Digestive Allergies And Intolerances

EOSINOPHILIC OESOPHAGITIS

A. Papadopoulou (GR)
EOSINOPHILIC ESOPHAGITIS

Alexandra Papadopoulou, Hon. Prof. Dr. Med.
Chief of the Division of Gastroenterology & Hepatology, First Department of Pediatrics, University of Athens
Children’s Hospital "AGIA SOPHIA", www.gastroped.gr

Chair of the ESPGHAN WG on Eosinophilic Gastrointestinal Disorders
Disclosures

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Advisory Board: Adare Pharmaceuticals; Adacyme Therapeutics.
Learning Objectives

- Definition of Eosinophilic Esophagitis
- Clinical presentation
- Diagnostic approach
- Treatment options
- Open questions for research
Definition of Eosinophilic esophagitis

Eosinophilic Esophagitis (EoE) represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.

Furuta et al 2007; Liacouras et al 2011; Papadopoulou et al 2014; Lucendo et al 2017
Management Guidelines of Eosinophilic Esophagitis in Childhood

*A. Papadopoulou, †S. Koletzko, ‡R. Heuschkel, §J.A. Dias, ¶K.J. Allen, ††S.H. Murch, 
‡‡S. Chong, **F. Gottrand, †††S. Husby, ‡‡‡P. Lionetti, §§§M.L. Mearin, ¶¶¶F.M. Ruemmele, 
**‡‡‡‡M.G. Schäppi, #A. Staiano, ***M. Wilschanski, and ¶¶¶¶Y. Vandenplas, for the ESPGHAN 
Eosinophilic Esophagitis Working Group and the Gastroenterology Committee
Eosinophilic Esophagitis is an *immune/antigen-mediated* disease.
EoE is a disease of *increasing incidence* and *prevalence*.

Incidence: 10 cases per 100.000 per year; Prevalence: 50 to 100 cases per 100.000

*Dellon ES, Liacouras CA. 2014;147:1238-54*
EoE is more common in males and in patients with atopy.

40-60% associated with atopic disease

- Family history of atopic diseases 73.5%
- Family history of EoE 6.8%
- Family history of esophageal dilatation 9.7%

Epidemiologic studies and case series show that EoE is more commonly seen in males and in patients with atopic diseases such as food allergy, asthma and allergic rhinitis.


EoE is characterized clinically by symptoms related to esophageal dysfunction.

Noel P. NEJM 2004
Characterization of Eosinophilic Esophagitis in a multicenter patient population from the European Pediatric Eosinophilic Esophagitis Registry (pEEr) of ESPGHAN

Salvatore Oliva, Noam Zevit, Francesca Rea, Monica Malamisura, Maria Céu Espinheiro, Alexandra Papadopoulou, Eleni Koutri, Danilo Rosse, Rok Orel, Matjas Homan, Bauraind Olivia, Marcus Auth, Carolina GuGerez Junquera, Saskia Vande Velde, Michal Kori, Koen Huysentruyt, Vaidotas Urbonas, ElePheria Roma, Sonia Fernández Fernández, Gloria Domínguez-Ortega, Eyal Zifman, Panayota Kafritsa, Erasmo Miele, Jorge Amil Dias on behalf of EGIDs WG
Participated centers

EGIDs WG
Eosinophilic Gastro Intestinal Diseases Working Group
Symptoms

- GERD: 31%
- Dysphagia: 25%
- Food impaction: 17%
- Vomiting: 16%
- Abdominal Pain: 15%
- Growth failure: 13%
- Incidental findings: 5%

* * * * *

Curtesy of Dr. S. Oliva
CHILDREN
INFLAMMATORY PHENOTYPE

ADULTS
FIBROSTENOTIC PHENOTYPE

Molina-Infante. Exp Rev Gastroenterol Hepatol 2014
Endoscopic features of EoE are *variable*.

