# Eosinophilic esophagitis in children

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# Learning objectives

Eosinophilic esophagitis (EoE) in **children** :

- Signs and symptoms ?
- How to diagnose EoE ?
- How to treat EoE ?

# Definition EoE in pediatrics and adults

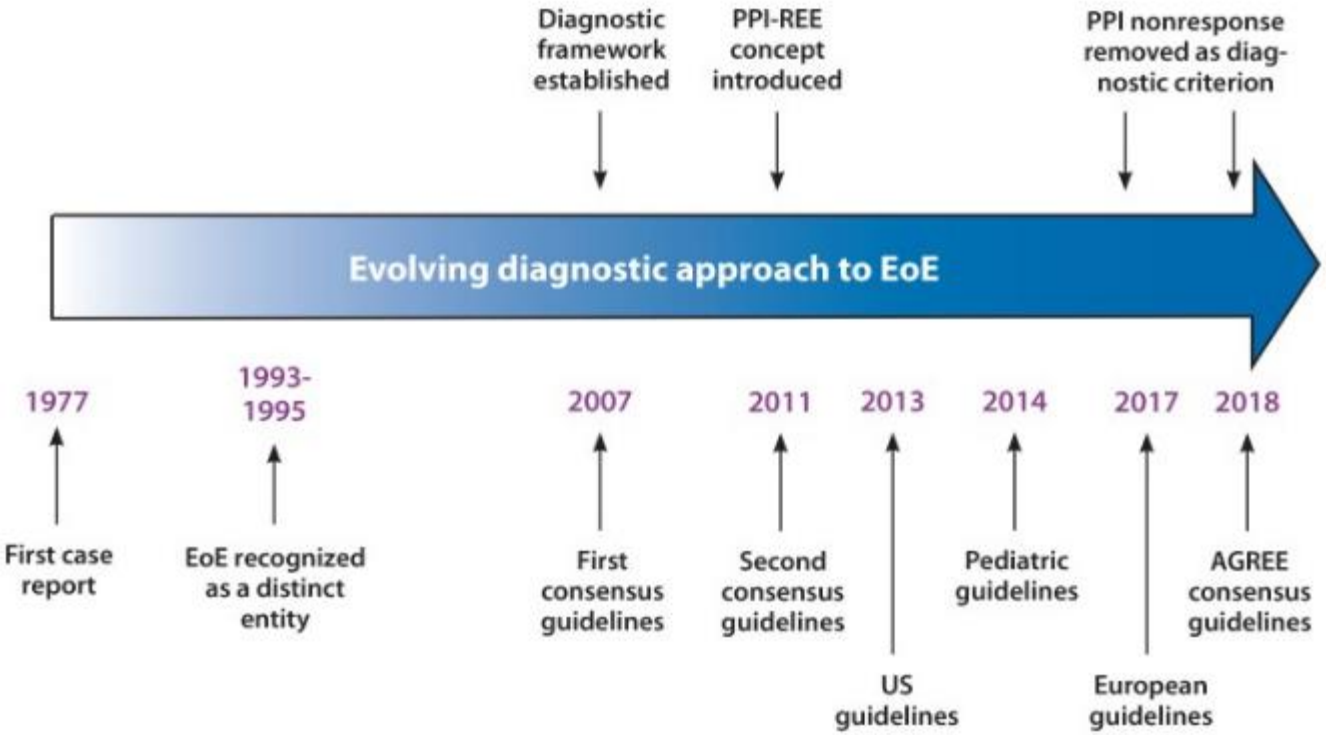
Chronic, antigen (food), driven immune-mediated disease characterized by :

- symptoms of esophageal dysfunction
- histologic evidence of eosinophilic inflammation of the mucosa
- affecting local esophageal tissue



