Eosinophilic esophagitis in children

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Pediatric gastroenterology, hepatology and nutrition
Learning objectives

Eosinophilic esophagitis (EoE) in children:

- Signs and symptoms?
- How to diagnose EoE?
- How to treat EoE?
Definition EoE in pediatrics and adults

Chronic, antigen (food), driven immune-mediated disease characterized by:
- symptoms of esophageal dysfunction
- histologic evidence of eosinophilic inflammation of the mucosa
- affecting local esophageal tissue

Dellon, 2018
Evolving diagnostic approach to EoE

1977
First case report

1993-1995
EoE recognized as a distinct entity

2007
First consensus guidelines

2011
Second consensus guidelines

2013
Pediatric guidelines

2014
US guidelines

2017
European guidelines

2018
AGREE consensus guidelines

Diagnostic framework established

PPI-REE concept introduced

PPI nonresponse removed as diagnostic criterion

History

Dellon, 2018
Epidemiology

• Incidence: 3.7/100,000/y
• Increasing prevalence: 1:1,000 (~ IBD)
• **Familial pattern** (2%), raising the possibility of either a genetic predisposition (monozygotic twins 41%, dizygotic twins 22%) or exposure to an unknown environmental factor (80%)
• Average age between **6 and 10 years**
• **Male predominance** (70% males)
• **Caucasian** predominance
• Associated with **atopy**:
  • 26-50% asthma
  • 30-90% allergic rhinitis
  • 19-55% atopic dermatitis
  • 9-24% IgE mediated food allergy

Markowitz, 2018
# Signs and symptoms in pediatrics

## Common symptoms of eosinophilic esophagitis

<table>
<thead>
<tr>
<th>Younger Children</th>
<th>Older Children and Adolescents</th>
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<tbody>
<tr>
<td>Vomiting</td>
<td>Epigastric pain</td>
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<tr>
<td>Chronic nausea</td>
<td>Dysphagia</td>
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<td>Regurgitation</td>
<td>Nighttime cough</td>
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<td>Irritability/feeding difficulties</td>
<td>Food impaction</td>
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## Less common symptoms of eosinophilic esophagitis

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<table>
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<tbody>
<tr>
<td>Growth failure</td>
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<tr>
<td>Hematemesis</td>
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<tr>
<td>Esophageal dysmotility</td>
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<tr>
<td>Failure to thrive</td>
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<td>Malnutrition</td>
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• Spontaneous coping mechanisms for the disease:
  • drinking a lot of fluids during meals
  • being unable to eat unless a drink is available
  • chew the food for a long time
  • cut the food in small pieces
Diagnosis

Clinical Presentation Suggestion of EoE

EGD with biopsy

Esophageal Eosinophilia
(≥ 15 eos/hpf or approximately 60 eos/mm²)

Evaluate for Non-EoE Disorders that cause or potentially contribute to Esophageal Eosinophilia

EoE

Dellon, 2018
Diagnosis

EREFS
Diagnosis

Endoscopy with biopsies – always!

- 15 eosinophils per high-powered field (60 eos/mm²)

- Sensitivity of 100% and specificity of 96%

- Remission criteria: < 15 eosinophils per high-powered field

- Sensitivity biopsies:
  - 1 biopsy: 55%
  - 3 biopsies 97%
  - > 2-4 biopsies proximal and distal esophagus
## Differential diagnosis

<table>
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<th>Differential diagnosis of eosinophilic esophagitis</th>
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<tr>
<td>Eosinophilic gastrointestinal diseases</td>
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<tr>
<td>Celiac disease</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Hypereosinophilic syndrome</td>
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<tr>
<td>Achalasia</td>
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<tr>
<td>Vasculitis</td>
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<tr>
<td>Pemphigus</td>
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<td>Connective tissue diseases</td>
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<td>Drug hypersensitivity</td>
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*Fahey, 2017*
Treatment

Indications for treatment:
- To improve the quality of life
- To stop deposition of subepithelial fibrous tissue in the esophageal wall
- To reduce the risk of severe esophageal injury by preventing long-lasting food impactions

