Nutricia Learning Center

Specialized Nutrition Education – Helping You Help Your Patients

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

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NUTRICIA

Pioneering Nutritional Discoveries

Webinar Presenter:

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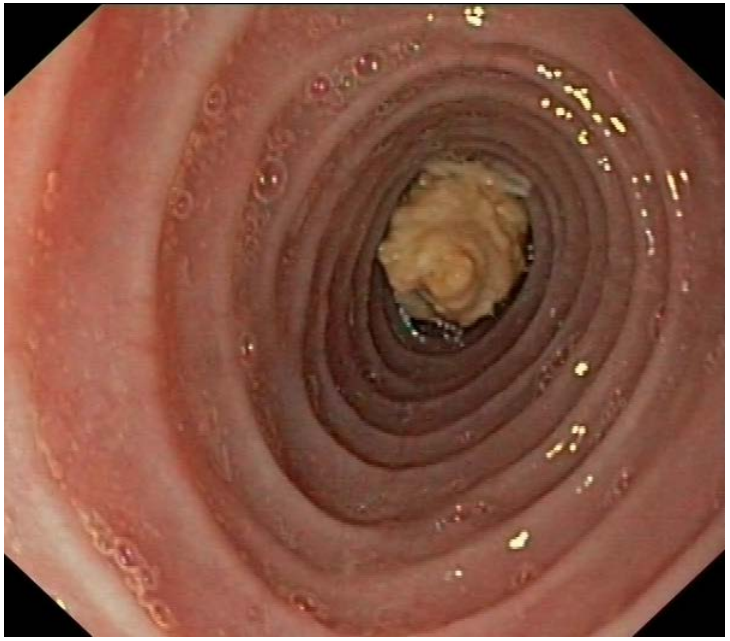
Department Gastroenterology & Hepatology,

Academic Medical Center, Amsterdam

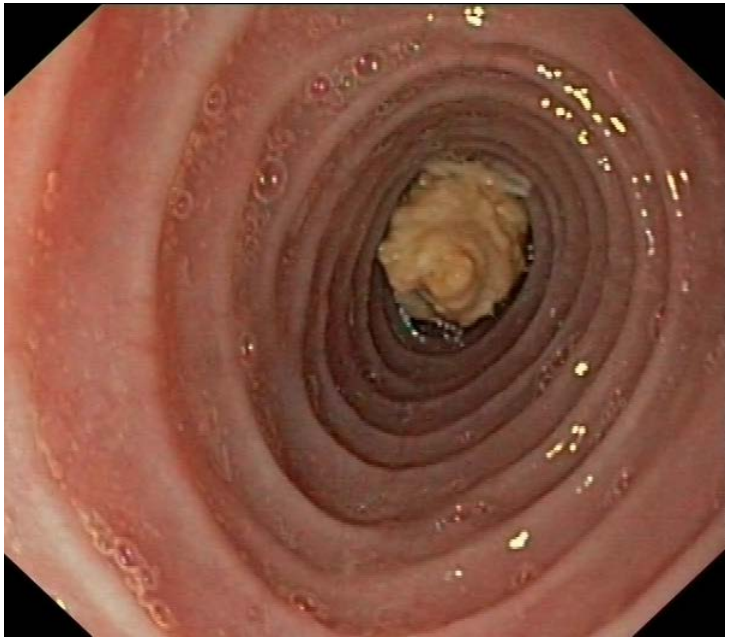
Case: help, my food gets stuck



Details:

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

Case: help, my food gets stuck



Additional findings:

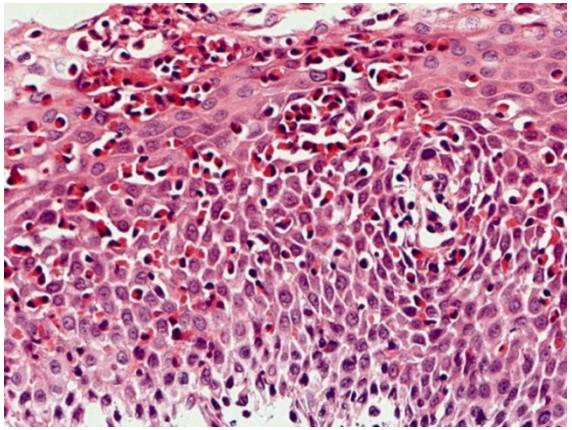
- Clinical Symptoms
  - Dysphagia
  - Food impaction
- Endoscopy
  - Concentric rings
  - Edema
  - Food impaction
- Biopsies
  - Pronounced eosinophilia
  - Eosinophilic micro abscesses