Normal appearing mucosa (30%)

Courtesy of ESPGHAN EoE WG
Endoscopy

- **NORMAL**: 17%
- **Rings**: 23%
- **Furrows**: 32%
- **Exudates**: 38%

**Median and range**
- **0-5**
- **6-10**
- **11-14**
- **15-18**

**Curtesy of Dr S. Oliva**
EoE is characterized histologically by *eosinophil-predominant inflammation*.

### Histological findings
- \( \geq 15 \) eosinophils/hpf (peak value)
- Eosinophil microabscesses
- Basal zone hyperplasia
- Lamina propria fibrosis

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*Increased esophageal fibrosis*

EoE is characterized histologically by *eosinophil-predominant inflammation*

**Histological findings**
- ≥15 eosinophils/hpf (peak value)
- Eosinophil microabscesses
- Basal zone hyperplasia
- Lamina propria fibrosis

**Esophageal wall thickening and subepithelial fibrosis**

**High-resolution EUS**

**Normal oesophagus**

**EoE**

Significant expansion of the esophageal wall and individual tissue layers including the combined mucosa, submucosa, and muscularis propria

*Fox et al, Gastrointest Endosc. 2003;57:30-6*

*Strauman et al. Clin Gastr Hepatology 2011*

? Underdiagnosis of the disease if the diagnosis is based on superficial biopsies
Differential Diagnosis

- GERD
- Infections (herpes & candida)
- Esophageal achalasia
- Crohn’s disease
- Connective tissue disorders
- Hypereosinophilia syndrome
- Drug sensitivity response
- Eosinophilic gastroenteritis
- Celiac disease
PPIs have **anti-inflammatory** effects
PPI-REE and EoE

- PPI-REE and EoE have similarities (phenotypic, genetic, pathogenetic mechanisms, clinical features)
  - Katzka D.A., Clin Gastroenterol Hepatol 2014

- Transcriptome analysis revealed recently a similar pattern of gene upregulation and downregulation in EoE and PPI-REE patients, but not in GERD patients
  - Wen T. et al., J Allergy Clin Immunol 2015

PPI-REE is NOT a separate entity but an EoE sub phenotype that responds clinically and histologically to PPIs
CLINICAL—ALIMENTARY TRACT

Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference


2018

Gastroenterology 2018;155:1022–1033
2018

Clinical presentation suggestive of EoE

EGD with biopsy

Esophageal eosinophilia $\geq 15$ eos/hpf ($\sim 60$ eos/mm$^2$)

Evaluate for non-EoE disorders that cause or potentially contribute to esophageal eosinophilia

Eosinophilic esophagitis
Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults


United European Gastroenterology Journal 2017, Vol. 5(3) 335–358
**Patient with confirmed EoE**

CONSIDER ONE AMONG THESE THERAPEUTIC OPTIONS*

- **PPI THERAPY**
  - No remission
  - Check the efficacy of alternative anti-inflammatory treatments above
    - No remission**
      - Elemental diet
      - Experimental drugs
  - Yes
    - Long-term treatment with an effective anti-inflammatory drug or diet

- **SWALLOWED TOPIC STEROIDS**
  - Histologic remission, with persistent symptoms
    - Strictures/narrow caliber esophagus
      - Yes
        - Long-term treatment with an effective anti-inflammatory drug or diet
      - No
        - Long-term treatment with an effective anti-inflammatory drug or diet
    - Endoscopic dilation
      - Rule out other conditions unrelated to esophageal inflammation
      - Reevaluation of the initial diagnosis
    - Clinics and histologic remission

*In patients with persistent symptoms under anti-inflammatory therapy, endoscopic dilation should be considered

** Refer the patient to an EoE center

Lucendo et al, United European Gastroenterology Journal 2017, Vol. 5(3) 335–358
PPIs are effective treatment of EoE
### Symptoms/EGD indication, n (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>PPI-REE (n=149)</th>
<th>EoE (n=433)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td>49 (33)</td>
<td>131 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>36 (24)</td>
<td>110 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Food Impaction</td>
<td>22 (15)</td>
<td>77 (18)</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (16)</td>
<td>69 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>25 (17)</td>
<td>62 (14)</td>
<td>NS</td>
</tr>
</tbody>
</table>