*Dellon, 2018*

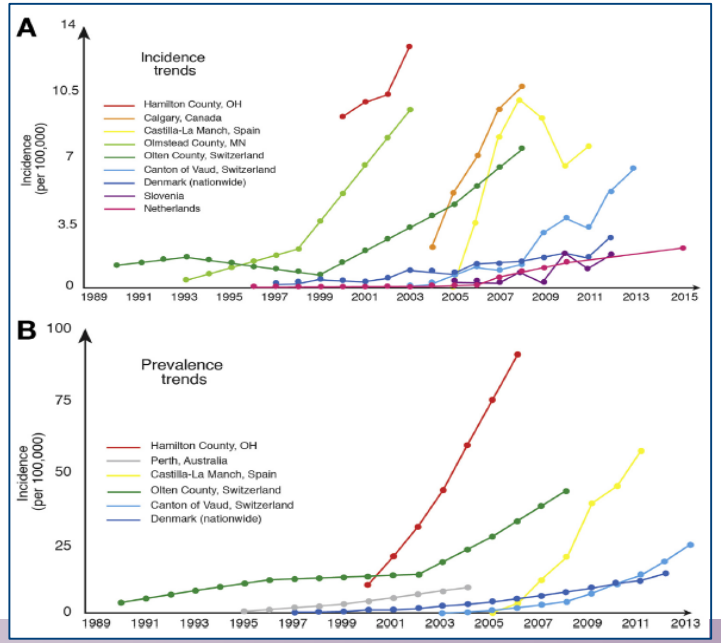
# History




*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** | |
|---|---|
| **Younger Children** | **Older Children and Adolescents** |
| Vomiting | Epigastric pain |
| Chronic nausea | Dysphagia |
| Regurgitation | Nighttime cough |
| Irritability/feeding difficulties | Food impaction |

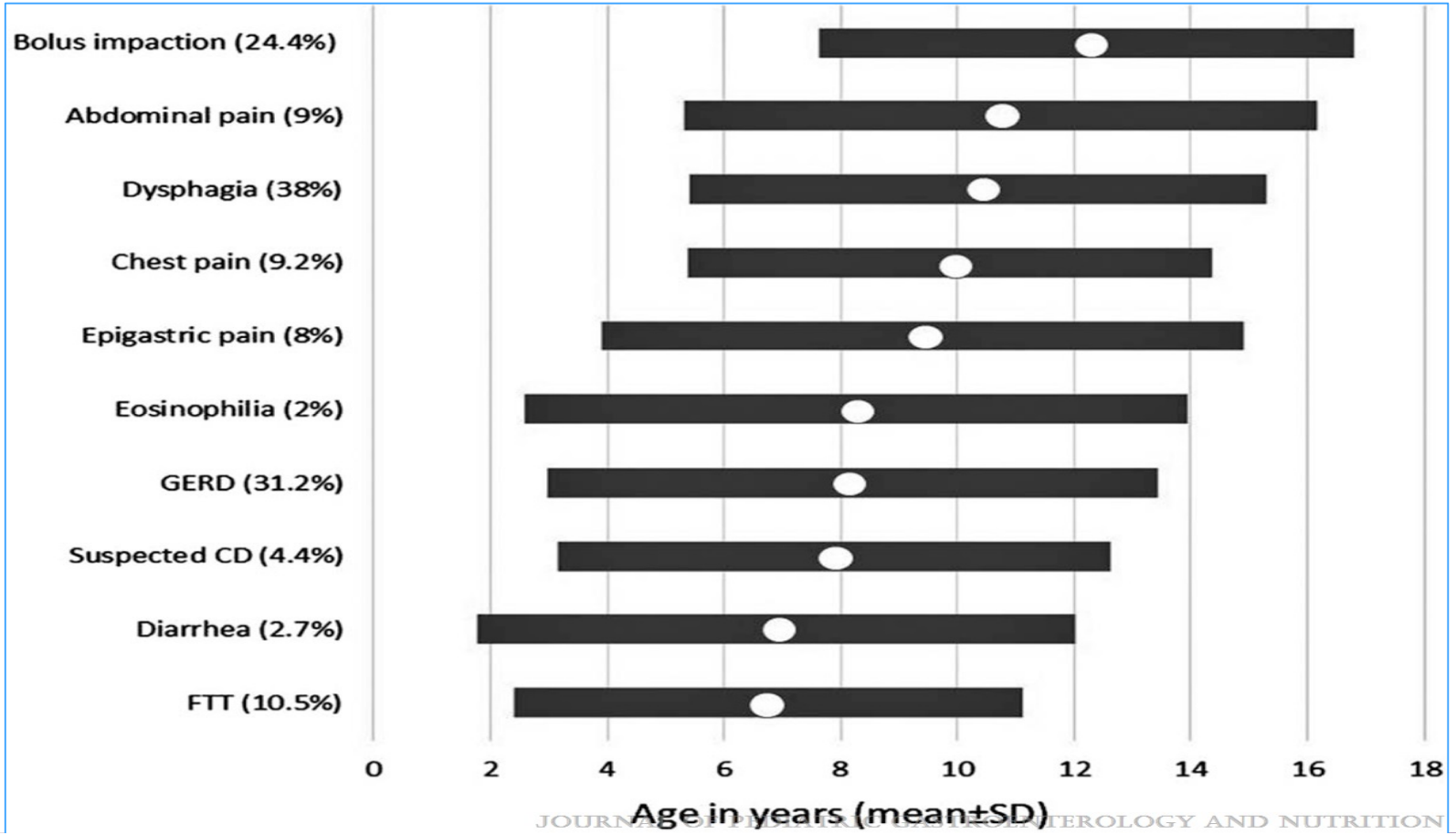
| **Less common symptoms of eosinophilic esophagitis** |
|---|
| Growth failure |
| Hematemesis |
| Esophageal dysmotility |
| Failure to thrive |
| Malnutrition |