Differential Diagnosis: Eosinophilic Esophagitis

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

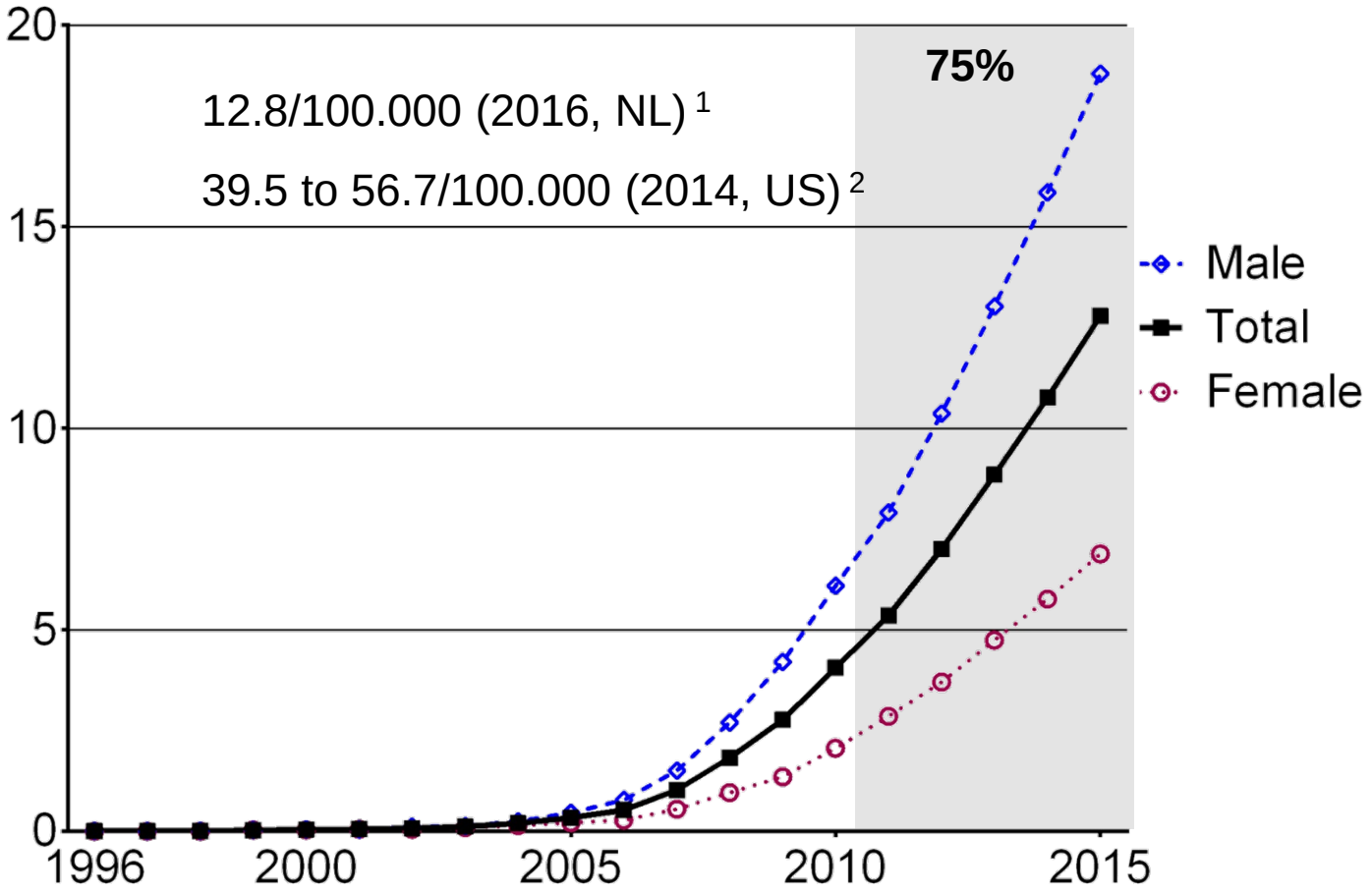
Epidemiology of EoE

- First cases of EoE described in1960-1970's:
  - Multiple esophageal rings, but no compelling evidence of GERD
- Initial description of EoE as a distinct entity by:
  - Atwood 1993[1]
  - Straumann 1994[2]
- New disease
  - Awareness
  - Accelerating incidence and prevalence
- Case reports from USA, Europe, Australia, New Zealand, China, Korea

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

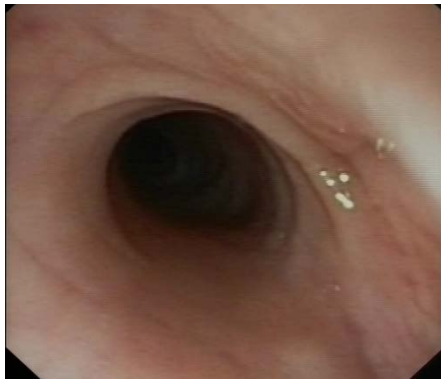
Prevalence of EoE

Per 100 000 / year

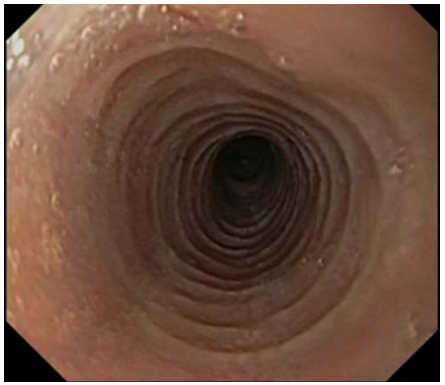


1) van Rhijn et al. Neurogastroenterol Motil. 2012, and unpublished data Warners et al, 2) Dellon et al. Clin Gastroenterol Hepatol. 2014.