None of the individual factors was independently predictive of the PPI response

<table>
<thead>
<tr>
<th>Condition</th>
<th>PPI-REE (n=149)</th>
<th>EoE (n=433)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any comorbidity</td>
<td>57 (39)</td>
<td>181 (42)</td>
<td>NS</td>
</tr>
<tr>
<td>Family History</td>
<td>85 (57)</td>
<td>233 (54)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Management of EoE

Discuss therapeutic options (Diet and/or Steroids)

Diet
- Empiric elimination diet
- Targeted elimination diet
- Amino Acid Formula

Steroids
- Off label topical swallowed steroids
- Rarely - Systemic oral steroids
  (see main text)

Repeat EGD & biopsies in 4 - 12 weeks,
Monitor for symptoms

Poor adherence? Adapt treatment

No resolution of inflammation
Resolution of inflammation

Drug titration and/or stepwise food reintroduction

Consider allergy history +/- food allergy testing

Follow up endoscopy
- If symptoms reoccur
- If asymptomatic - consider on individual basis

Papadopoulou et al. JPGN 2014;58: 107–118
Overall combined effects of elemental diet for inducing histologic remission of EoE

- 13 studies: 429 patients (411 children; 18 adults)

Arias A et al. Gastroenterology 2014;146:1639–1648
Overall combined effects of EED for inducing histologic remission of EoE

- 7 studies (4 in children; 3 in adults); 197 (75 children; 122 adults); SFED

Arias A et al. Gastroenterology 2014;146:1639–1648
Overall combined effects of allergy testing-directed diet for inducing histologic remission of EoE

- **14 studies** (12 children; 2 adults)
- **626 patients** (594 children; 32 adults)

Arias A et al. Gastroenterology 2014;146:1639–1648
Why TED fails?

• Prick tests

EoE is characterized by a non-IgE-mediated food hypersensitivity

Simon et al. Allergy 2016 May;71(5):611-20

• APT

Allergy tests cannot accurately detect causative food antigens for EoE
Management Guidelines of Eosinophilic Esophagitis in Childhood

Stat 1
In patients with EoE, allergy tests such as serum specific IgE, skin prick tests and microarrays as well as atopy patch - alone or in combination – are unable to reliably identify causative foods.

Agreement 96%

Rec 1
ESPghAN EGID WG recommends against the use of available allergy tests for identifying food triggers of EoE. Triggering foods should be identified by an elimination diet and consequent food reintroduction with histological assessment of esophagus.

Agreement 96%
How to choose the most feasible diet as the initial treatment of childhood EoE?
Feasibility means..
SFED: ARE YOU KIDDING ME??

Increased costs:
- Multiple follow up endoscopies
- Loss of work/school days
Can we use elemental diet or SFED as the initial treatment of childhood EoE?
BUT.. SHOULD WE?
**Most common food combinations in patients with EoE**

<table>
<thead>
<tr>
<th>Food</th>
<th>No. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>78</td>
</tr>
<tr>
<td>Milk, meats*</td>
<td>24</td>
</tr>
<tr>
<td>Milk, egg, wheat, soy</td>
<td>20</td>
</tr>
<tr>
<td>Milk, soy</td>
<td>15</td>
</tr>
<tr>
<td>Grains*</td>
<td>13</td>
</tr>
<tr>
<td>Milk, egg, wheat, meats</td>
<td>11</td>
</tr>
<tr>
<td>Egg, wheat</td>
<td>10</td>
</tr>
<tr>
<td>Milk, egg</td>
<td>8</td>
</tr>
<tr>
<td>Milk, egg, wheat</td>
<td>8</td>
</tr>
<tr>
<td>Egg</td>
<td>8</td>
</tr>
<tr>
<td>Soy</td>
<td>7</td>
</tr>
<tr>
<td>Wheat</td>
<td>5</td>
</tr>
</tbody>
</table>