- 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





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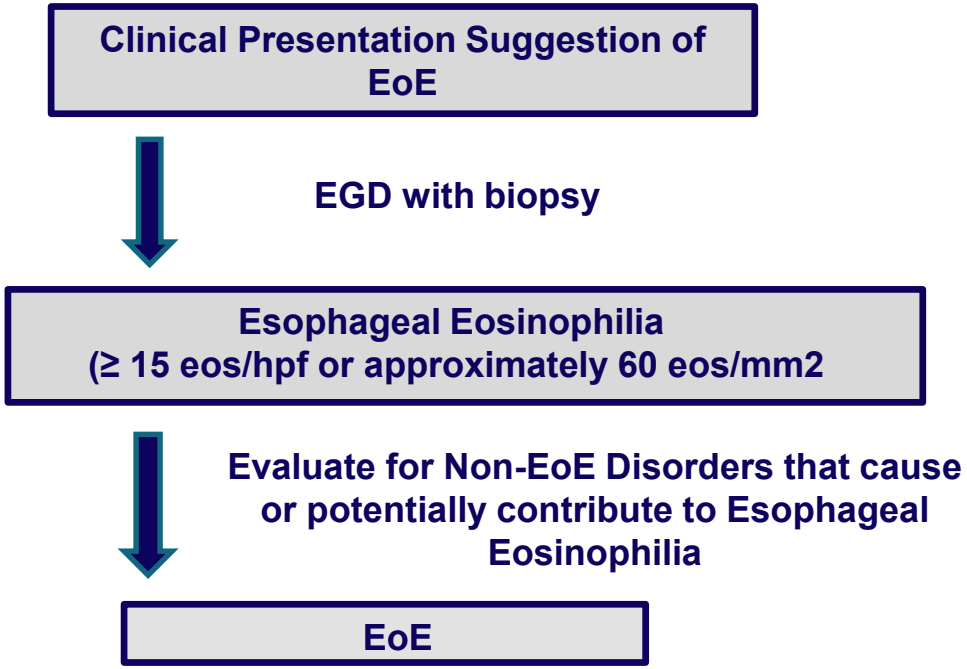
*Hoofien, 2019*

