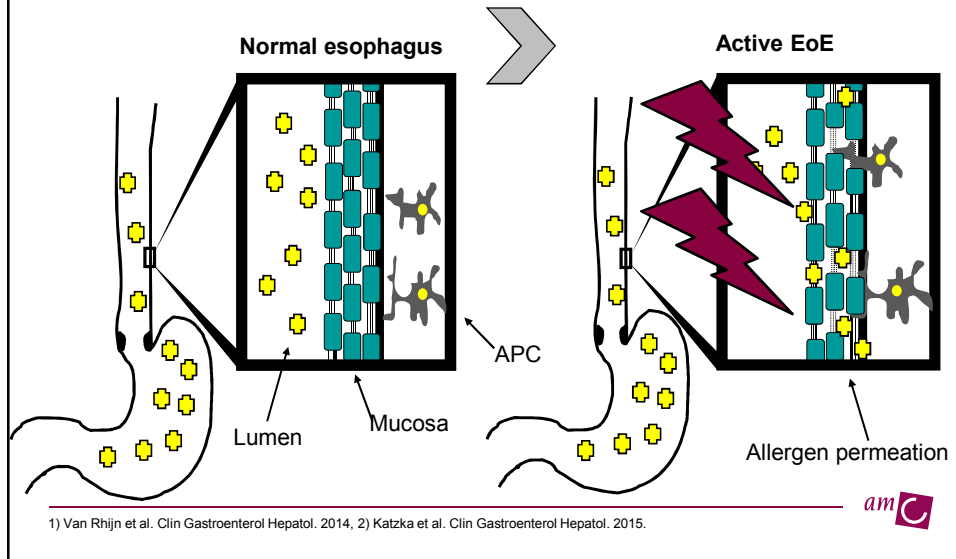
EoE Pathogenesis



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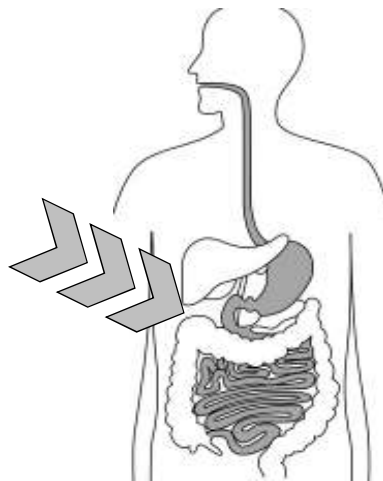
Esophageal Mucosal Integrity in EoE



Is the esophagus the sole site of allergen uptake?

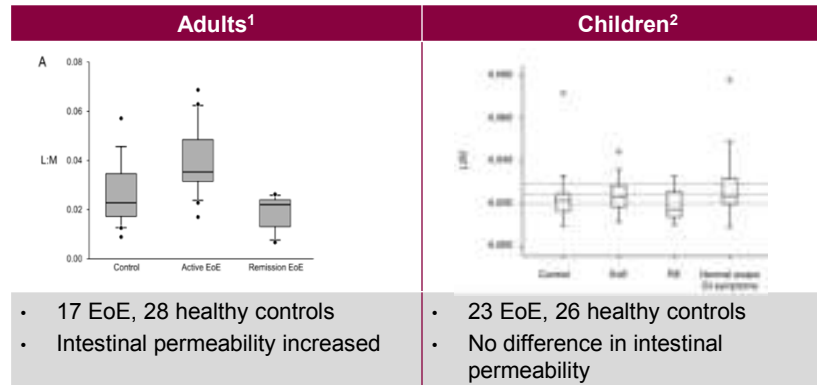
Increased small bowel permeability:

- Atopic dermatitis¹
- Food allergy²
- Eosinophilic esophagitis³



1) Miraglia et al. J Clin Gastroenterol. 2004. 2) Bischoff et al. BMV. Gastroenterol. 2013. 3) Katzka et al. Gut. 2015

Intestinal Permeability in EoE



1) Katzka et al. Gut. 2015. 2) Leung et al. Pediatr Gastroenterol Nutr. 2015.