Endoscopic Signs



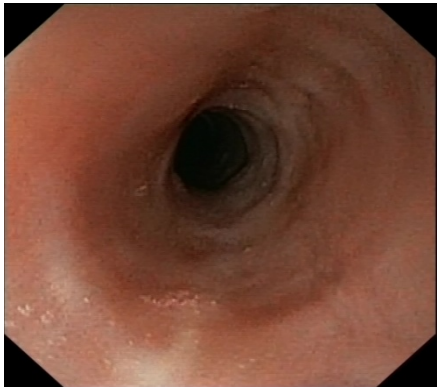
Edema



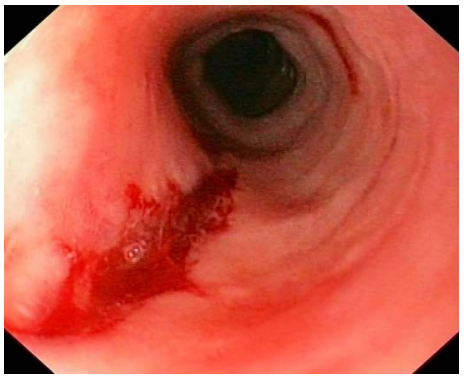
Rings

Exudates

Furrows



Stricture



Crepe paper esophagus

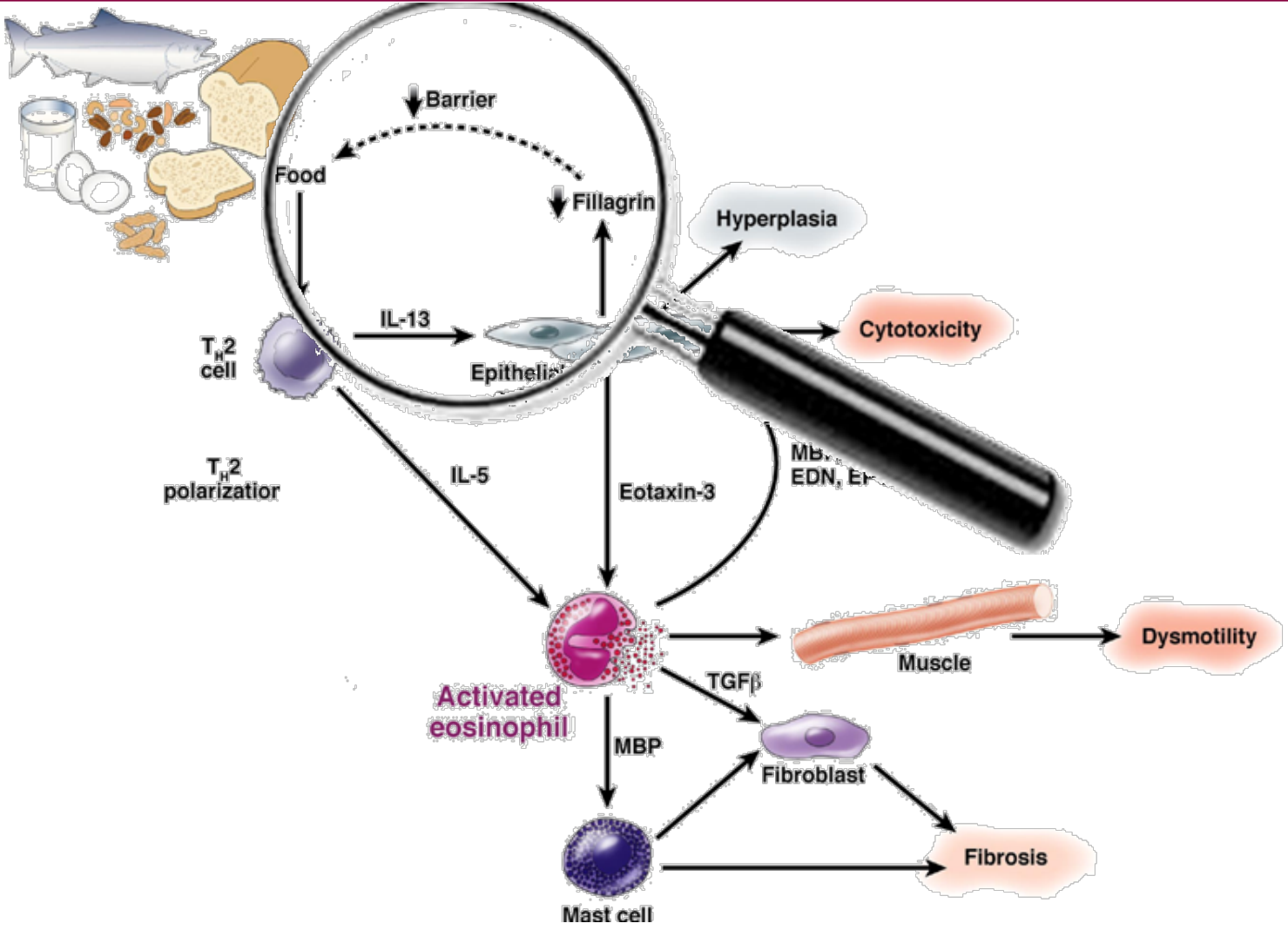
1) Hirano et al. Gut. 2013

EoE Pathogenesis

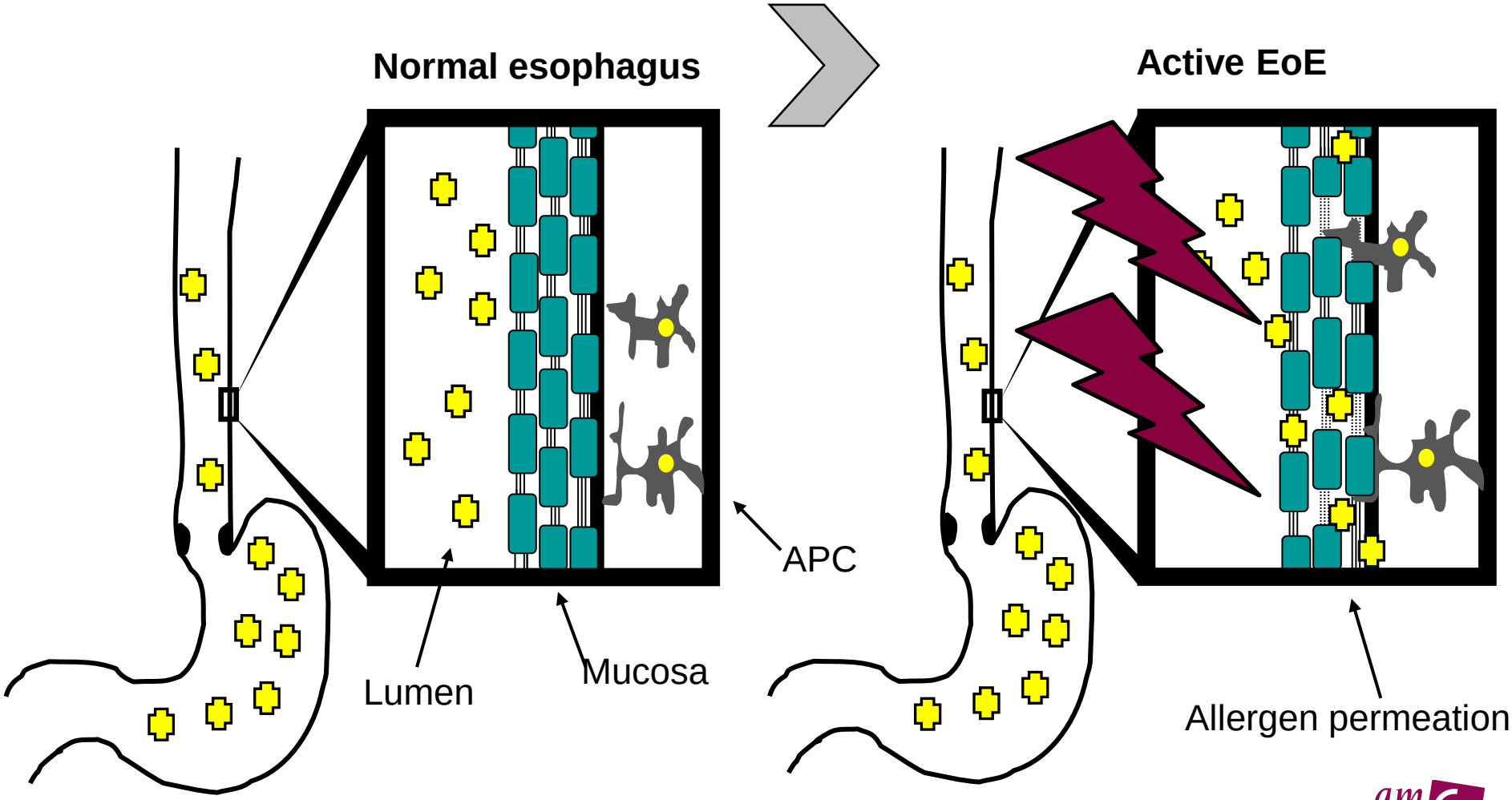
- Immune mediated chronic allergic disease of the esophagus
- Genetic component
  - Five susceptibility loci have been identified [1]
  - Familial clustering of EoE [2]
- High prevalence of other atopic diseases and mutual suspected loci [3]
- Role of (food) allergens
  - Remission after elemental diet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



Esophageal Mucosal Integrity in EoE

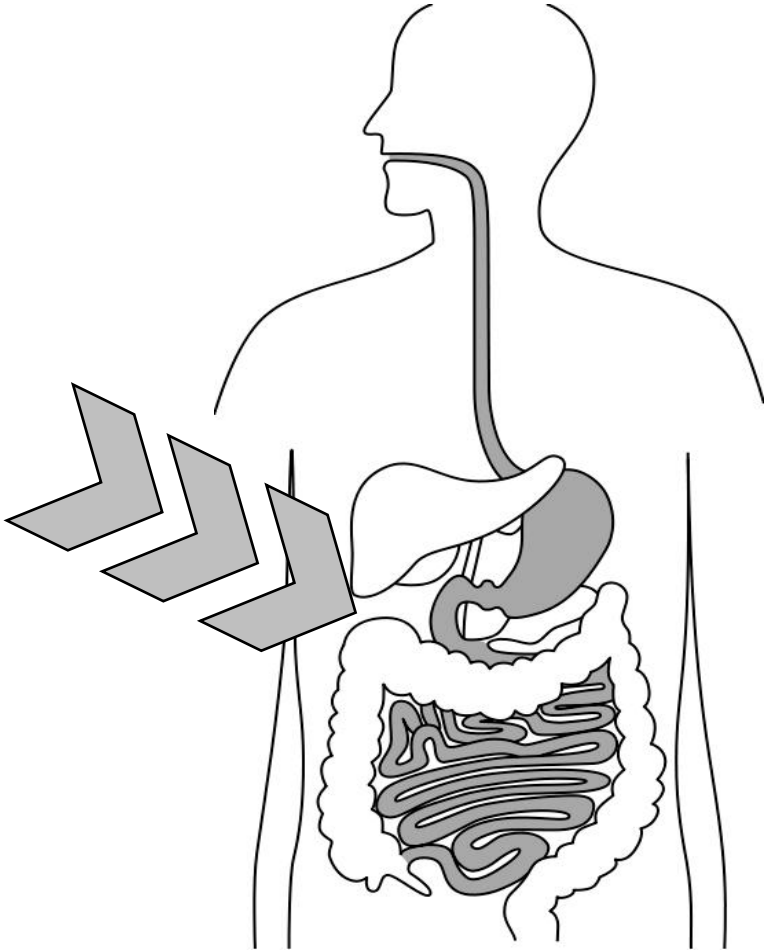


1) Van Rhijn et al. Clin Gastroenterol Hepatol. 2014, 2) Katzka et al. Clin Gastroenterol Hepatol. 2015.

Is the esophagus the sole site of allergen uptake?