# Diagnosis

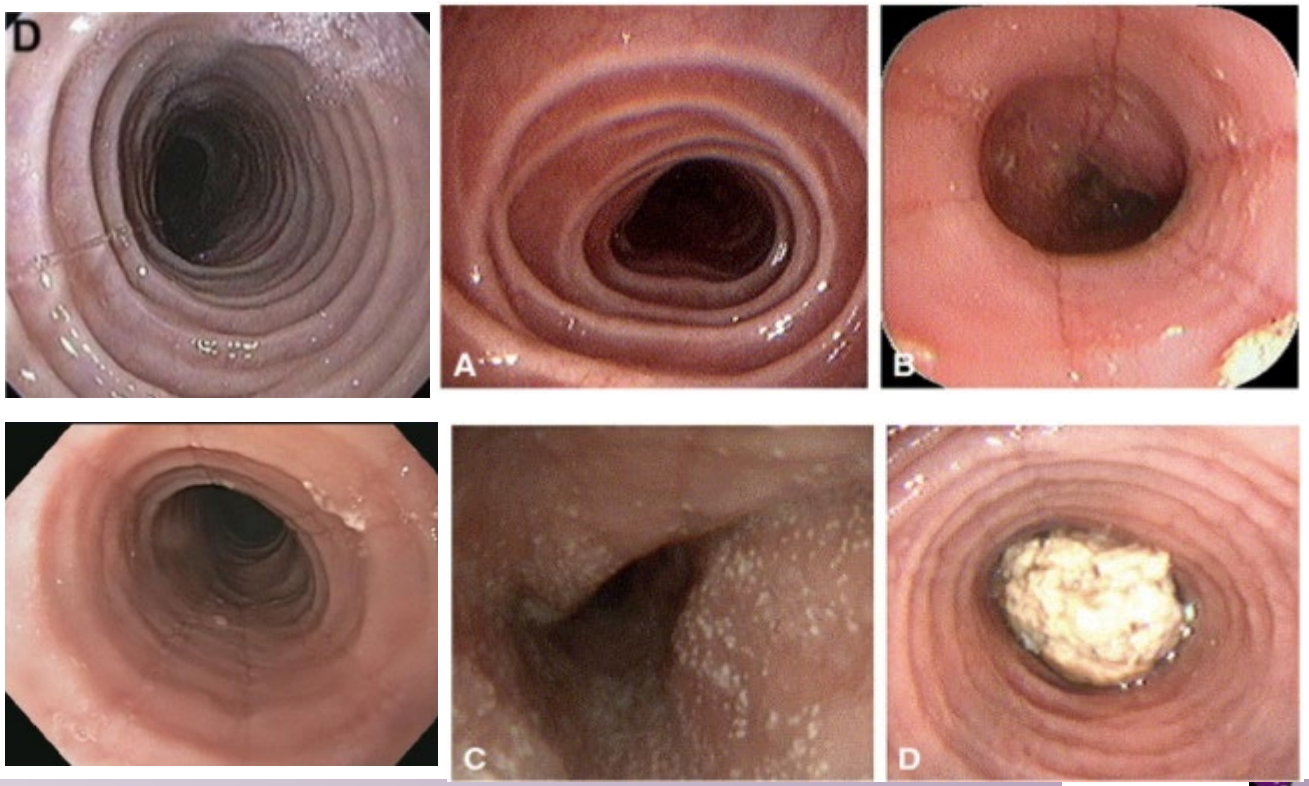



*Dellon, 2018*

# Diagnosis



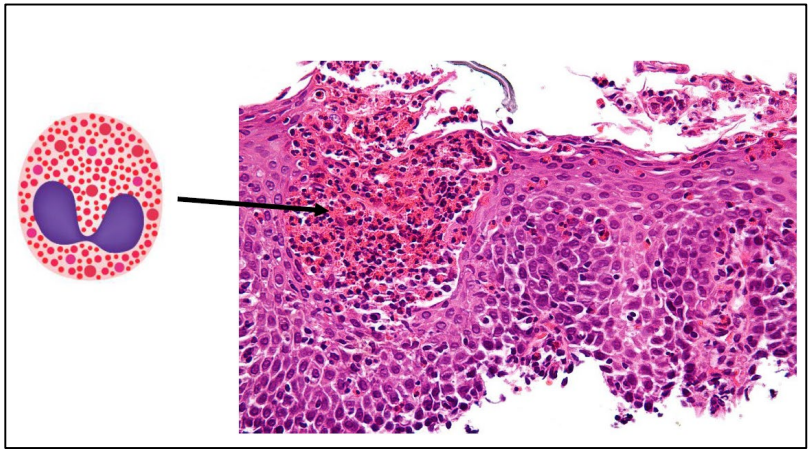
EREFS



# Diagnosis

Endoscopy with biopsies – always !

➢ 15 eosinophils per high-powered field (60 eos/mm$^2$)



- ➢ 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

| Differential diagnosis of eosinophilic esophagitis |
| --- |
| Eosinophilic gastrointestinal diseases |
| Celiac disease |
| Infection |
| Hypereosinophilic syndrome |
| Achalasia |
| Vasculitis |
| Pemphigus |
| Connective tissue diseases |
| Drug hypersensitivity |



*Fahey, 2017*

| Risk factor | Comment |
|---|---|
| Aeroallergens | Might cause EoE or increase disease activity; can cross react with food allergens; may explain seasonal variation in diagnosis |
| Food allergens<br>Helicobacter pylori | Directly trigger EoE; elimination can lead to disease remission<br>Inversely associated with EoE; decrease in H. Pylori prevalence has accompanied increase in EoE prevalence over the last 20 years; mechanistic data lacking |
| Infections (herpex simplex virus; mycoplasma)<br>Oral or sublingual immunotherapy | Associated with EoE; mechanistic data lacking<br>Causes or induces EoE in certain patients; baseline EoE status for reported cases usually not know prior to immunotherapy |
| Proton pump inhibitors<br>Cold or arid climates | Reported to induce IgE antibodies to certain foods<br>Increased odds of EoE in these climate zones, but not in temperate or tropical zones |
| Population density<br>Early life factors | Odds of EoE increase as population density decreases<br>Antibiotic use, Cesaeran section, and preterm delivery increase the odds of pediatric EoE |
| Connective tissue disorders | Ehlers-Danlos, Marfan syndrome, and Loeys-Dietz syndrome have been associated with EoE |
| Celiac disease | Associated with EoE; EoE is more common in patients with celiac disease than would be expected |
| Autoimmune conditions | Inflammatory bowel disease , rheumatoid arthritis, igA deficiency, multiple sclerosis, and Hashimoto's thyroiditis associated with EoE |