Management of EoE: (D³)

1. Dietary elimination

- Improves symptoms and promotes histologic remission
- Permits identification of the disease triggering allergen
- Requires upfront time investment
- Is more cost effective than topical corticosteroids¹

2. Drugs: (Topical) Corticosteroids

- Improves symptoms and reduces inflammation
- Side-effects
- Relapses after cessation
- More costly than dietary elimination over entire disease course¹

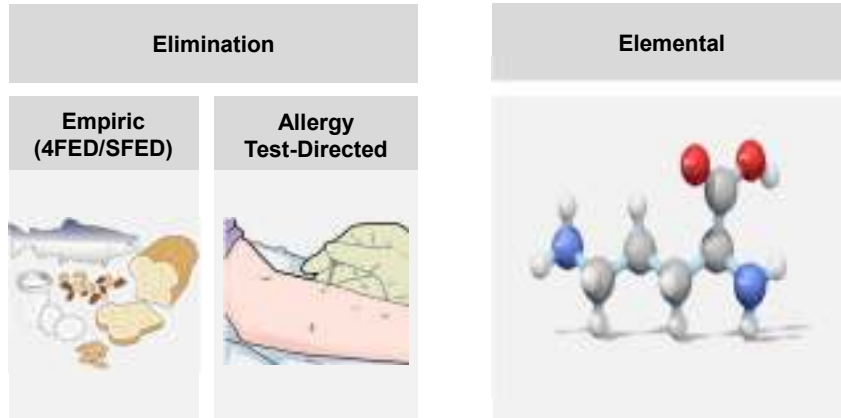
3. Dilatation

- Improves symptoms
- Does not influence the underlying inflammation
- Risk of perforation

1) Cotton et al. Gastroenterology . 2015..



Dietary Management of EoE



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Dietary Management of EoE

Diet	Response	N	Children	N	Adult	N
All	66.3 %	47	67.2 %	36	63.6 %	10
Elemental	90.8 %	13	90.4 %	12	94.4 %	1 ¹
SFED	72.1 %	7	72.8 %	4	71.3 %	2
Test-directed	45.5 %	14	47.9 %	12	32.2 %	2

1) Arias et al. Am. J. Gastroenterol. 2014.

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Elemental diet



Cons

- Formula fatigue
- Lengthy food reintroduction process
- Nasogastric feeding



Pros

- Highly effective, rapid remission
- Ready-to-drink formula
- Drug-free, long-term
- State mandates for formula coverage



Effectiveness of an amino acid-based diet in the management of adult patients with EoE

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Academic Medical Center, Amsterdam, the Netherlands
Nutricia Research, Advanced Medical Nutrition, Utrecht, the Netherlands

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Study Aim

To evaluate the effect of an amino acid-based diet (Neocate™, Nutricia) in adult EoE patients on:

- 1) Eosinophilic inflammation
 - Symptoms
 - Endoscopic features
- 2) Esophageal and duodenal mucosal integrity
- 3) Diet adherence

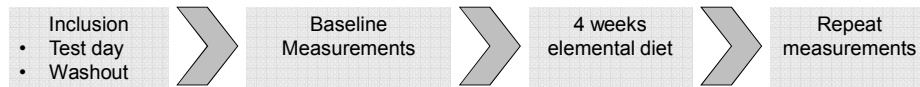


Methods

- **Design**
 - Prospective intervention study
 - Academic Medical Center Amsterdam, the Netherlands
- **Inclusion**
 - Adult patients (>18 years) with active EoE (>15 eosinophils/hpf)
 - 8 healthy controls used to compare esophageal and small bowel integrity
- **Measurements**
 - Questionnaires: dysphagia, reflux related symptoms and quality of life
 - Histology
 - Electrical tissue impedance spectroscopy (ETIS)
 - Trans Epithelial Resistance (TER)
 - Transepithelial molecule flux
 - Dual sugar absorption test lactulose : mannitol ratio (L/M)
 - Gene expression analysis of IL5, IL13, Eotaxin-3 (CCL26) and TSLP by qPCR



Study Outline



Intervention: Four weeks elemental diet

- Dietary counseling by Dietitian:
 - Calculation daily formula consumption (BMI and physical activity level)
 - 24 hour elemental diet test day (prior to study entry)
 - Weekly consult to evaluate weight loss, side effects and patients' motivation
- Complete nutrition:
 - 7-13 drink boxes (237 mL each)
 - Daily patient adherence diary
- Amino acid-based formula:
 - Two flavors offered
- Chewing gum was allowed to maintain:
 - Dental health
 - Oral-motor stimulation



Electrical Tissue Impedance Spectroscopy (ETIS)

- Indicator for mucosal integrity in vivo
- Measures impedance to the injected current in the esophagus
 - Extracellular impedance ($\Omega \bullet m$)