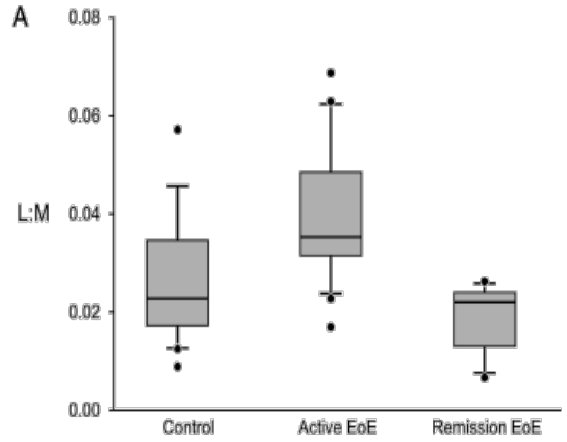
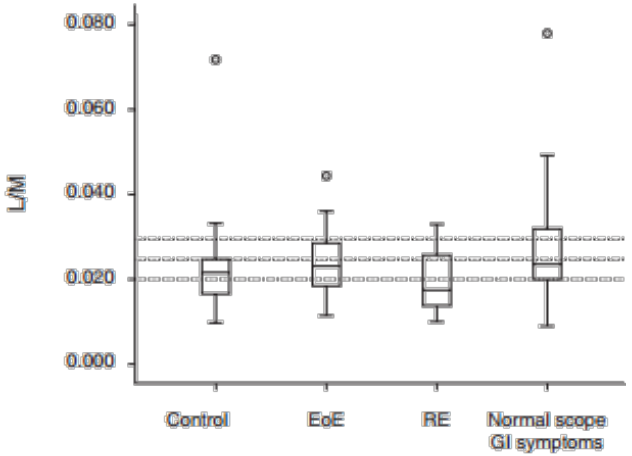
Increased small bowel permeability:

- Atopic dermatitis[1]
- Food allergy[2]
- Eosinophilic esophagitis[3]



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

Adults[1]	Children[2]
	
• 17 EoE, 28 healthy controls • Intestinal permeability increased	• 23 EoE, 26 healthy controls • No difference in intestinal permeability

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

Management of EoE: (D^3)

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 corticosteroids[1]

2. **Drugs: (Topical) Corticosteroids**
   - Improves symptoms and reduces inflammation
   - Side-effects
   - Relapses after cessation
   - More costly than dietary elimination over entire disease course[1]

3. **Dilatation**
   - Improves symptoms
   - Does not influence the underlying inflammation
   - Risk of perforation

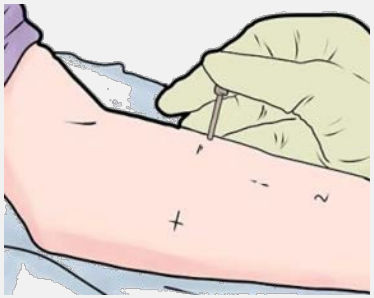
1) Cotton et al. Gastroenterology . 2015..

Dietary Management of EoE

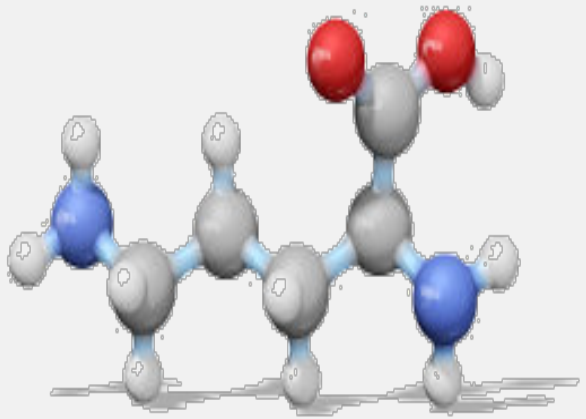
Elimination

Empiric (4FED/SFED)

Allergy Test-Directed



Elemental



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.

Elemental diet

Cons

- Formula fatigue
- Lenghty 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

M. Warners, B. Vlieg – Boerstra, J. Verheij, M. Van Ampting, L. Harthoorn, W. de Jonge, A. Smout, A. Bredenoord

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

This trial was partially funded by Nutricia Research and by the Academic Medical Center

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

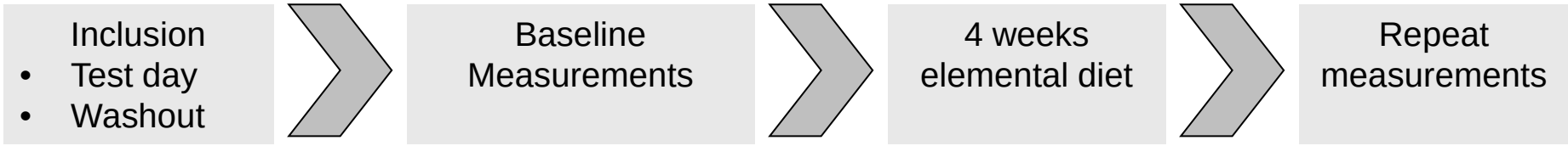
Methods

- **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)

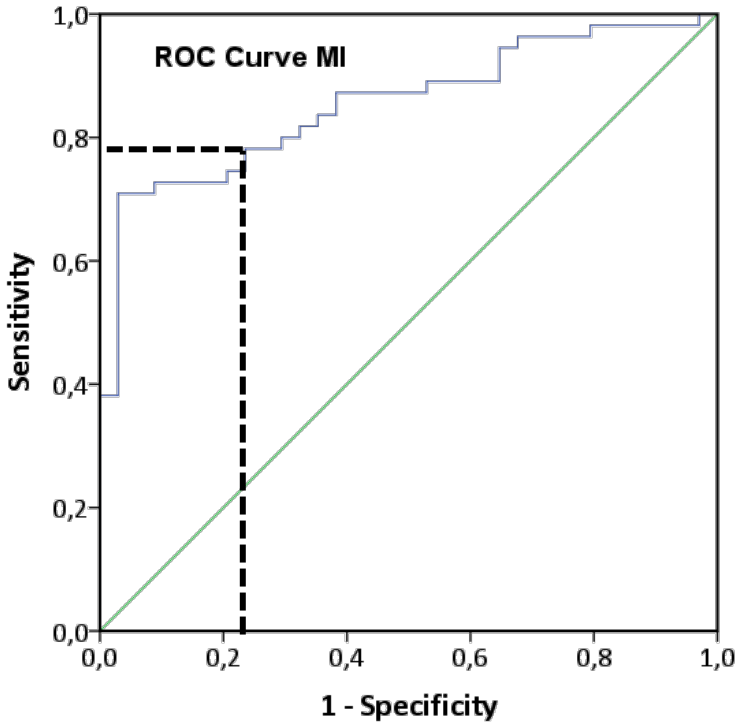
- **Indicator for mucosal integrity in vivo**

- **Measures impedance to the injected current in the esophagus**
  - Extracellular impedance (Ω ● m)