*Gastroenterol 2018*

# Treatment

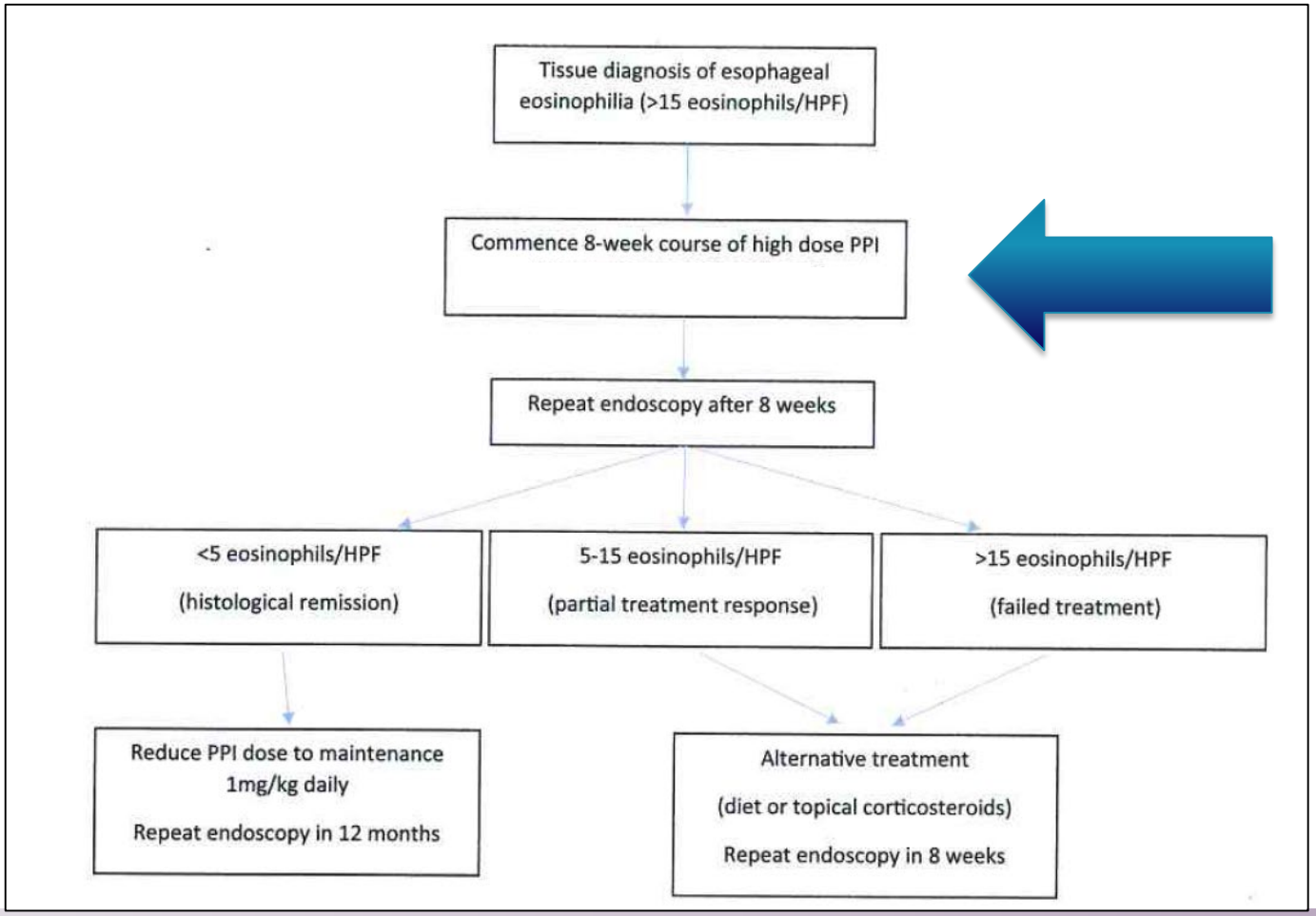
**Indications for treatment :**

- 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 esosinophilic 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)
5-15 eosinophils/HPF
(partial treatment response)
>15 eosinophils/HPF
(failed treatment)
Reduce PPI dose to maintenance 1mg/kg daily
Repeat endoscopy in 12 months
Alternative treatment
(diet or topical corticosteroids)
Repeat endoscopy in 8 weeks