Treatment goals:
- Improvement of symptoms
- Reducing eosinophilic inflammation
- Prevention of remodeling and reversal of fibrosis

➢ Subject of intensive debate!
Tissue diagnosis of esophageal eosinophilia (>15 eosinophils/HPF) → Commence 8-week course of high dose PPI → Repeat endoscopy after 8 weeks

- <5 eosinophils/HPF (histological remission)
  - Reduce PPI dose to maintenance 1mg/kg daily
  - Repeat endoscopy in 12 months

- 5-15 eosinophils/HPF (partial treatment response)
  - Alternative treatment (diet or topical corticosteroids)
  - Repeat endoscopy in 8 weeks

- >15 eosinophils/HPF (failed treatment)
Proton pump inhibitors

- Gastric acid inhibition
- Anti-inflammatory effects (inhibition of Th2-mediated eotaxin 3 secretion and to improve epithelial integrity)

- From diagnostic tool to therapeutic agent
- Remission rate: 54% (33%-74%)

- Long-term therapy, 1-year follow up 78.6% remained histologic remission
- Progressive decrease in dosage to the lowest point with remission

Lucendo, 2017
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Corticosteroids

• Strong evidence that EoE can be controlled without the use of systemic corticosteroids (Schaefer 2008)

• Swallow corticosteroids are highly effective (response rate 50-87%)
  • Fluticasone (110 microgram, 2-4 times/day)
  • Budesonide (Xanthaangum)
    • <10 years: 1 mg
    • >10 years: 2 mg
  • Avoid drinking and eating for at least half an hour after administration

• Side effects:
  • Infection: Candida albicans (10-15%)
  • Adrenal suppression
  • Epithelial atrophy
  • Growth

Lucendo, 2017
Corticosteroids

• Both budesonide and fluticasone are significantly superior to placebo in:
  • Inducing histologic remission
  • Any improvement in dysphagia scores
• Budesonide was significantly superior – different administration
• Long-term therapy effective in remaining remission: 63% > 2 year follow-up

Corticosteroids are able to control EoE not to cure!!
Tissue diagnosis of esophageal eosinophilia (>15 eosinophils/HPF)

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Repeat endoscopy after 8 weeks

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Reduce PPI dose to maintenance
1mg/kg daily
Repeat endoscopy in 12 months

Alternative treatment
(diet or topical corticosteroids)
Repeat endoscopy in 8 weeks
Dietary assessment

Avoid the ‘trigger’ food

• Exclusive feeding with elemental diets
• Empiric elimination of common dietary antigens
• Allergy test-driven food elimination

Kliewer, 2018
Dietary assessment

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Exclusive feeding with elemental diets

• First publication by Kelly in 1995
• Elemental diet
  • amino acid-based diet
  • remission rate in children 90%-95%
  • minimum 6 weeks
  • clinical improvement 8.5 ± 3.8 days, histological remission in 2 weeks

• Nutricia (Neocate, Neocate advance, Neocate Junior)
• Mead-Johnson (Puramino)

Molina-Infante 2017
• Induce remission
• Easy in young children
• Ultimate rescue therapy
• Temporary solution

• Palatability
• Delayed speech
• Cost of elemental formula
• Emotional cost
Dietary assessment

- Exclusive feeding with elemental diets
- Empiric elimination of common dietary antigens
- Allergy test-driven food elimination

Avoid the ‘trigger’ food
Empiric elimination of common dietary antigens

• Empirical diet :
  • 6-food, 4-food, 2-food diet :
    • 6 food : cow’s milk, soy, eggs, wheat, nuts and fish
    • 4 food : cow’s milk, eggs, wheat, soy
    • 2 food : cow’s milk and wheat
    • 1 food : cow’s milk
STEP-DOWN elimination diet
STEP-DOWN elimination diet

High level of restrictions
Lenghty diagnostic procedures
High number of endoscopies

4-FED (6-8 weeks)

