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

Dr. Marijn Warners
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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
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: \(\geq 15\) eosinophils / High Power Field (HPF)
- PPI trial failure
- Exclusion of other causes: Crohn's disease, GERD, infections ……

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 1993
  – Straumann 1994
• New disease
  – Awareness
  – Accelerating incidence and prevalence
• Case reports from USA, Europe, Australia, New Zealand, China, Korea

Prevalence of EoE

Per 100 000 / year

12.8/100.000 (2016, NL)¹
39.5 to 56.7/100.000 (2014, US)²

Endoscopic Signs

1) Hirano et al. Gut. 2013
EoE Pathogenesis

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

EoE Pathogenesis
Esophageal Mucosal Integrity in EoE


Diagram showing the transition from normal esophagus to active EoE, highlighting the impact of allergen permeation on mucosal integrity.

Normal esophagus:
- Lumen
- Mucosa

Active EoE:
- Allergen permeation

Is the esophagus the sole site of allergen uptake?

Increased small bowel permeability:
- Atopic dermatitis
- Food allergy
- Eosinophilic esophagitis

Intestinal Permeability in EoE

### Adults¹
- 17 EoE, 28 healthy controls
- Intestinal permeability increased

### Children²
- 23 EoE, 26 healthy controls
- No difference in intestinal permeability

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¹ Katzka et al. Gut. 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

<table>
<thead>
<tr>
<th>Diet</th>
<th>Response</th>
<th>N</th>
<th>Children</th>
<th>N</th>
<th>Adult</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>66.3 %</td>
<td>47</td>
<td>67.2 %</td>
<td>36</td>
<td>63.6 %</td>
<td>10</td>
</tr>
<tr>
<td>Elemental</td>
<td>90.8 %</td>
<td>13</td>
<td>90.4 %</td>
<td>12</td>
<td>94.4 %</td>
<td>11</td>
</tr>
<tr>
<td>SFED</td>
<td>72.1 %</td>
<td>7</td>
<td>72.8 %</td>
<td>4</td>
<td>71.3 %</td>
<td>2</td>
</tr>
<tr>
<td>Test-directed</td>
<td>45.5 %</td>
<td>14</td>
<td>47.9 %</td>
<td>12</td>
<td>32.2 %</td>
<td>2</td>
</tr>
</tbody>
</table>

# 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

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

- Inclusion
  - Test day
  - Washout
- Baseline Measurements
- 4 weeks elemental diet
- Repeat measurements
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 ($\Omega \cdot m$)

ETIS is a marker for disease activity

Mucosal impedance (Ω \cdot m)

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

Ussing Chamber: TER
Ussing Chamber: Molecule Flux

- 0.3 kDa ➤ Fluorescein
- 40 kDa ➤ Rhodamine (size of food allergens)
Ussing Chamber: Molecule Flux

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>71% male</td>
</tr>
<tr>
<td>Age</td>
<td>47 (30-50)</td>
</tr>
<tr>
<td>BMI</td>
<td>24 (22-26)</td>
</tr>
<tr>
<td>Race</td>
<td>77% Caucasian</td>
</tr>
<tr>
<td>Allergies</td>
<td>71%</td>
</tr>
<tr>
<td>Food allergies</td>
<td>47%</td>
</tr>
<tr>
<td>Family history allergies</td>
<td>71%</td>
</tr>
<tr>
<td>Dysphagia 2-7 times a week</td>
<td>77%</td>
</tr>
</tbody>
</table>
Results: Eosinophilic inflammation

<table>
<thead>
<tr>
<th>Eosinophils/HPF</th>
<th>Mast cells/HPF</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Graph Eosinophils" /></td>
<td><img src="image2" alt="Graph Mast cells" /></td>
</tr>
</tbody>
</table>

- Non-responder
- Responders and partial responders
## Results: Symptoms and endoscopy

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After diet</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Median</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Dysphagia score</td>
<td>8</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RDQ</td>
<td>18</td>
<td>5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>19</td>
<td>6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Endoscopy</strong>**</td>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs of EoE</td>
<td>3.5</td>
<td>2.5</td>
<td>.024</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Baseline</th>
<th>After diet</th>
<th>After reintroduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Baseline Image]</td>
<td>![After diet Image]</td>
<td>![After reintroduction Image]</td>
</tr>
</tbody>
</table>
### Results: Quality of Life (SF-36)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After diet</th>
<th>General population (GP)</th>
<th>Baseline vs diet</th>
<th>GP vs diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean, sd</td>
<td>Mean, sd</td>
<td>Mean, sd</td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>88.9 (15.6)</td>
<td>91.6 (10.4)</td>
<td>83.2 (22.6)</td>
<td>0.88</td>
<td>0.006</td>
</tr>
<tr>
<td>Mental health</td>
<td>76.2 (16.1)</td>
<td>84.0 (12.9)</td>
<td>74.9 (17.4)</td>
<td>0.176</td>
<td>0.044</td>
</tr>
<tr>
<td>Social functioning</td>
<td>85.6 (26.4)</td>
<td>74.2 (22.1)</td>
<td>84.2 (22.3)</td>
<td>0.018</td>
<td>0.091</td>
</tr>
</tbody>
</table>
Results: ETIS (Ω • m)