**No fish!**

**No peanuts!**
Most common food triggers of EoE: cow’s milk, eggs and wheat
WHY NOT FOUR INSTEAD OF SIX?
Cow’s milk was trigger of EoE in 85% of children

64% of children with EoE achieved remission on four food elimination diet (cows milk, wheat, soy and egg)

8/10 HAD ONE OR TWO FOOD TRIGGERS

Kagalwalla et al. Clinical Gastroenterology and Hepatology 2017
WHY NOT TWO INSTEAD OF FOUR?
Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2-4-6 Study

130 patients (25 children). 14 centers from Spain and Italy

EoE unresponsive to PPI therapy

Two-food elimination diet
Milk and gluten

Individual reintroduction of milk and gluten
No Response

Four-food elimination diet
(milk, gluten, egg, legumes/soy)

Individual reintroduction of the 4 food groups
No Response

Six-food elimination diet
(milk, gluten, egg, legumes/soy, nuts, fish/seafood)

Individual reintroduction of the 6 food groups

WHY NOT ONE
INSTEAD
OF TWO?
GI symptoms of CMPA in infants and children

<table>
<thead>
<tr>
<th>Infants &amp; toddlers</th>
<th>Older children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Frequent regurgitation</td>
<td>Food impaction</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Regurgitation</td>
</tr>
<tr>
<td>Colic, abdominal pain</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Food refusal</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td><strong>Failure to thrive</strong></td>
<td>Anorexia, early satiety</td>
</tr>
</tbody>
</table>
• 410 pediatric patients diagnosed with EoE between 1999-2016
• 154/410 were treated solely with elimination diet
• 15/154 had sustained clinical and histological remission following food reintroduction
• Failure to thrive was the most frequent clinical manifestation of EoE

Diagnosis: Age 1.3 yrs.
Regular Diet
Symptoms – Vomiting
>100 Eos/HPF (prox+distal)

After 4.5 months
Elemental Formula
Symptoms – none
4 Eos/HPF

Last follow-up Age 6.8 yrs.
Regular Diet 3 years
Symptoms – none
1-2 Eos/HPF

Assaaf et al JPGN 2019
Starting an Elimination Diet: the path to gut healing
Stepwise empiric elimination diet

- TFED
- FFED
- SFED
- AAF
Treatment of EoE: Topical steroids

Discuss therapeutic options (Diet and/or Steroids)

Diet
Empiric elimination diet
Targeted elimination diet
Amino Acid Formula

Steroids
Off label topical swallowed steroids
Rarely - Systemic oral steroids
(see main text)

Repeat EGD & biopsies in 4 - 12 weeks,
Monitor for symptoms

Follow up endoscopy
• If symptoms reoccur
• If asymptomatic – consider on individual basis

Poor adherence?
Adapt treatment

No resolution of inflammation

Resolution of inflammation

Drug titration and/or stepwise food reintroduction

Papadopoulou et al. JPGN 2014;58: 107–118
Fluticasone

- Fluticasone dose according to age:
  - 1-4 years: 44 microg/puff
  - 5-10 years: 110 microg/puff
  - >11 yrs: 220 microg/puff
- Puffs twice daily after breakfast and dinner
- Ensure delivery to esophagus by removing the spacer
- Inspire deeply and swallow the aerosol
- Rinse mouth with water; Avoid drinking for 2-3 hrs

Oral Viscous Budesonide

- It is prepared by mixing liquid solution of budesonide (the preparation used for inhalations) and sucralose
- The recommended starting dose of budesonide as a viscous suspension is
  - 1 mg daily for children < 10 years
  - 2 mg daily for older children and adults
  - split into two divided doses
- In case of no response, the starting dose may be gradually increased to 2.8 and 4 mg, respectively
Most patients relapse in the absence of maintenance treatment.