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

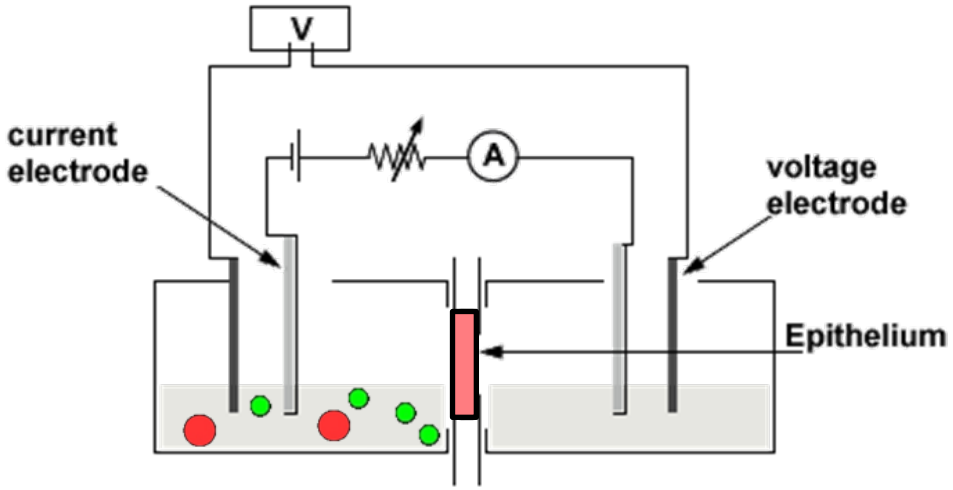
ETIS is a marker for disease activity

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

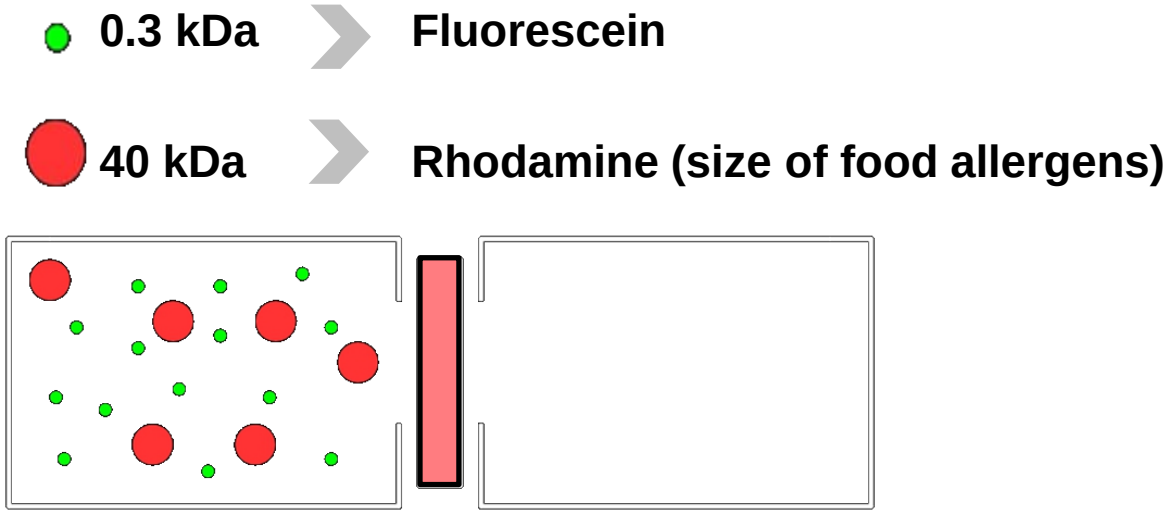


1) Warners et al. DDW 2016.