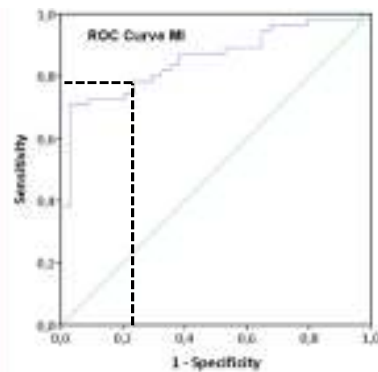
1) Lundin et al. Dis Esophagus. 2011, 2) Weijenborg et al. Neurogastroenterol Motil. 2013



ETIS is a marker for disease activity

Mucosal impedance ($\Omega \bullet m$)

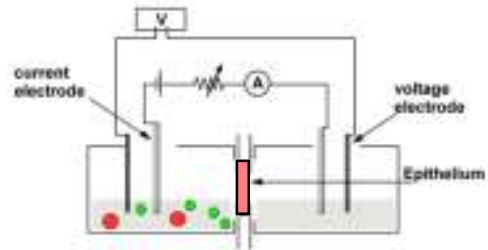
AUC	.86 (.78 – .93)
Sensitivity	78 (65 – 88)
Specificity	76 (58 – 89)
NPV	68 (52 – 82)
PPV	84 (71 – 93)
Diagnostic accuracy	78 %



1) Wamers et al. DDW 2016.



Ussing Chamber: TER

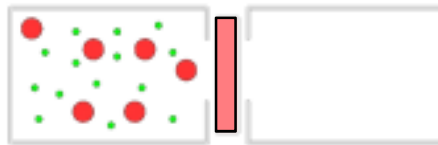


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Ussing Chamber: Molecule Flux

● 0.3 kDa ➤ Fluorescein

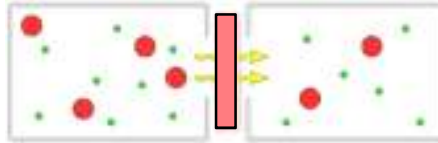
● 40 kDa ➤ Rhodamine (size of food allergens)



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Ussing Chamber: Molecule Flux

- 0.3 kDa ➤ Fluorescein
- 40 kDa ➤ Rhodamine (size of food allergens)



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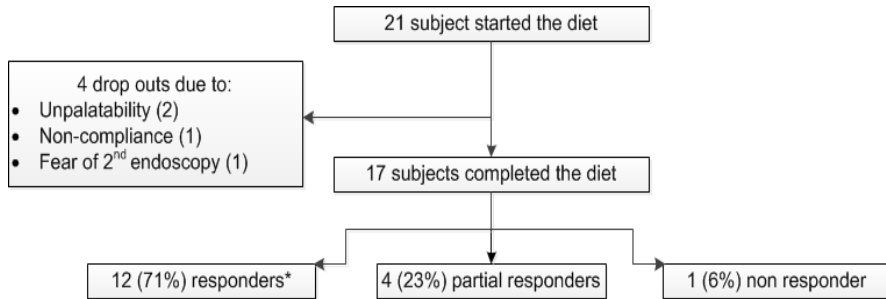
Lactulose Mannitol Test

- Golden standard to measure small intestinal permeability
- Orally administered dual sugar absorption test
- Ratio urinary excretion lactulose   to mannitol 