**ORIGINAL ARTICLES—ALIMENTARY TRACT**

**Long-Term Budesonide Maintenance Treatment Is Partially Effective for Patients With Eosinophilic Esophagitis**

Alex Straumann, Sébastien Conus, Lukas Degen, Cornelia Fröb, Christian Bussmann, Christoph Beglinger, Alain Schöpp, and Hans-Uwe Simon

*Department of Gastroenterology, University Hospital Basel, Basel; Institute of Pharmacology, University of Bern, Bern; Institute of Clinical Pathology, Hospital Luzern, Luzern; Department of Gastroenterology, Hospital University Hospital Basel, Basel, Switzerland*

- **0.25 mg bid (75% dose reduction) for 1 year**
  - 37.5% achieved complete remission
- **Placebo for 1 year**
  - 0% achieved complete remission

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**Efficacy, Dose Reduction, and Resistance to High-Dose Fluticasone in Patients With Eosinophilic Esophagitis**


*Division of Allergy and Immunology, *Division of Biostatistics and Epidemiology, *Division of Pathology, and *Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children’s Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio; Department of Dermatology, Department of Medicine, School of Medicine, *Division of Pulmonology, Gastroenterology, University of Utah, Salt Lake City, Utah; Section of Pediatric Gastroenterology, Hepatology, and Nutrition, Children’s Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado; *Division of Allergy and Immunology, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania*

**Fluticasone 1760 mcg/day 50% dose reduction for 3 months**

- **73% complete remission**

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**Graph**

- Y-axis: Peak Eosinophil Count/ClinPFP
- X-axis: Screening, Month 3, Month 6
- **Phase I**
- **Phase II**
Children are not small adults..
Steroid resistant or refractory disease: what next?

? Immunomodulators
AZA, 6-MP, sirolimus

? Anti IL-5 (mepolizumab, resluzimab)

? Anti-IL13 (QAX576)

? Anti IgE (omalizumab)?

Anti-CRTH2 (OC000459)

?? Anti-TNFα (infliximab)

??? Cromolyn sodium/leukotriene receptor antagonists

% of patients
Rec 10a
ESPGHAN EGID WG recommends against the use of cromolyn sodium, CRTH2 antagonist OC000459 or leukotriene receptor antagonists as treatment options for children with EoE.

Agreement 100%

Rec 10b
ESPGHAN EGID WG recommends against the routine use of thiopurines for the treatment of children with EoE refractory to first line treatment.

Agreement 92%

Rec 10c
ESPGHAN EGID WG recommends against the use of omalizumab for the treatment of pediatric EoE.

Agreement 100%

Rec 10d
ESPGHAN EGID WG recommends against the routine use of biologics for the treatment of childhood EoE, but they may be considered in clinical trials or in selected cases with EoE refractory to conventional treatment in specialized centers.

Agreement 100%
**ESPGHAN 2014 Recommendations on the use of esophageal dilatation**

- Esophageal dilatation is only recommended in **highly selected cases** with severe esophageal narrowing that persists despite other forms of treatment

- In all cases, esophageal dilatation **must be accompanied by medical treatment** of EoE

*Papadopoulou et al, JPGN 2014;58: 107–118*
Rec 9c
ESPGHAN EGID WG recommends the use of either hydrostatic balloons or Savary-Guiliard bougies for esophageal dilation as both are safe and effective. Choice of technique should be based on the experience of treating physician.

Agreement 88%

Rec 9d
ESPGHAN EGID WG recommends to consider the use of systemic steroids in the presence of esophageal stenosis with severe symptoms as an alternative to dilation (expert opinion).

Agreement 92%
Conclusions

• *EoE is a chronic, relapsing inflammatory disease of the esophagus with largely unquantified long term consequences*

• *Investigations and treatment are tailored to the individual and must not create more morbidity for the patient and family than the disease itself*

• *Better maintenance treatment and novel therapies for long-lasting, treatment resistant disease, as well as biomarkers for assessing treatment response and predicting long-term complications, are urgently needed*

*Papadopoulou et al, JPGN 2014;58: 107–118*
Update 2019

Management Guidelines of Eosinophilic Esophagitis in Childhood

Taskforce working in the manuscript

Thank you for your kind attention!

www.espen.org

www.espencongress.com