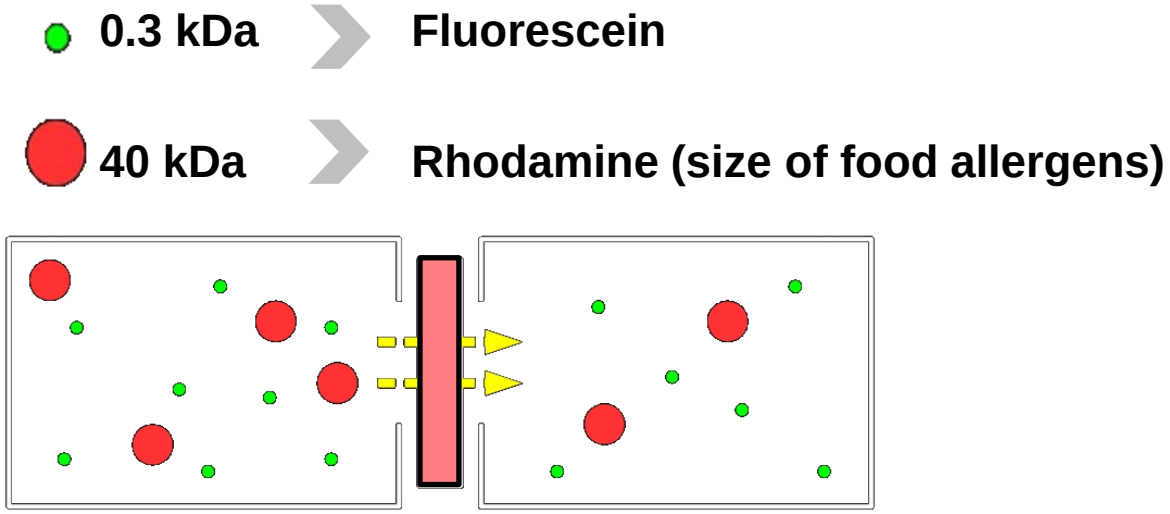
Ussing Chamber: TER



Ussing Chamber: Molecule Flux



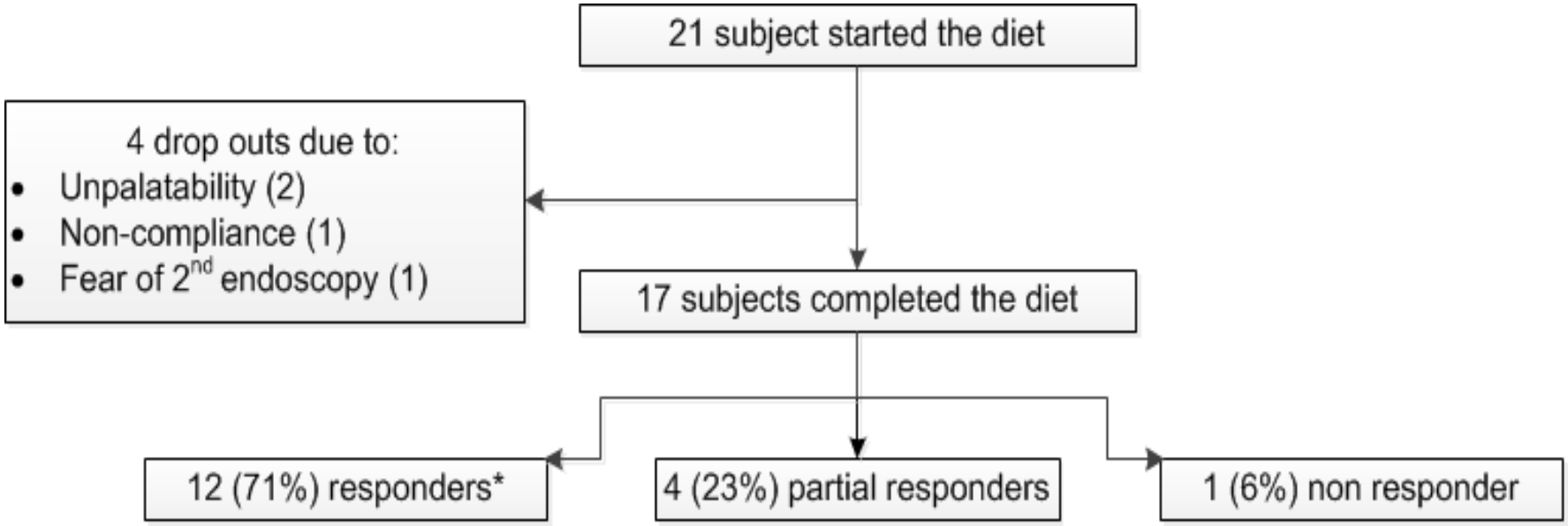
Ussing Chamber: Molecule Flux



Lactulose Mannitol Test

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

Results



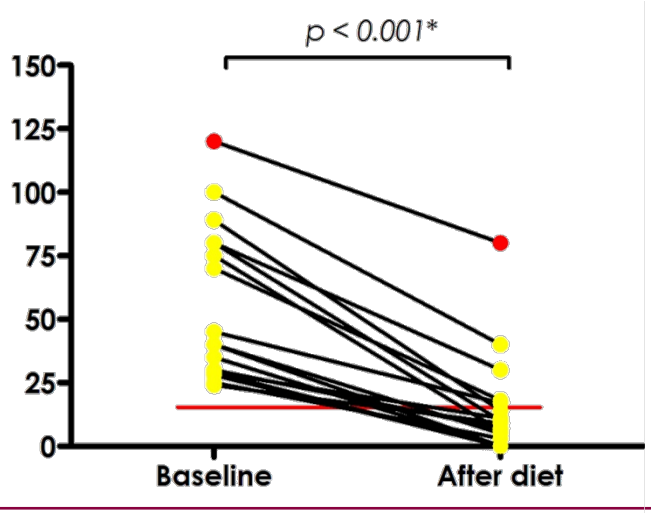
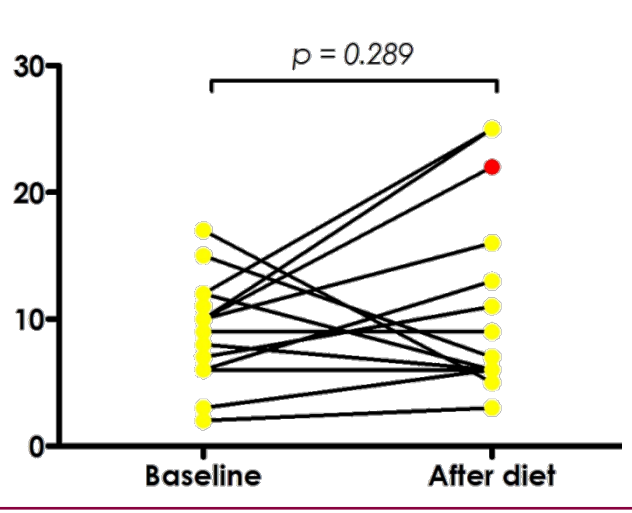
* **Responders: ≤ 15 eosinophils/hpf**

** **Partial responders: decline of baseline peak eosinophil count ≥ 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

Eosinophils/HPF	Mast cells/HPF
	

Non-responder

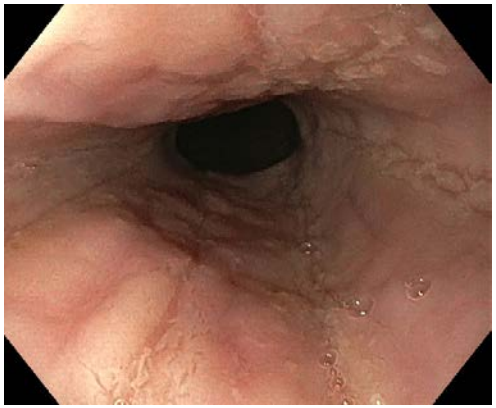
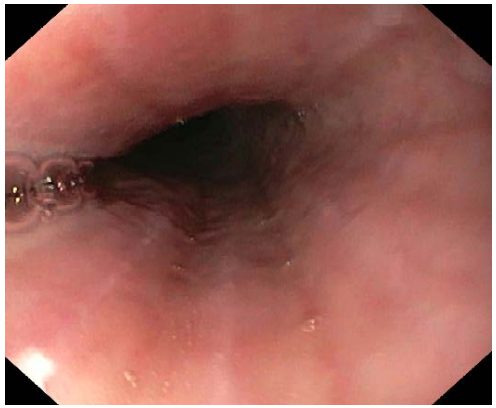
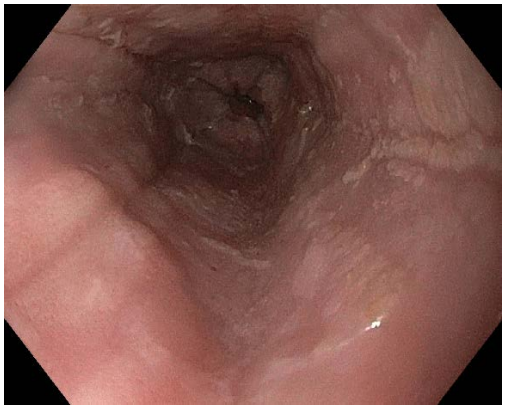