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Results



* **Responders:** ≤ 15 eosinophils/hpf

** **Partial responders:** decline of baseline peak eosinophil count $\geq 50\%$ but still >15 eosinophils/hpf

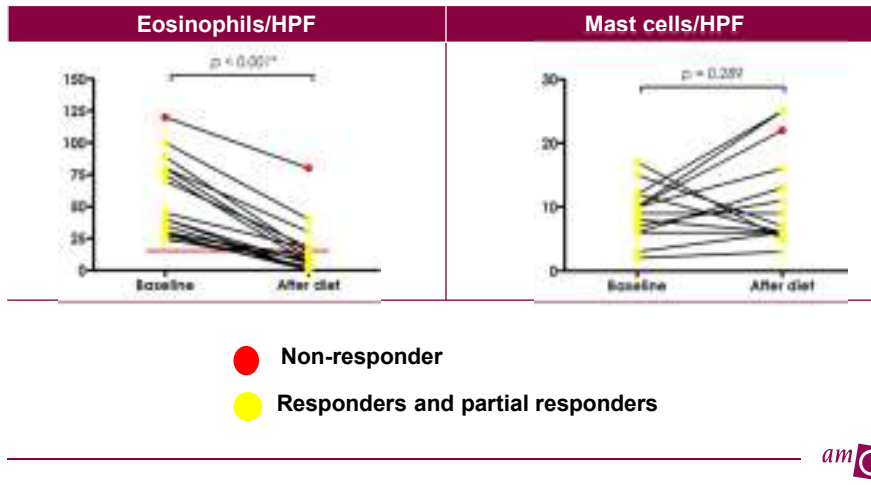


Patient Demographics

Characteristics	
Sex	71% male
Age	47 (30-50)
BMI	24 (22-26)
Race	77% Caucasian
Allergies	71%
Food allergies	47%
Family history allergies	71%
Dysphagia 2-7 times a week	77%



Results: Eosinophilic inflammation

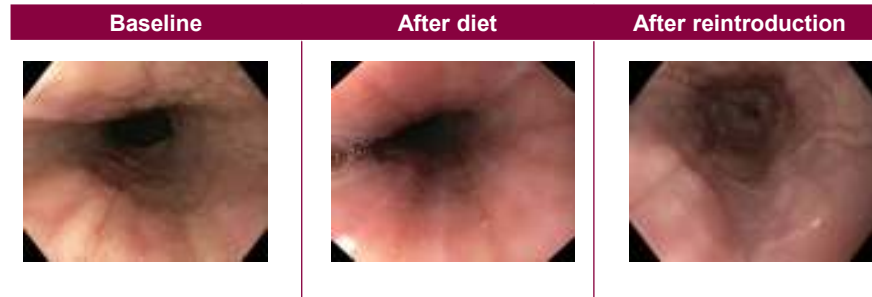


Results: Symptoms and endoscopy

	Baseline	After diet	P-value
	Median	Median	
Symptoms			
Dysphagia score	8	0	<.001
RDQ	18	5	<.001
GI symptoms	19	6	<.001
Endoscopy**			
Signs of EoE	3.5	2.5	.024

RDQ: reflux disease questionnaire; GI: general gastrointestinal symptoms GHP: General Health Perceptive (SF-36 QoL); **Endoscopic Reference Score (EREFS)

Results: Endoscopic signs

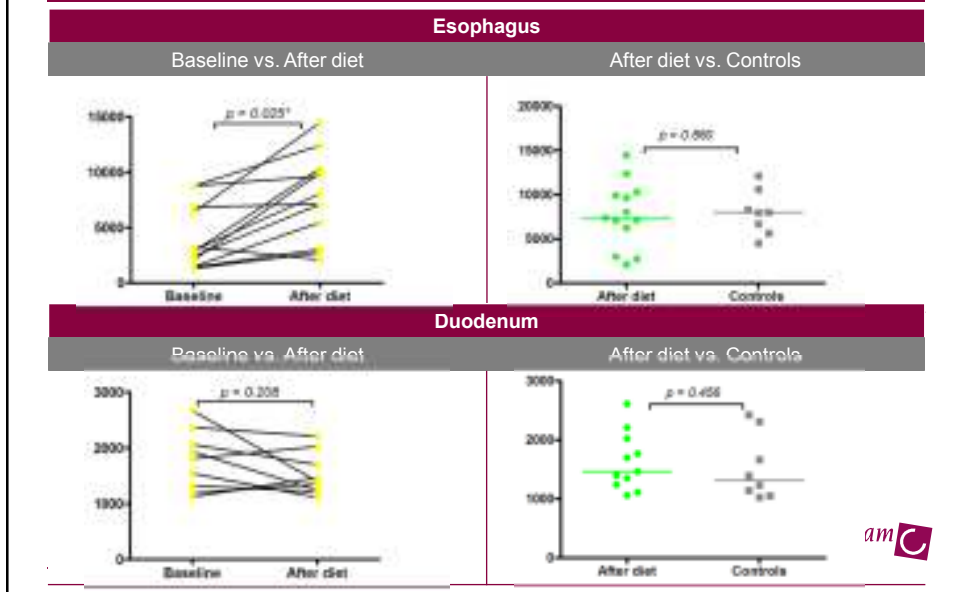



Results: Quality of Life (SF-36)