<table>
<thead>
<tr>
<th></th>
<th>Esophagus</th>
<th>Duodenum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline vs. After diet</td>
<td>Baseline vs. After diet</td>
</tr>
<tr>
<td></td>
<td>After diet vs. Controls</td>
<td>After diet vs. Controls</td>
</tr>
</tbody>
</table>

For Esophagus:
- Baseline vs. After diet: $p = 0.025^*$
- After diet vs. Controls: $p = 0.860$

For Duodenum:
- Baseline vs. After diet: $p = 0.208$
- After diet vs. Controls: $p = 0.456$
## Results: TER (Ω • cm²)

### Esophagus

<table>
<thead>
<tr>
<th>Baseline vs. After diet</th>
<th>After diet vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Graph 1" /></td>
<td><img src="image2" alt="Graph 2" /></td>
</tr>
</tbody>
</table>

- **Baseline vs. After diet**: $p = 0.017^*$
- **After diet vs. Controls**: $p \leq 0.001^*$

### Duodenum

<table>
<thead>
<tr>
<th>Baseline vs. diet</th>
<th>After diet vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3" alt="Graph 3" /></td>
<td><img src="image4" alt="Graph 4" /></td>
</tr>
</tbody>
</table>

- **Baseline vs. diet**: $p = 0.327$
- **After diet vs. Controls**: $p = 0.07$
Results: Esophageal Permeability

Fluorescein (nmol/cm²/h) 0.3 kDA

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Baseline vs. After diet</th>
<th>After diet vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>p = 0.004*</td>
<td>p = 0.110</td>
</tr>
</tbody>
</table>

Rhodamine (nmol/cm²/h) 40 kDA

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Baseline vs. After diet</th>
<th>After diet vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>p = 0.011*</td>
<td>p = 0.374</td>
</tr>
</tbody>
</table>
## Results: Duodenal Permeability

<table>
<thead>
<tr>
<th>Duodenum</th>
<th>Baseline, median (IQR)</th>
<th>After diet, median (IQR)</th>
<th>Controls, median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescein (µmol/cm²/h)</td>
<td>0 (0 – 0)</td>
<td>0 (0 – 0)</td>
<td>0 (0 – 0)</td>
</tr>
<tr>
<td>Rhodamine (µmol/cm²/h)</td>
<td>0 (0 – 0)</td>
<td>0 (0 – 0)</td>
<td>0 (0 – 0)</td>
</tr>
<tr>
<td>L/M Ratio</td>
<td>.030 (.016 – .083)</td>
<td>.054 (.020 – .158)</td>
<td>.020 (.017 – .026)</td>
</tr>
</tbody>
</table>

![Graph showing L/M ratios for Baseline, After diet, and Controls compared to Median and IQR]
Inflammatory cytokines

- Food
- Barrier
- Fillagrin
- Hyperplasia
- Cytotoxicity
- MBP, ECP, EDN, EPO
- Dysmotility
- Muscle
- MBP
- Fibroblast
- Fibrosis

- IL-13
- IL-5
- Eotaxin-3
- Activated eosinophil
- TGFβ
- Activated T cell
- T helper 2 (Th2)
- T helper 2 (Th2) polarization

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Results: gen expression

Relative gen expression of inflammatory cytokines

<table>
<thead>
<tr>
<th></th>
<th>IL 13</th>
<th>IL 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL 13</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IL 5</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graphs showing relative expression changes for IL13 and IL5](image)

**TSLP**

**Eotaxin (CCL26)**

![Graphs showing relative expression changes for TSLP and Eotaxin](image)

Legend:
- **p < 0.001**
- **p < 0.722**
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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Dr. A.J. Bredenoord
Prof. Dr. A. Smout

Nutricia Research
Dr. M van Ampting
Dr. L Harthoorn

Collaborators

Emma Children’s Hospital
Dr. B Vlieg-Boerstra

Pathology
Dr. J. Verheij
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.
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