Responders and partial responders

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

Baseline	After diet	After reintroduction
		

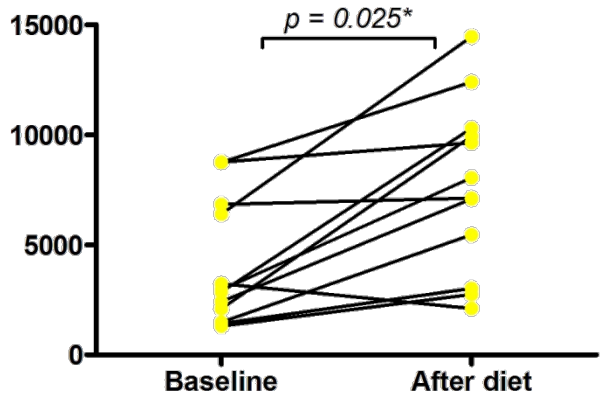
Results: Quality of Life (SF-36)

	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

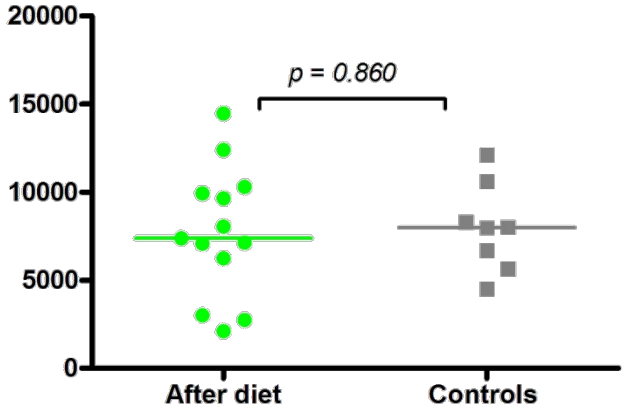
Results: ETIS (Ω • m)

Esophagus

Baseline vs. After diet

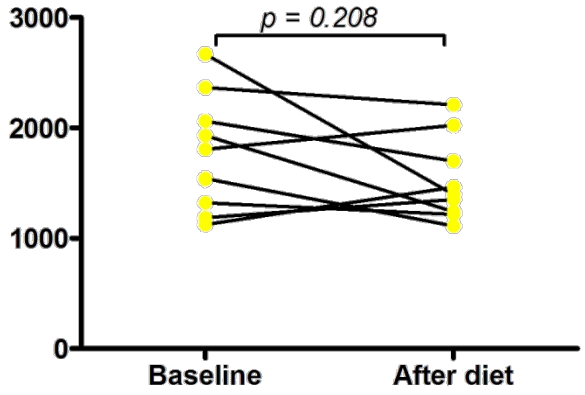


After diet vs. Controls

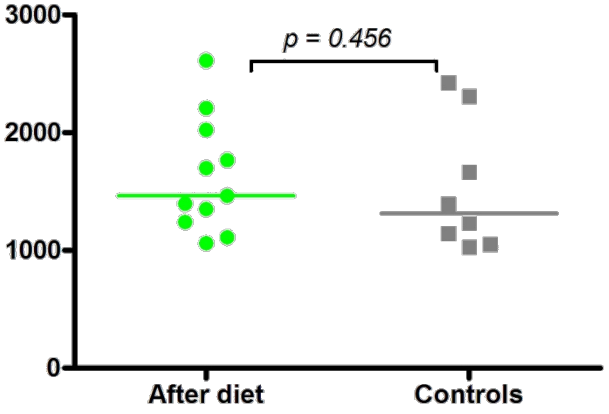


Duodenum

Baseline vs. After diet



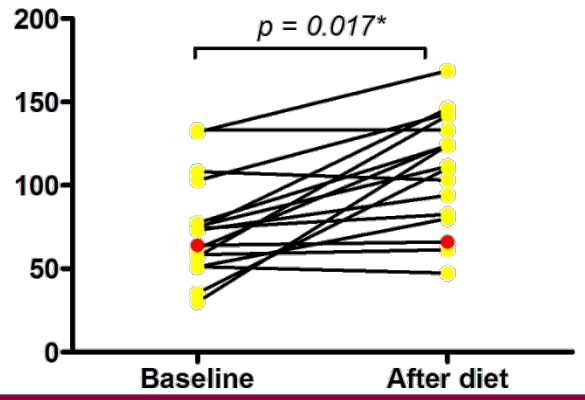
After diet vs. Controls



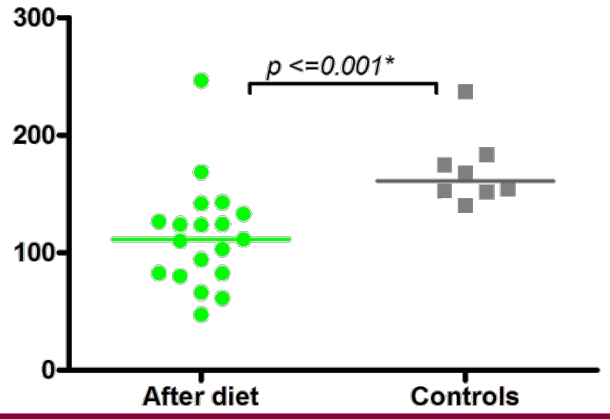
Results: TER ($\Omega \bullet cm^2$)