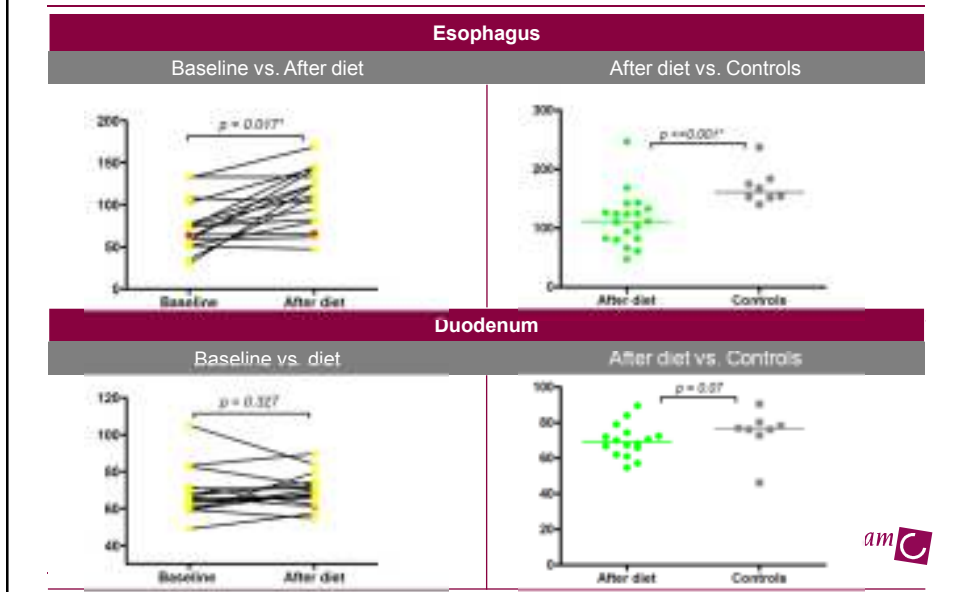
	Baseline	After diet	General population (GP)	Baseline vs diet	GP vs diet
	Mean, sd	Mean, sd	Mean, sd	P-value	P-value
Physical functioning	88.9 (15.6)	91.6 (10.4)	83.2 (22.6)	0.88	0.006
Mental health	76.2 (16.1)	84.0 (12.9)	74.9 (17.4)	0.176	0.044
Social functioning	85.6 (26.4)	74.2 (22.1)	84.2. (22.3)	0.018	0.091



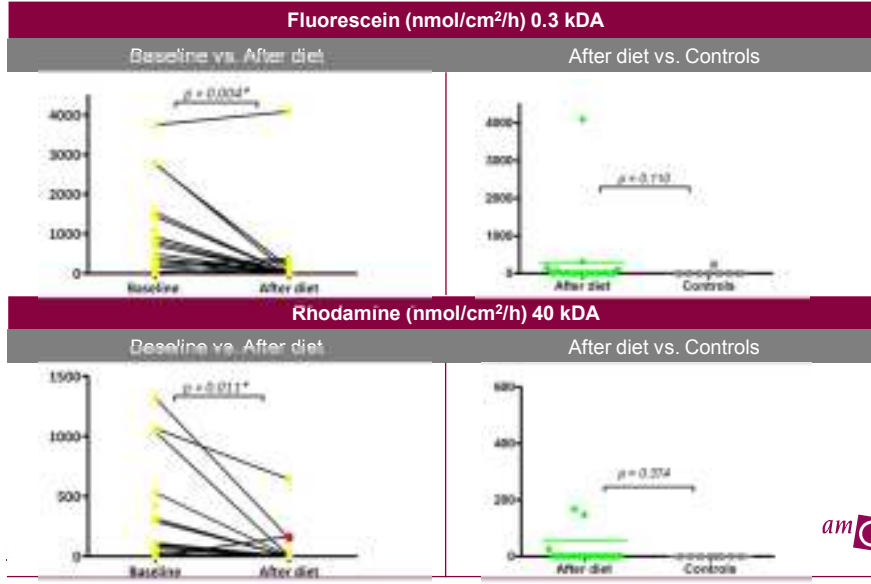
Results: ETIS ($\Omega \cdot m$)



Results: TER ($\Omega \cdot cm^2$)