Non responder

EGD <15 eos/hpf

Soy

EGD <15 eos/hpf

Egg

EGD <15 eos/hpf

Wheat

EGD <15 eos/hpf

Milk

EGD <15 eos/hpf

Trigger food(s) identified

Gastroenterol 2018: 154
STEP-UP elimination diet

• Empirical diet
  • 6-food, 4-food, 2-food diet
    • 6 food: cow’s milk, soy, eggs, wheat, nuts and fish - remission rate in children 74%
    • 4 food: cow’s milk, eggs, wheat, soy - remission rate in children 64%
    • 2 food: cow’s milk and wheat - remission rate in children 40%
    • 1 food: cow’s milk - remission rate in 33% in children and 13% in adults

• Studies:
  • Belgium: cow’s milk, wheat and eggs
  • Soy/legumes less common
  • Seafood and nuts very rare
  • > 75% of responding patients have 1 or 2 food triggers after six food challenges
STEP-UP elimination diet

130 EoE patients (non-responders to PPI) underwent a 2-food group elimination diet

- 56 patients (43%) achieved clinicohistologic remission
- 74 patients (57%) without clinicohistologic remission

54 patients stepped up to a 4-food group elimination diet

- 10 patients (19%) achieved clinicohistologic remission
- 44 patients (81%) without clinicohistologic remission

27 patients stepped up to a 6-food group elimination diet

- 8 patients (29%) achieved clinicohistologic remission
- 19 patients (70%) without clinicohistologic remission

20 patients unwilling to continue with dietary therapy

**FIG 1.** Flowchart of patients during the study.

Molina-infante, 2017
STEP-UP elimination diet

- Empirical diet
  - 6-food, 4-food, 2-food diet
    - 6 food: cow’s milk, soya, eggs, wheat, nuts and fish - remission rate in children 74%
    - 4 food: cow’s milk, eggs, wheat, soy - remission rate in children 64%
    - 2 food: cow’s milk and wheat - remission rate in children 40%
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Dietary assessment

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Avoid the ‘trigger ‘ food
Allergy test-driven food elimination

- Inspired by the success of the use of AA
- Allergists try to find the food or foods responsible for the disease through:
  - Skin prick tests
  - Atopy patch tests
  - Serum specific IgE testing
- Histologic remission in 45.5% of patients
- Routine part of the workup in EoE patients with history of IgE-mediated food or allergic rhinitis
- ? EoE is primarily non-Ig E mediated, possible IgG4

Erwin, 2017
Success rate

Markowitz, 2018
How to choose a therapeutic option for an EoE patient?

- Individually discussed with the patient and parents
- Might be potentially interchangeable over time
- Efficacy of any therapy checked by endoscopy after 6 to 12 weeks

Remission: repeat endoscopy every 6-12 months, even when there are no symptoms!
Therapeutic option if PPI treatment is not successful:

- Nutrition therapy
  - Elimination of milk in infants & small children
    - If unsuccessful, step-up to 3 food elimination diet - milk + egg + wheat
- OR
  - Elimination of 2 or 3 foods in school children, adolescents & adults - milk, egg, wheat
    - If unsuccessful, step-up to 6 food elimination diet
- Topical steroids
  - If unsuccessful
    - If successful, continue long-term lowest possible dose

Whatever successful, continue long-term (!?)
Prognosis

Is EoE clinically, endoscopically, histologically and functionally a progressive disorder?

- natural history in 89 children 8-year FU: EoE chronic and relapsing condition
- majority of young adults diagnosed during childhood continued to require pharmacologic treatment and/or dietary modification for EoE
- 200 Swiss adult EoE: prevalence of fibrotic esophageal features, in diagnostic delay: up to 2 years: 46.5%, >20 years: 87.5%
- ability of both topical steroids and dietary treatment to reverse esophageal remodeling in children

Straumann, 2018
Pediatrics

• Quality of life :
  • 69 % of the children: social difficulty, anxiety, sleep disorders, depression and school problems
  • Not associated with esophageal perforation, mortality or malignancy

• Future: database, studies, less invasive tests
Key messages EoE in children

- Chronic immune mediated response to food allergens
- Symptoms can be nonspecific
- Diagnosis by endoscopy with biopsies
- Treatment with PPI, topical steroids or diet
- A lot of remaining questions
Eosinophilic Esophagitis (EoE)
Hard to Say, Even Harder to Live With