Esophagus

Baseline vs. After diet

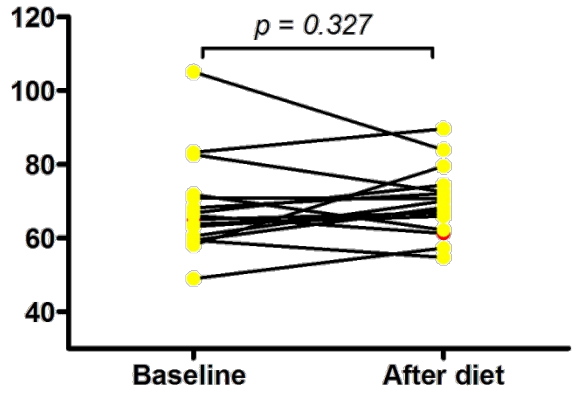


After diet vs. Controls

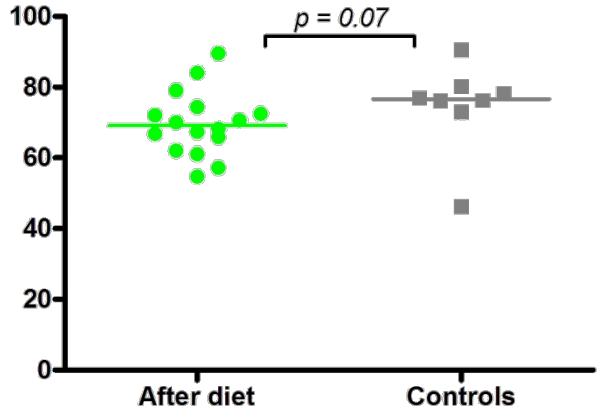


Duodenum

Baseline vs. diet



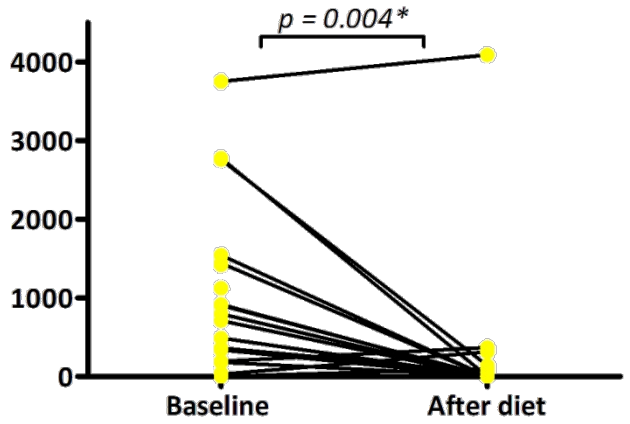
After diet vs. Controls



Results: Esophageal Permeability

Fluorescein (nmol/cm²/h) 0.3 kDA

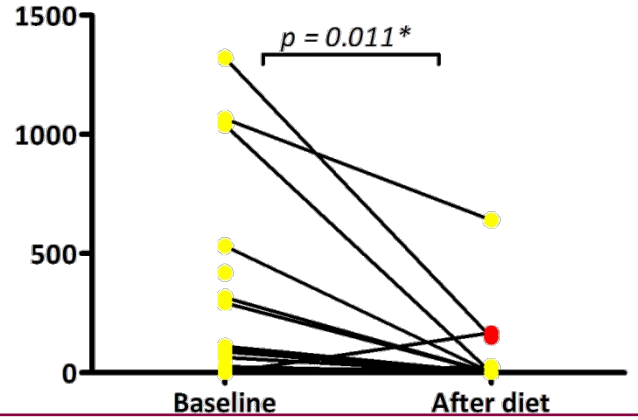
Baseline vs. After diet



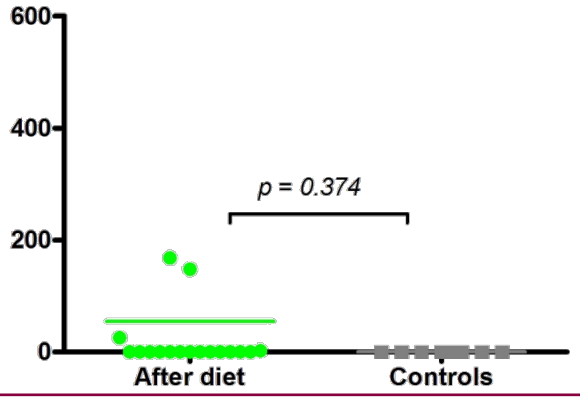
After diet vs. Controls

Rhodamine (nmol/cm²/h) 40 kDA

Baseline vs. After diet

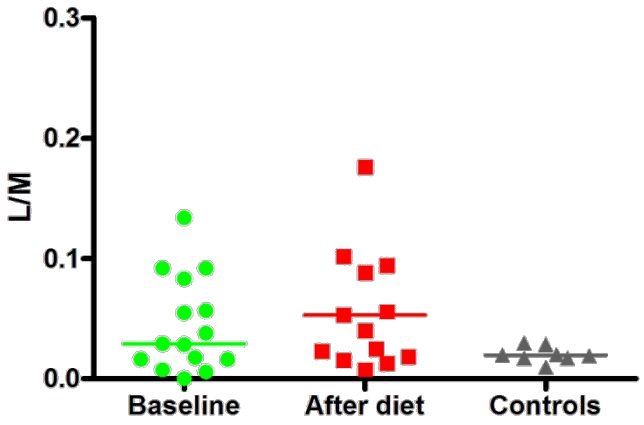


After diet vs. Controls

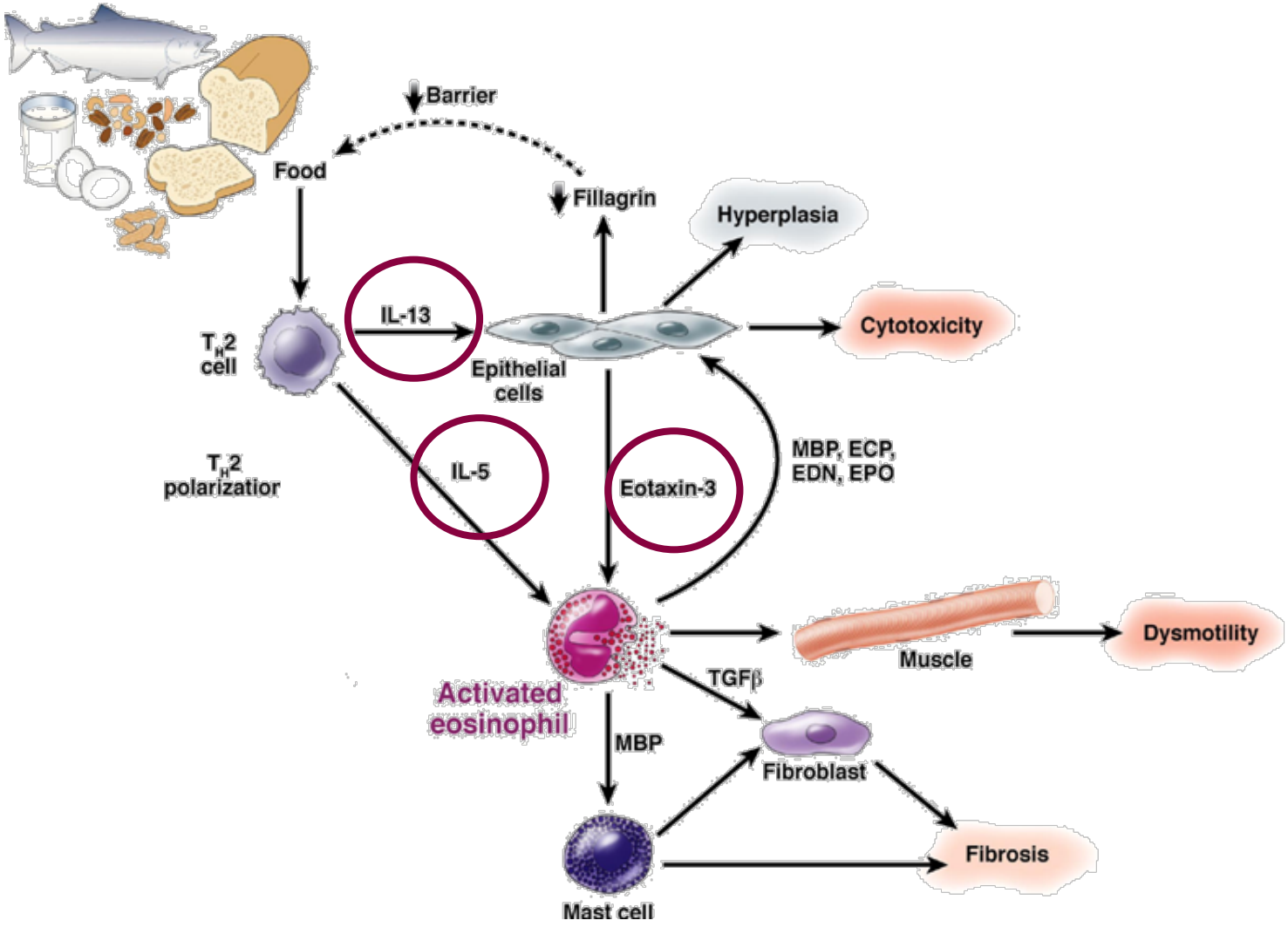


Results: Duodenal Permeability

Duodenum	Baseline, median (IQR)	After diet, median (IQR)	Controls, median (IQR)
Fluorescein (µmol/cm²/h)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)
Rhodamine (µmol/cm²/h)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)
L/M Ratio	.030 (.016 – .083)	.054 (.020 – .158)	.020 (.017 – 026)



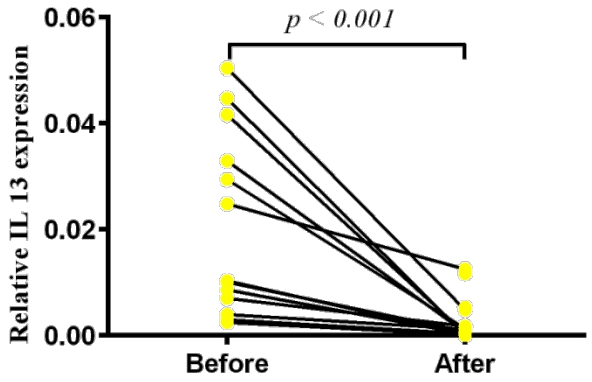
Inflammatory cytokines



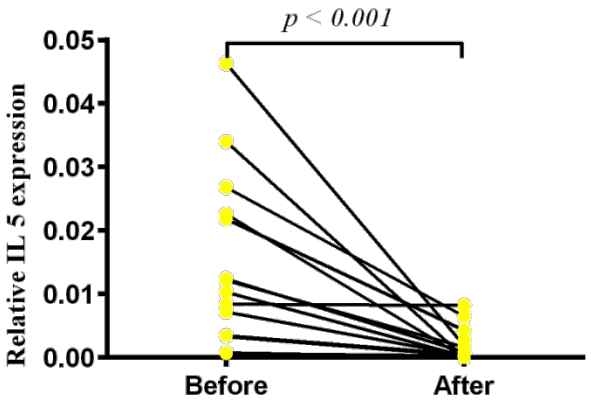
Results: gen expression

Relative gen expression of inflammatory cytokines

IL 13

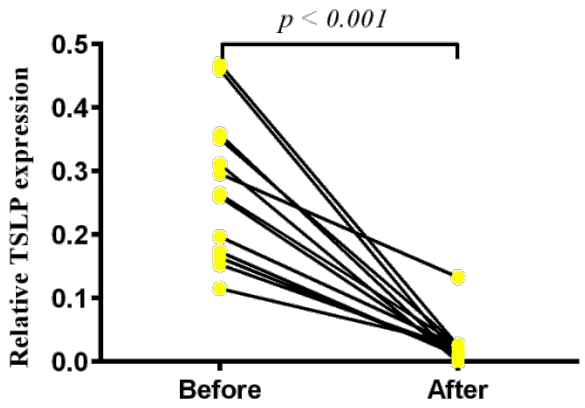


IL 5

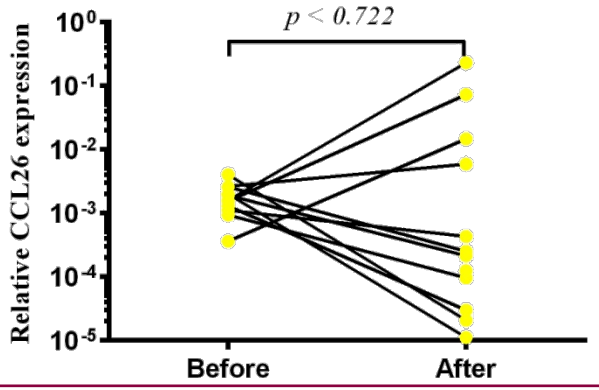


Relative gen expression of inflammatory cytokines

TSLP

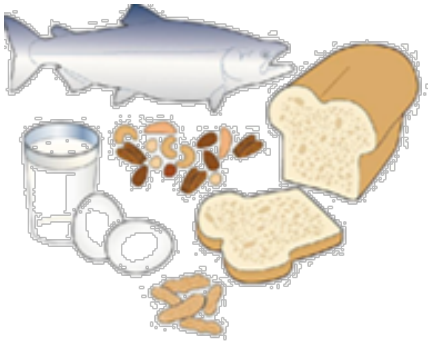


Eotaxin (CCL26)



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

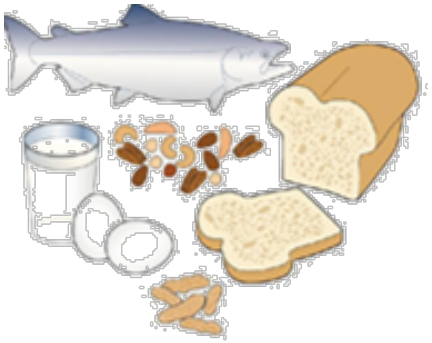


Food Reintroduction Results

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)



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**

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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?

- **Registered Dietitians and Nurses interested in obtaining a Certificate of Attendance for 1 CEU credit please visit:**

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Information needed:

Event code = **GWEOE** 11

Event date = **6.23.16**