Results: Esophageal Permeability

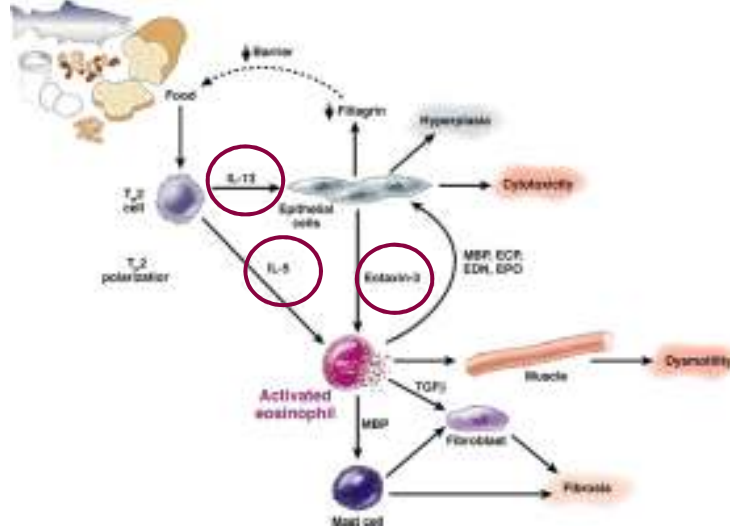


Results: Duodenal Permeability

Duodenum	Baseline, median (IQR)	After diet, median (IQR)	Controls, median (IQR)
Fluorescein (μmol/cm ² /h)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
Rhodamine (μmol/cm ² /h)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
L/M Ratio	.030 (.016 - .083)	.054 (.020 - .158)	.020 (.017 - 0.26)



Inflammatory cytokines



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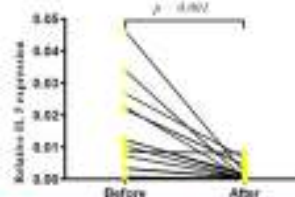
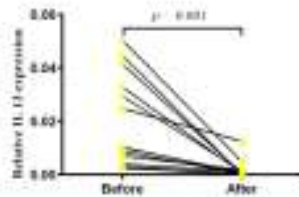


Results: gen expression

Relative gene expression of inflammatory cytokines

IL 13

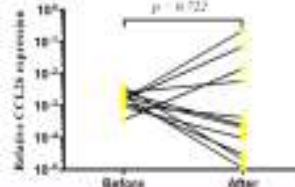
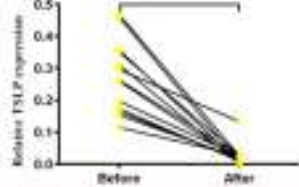
IL 5



Relative gene expression of inflammatory cytokines

TSLP

Eotaxin (CCL26)



Optional Food Reintroduction after Remission

- Schedule for sequential food reintroduction:
 - Starting with egg followed by soy, wheat and milk
- Assessment of sustained effect (surveyed after each food reintroduction):
 - Dysphagia questionnaire
 - Endoscopic evaluation
- If symptoms recurred after reintroduction:
 - Re-elimination offending food
 - Repeat endoscopic evaluation



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Food Reintroduction Results

10/17 (59%) patients completed the food reintroduction phase

Identification of causative allergens:

- Milk (n=5)
 - In 3 patients histopathology confirmed disease recurrence
 - In 2 patients suspected based on symptom recurrence
- Egg (n=1)
- Wheat (n=1)
- Nuts and/or seeds (n=1)
- Unknown (n=2)



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Summary

- 17 out of 21 (81%) patients completed the diet
- 16 out of 17 (94%) patients showed (partial/complete) remission
- Esophageal mucosal integrity restored and reached levels similar to those in healthy controls
- Duodenal mucosal integrity seems not to be affected




Discussion

- Amino acid-based diet is highly effective, with acceptable adult patient adherence
- Our data suggest a favorable role for an amino acid-based diet in clinical practice for adult EoE patients
- Mucosal integrity is restored in the absence of food allergen exposure
- Small intestinal integrity is not impaired in adult EoE patients



<p>Gastroenterology</p> <p>MD. M.J Warners Dr. A.J. Bredenoord Prof. Dr. A. Smout</p>	<p>Nutricia Research</p> <p>Dr. M van Ampting Dr. L Harthoorn</p>
<p>Collaborators</p>	
<p>Emma Children's Hospital</p> <p>Dr. B Vlieg-Boerstra</p>	<p>Pathology</p> <p>Dr. J. Verheij</p>





Question & Answer Session

Nutricia North America would like to thank Dr. Marijn Warners, for her expertise in the development of this presentation. The opinions expressed are those of the presenter and not necessarily reflective of the views of Nutricia North America. Any specific brands mentioned are examples or recommendations from this healthcare professional and, aside from those which specify they are manufactured by Nutricia, are not affiliated with or endorsed by Nutricia.

Thank you. . .
Questions?



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