*JPGN; 2018*

# Proton pump inhibitors

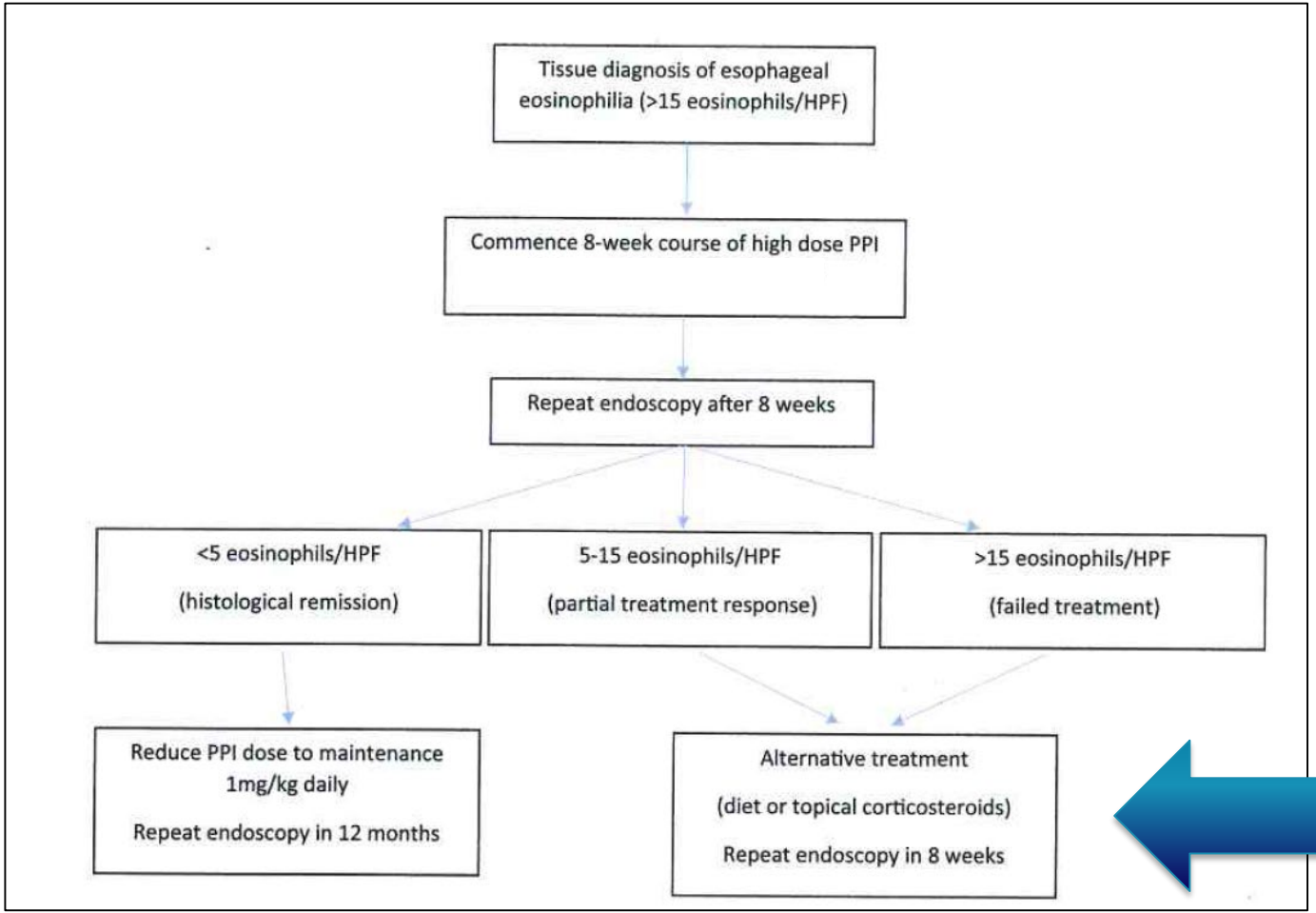
- Gastric acid inhibition
- Anti-inflammatory effects (inhibition of Th2-mediated eotaxin 3 secretion and to improve epithelial integrity)

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

- Long-term therapy, 1-year follow up 78,6% remained histologic remisson
- Progressive decrease in dosage to the lowest point with remission



*Lucendo, 2017*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*JPGN; 2018*

# 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

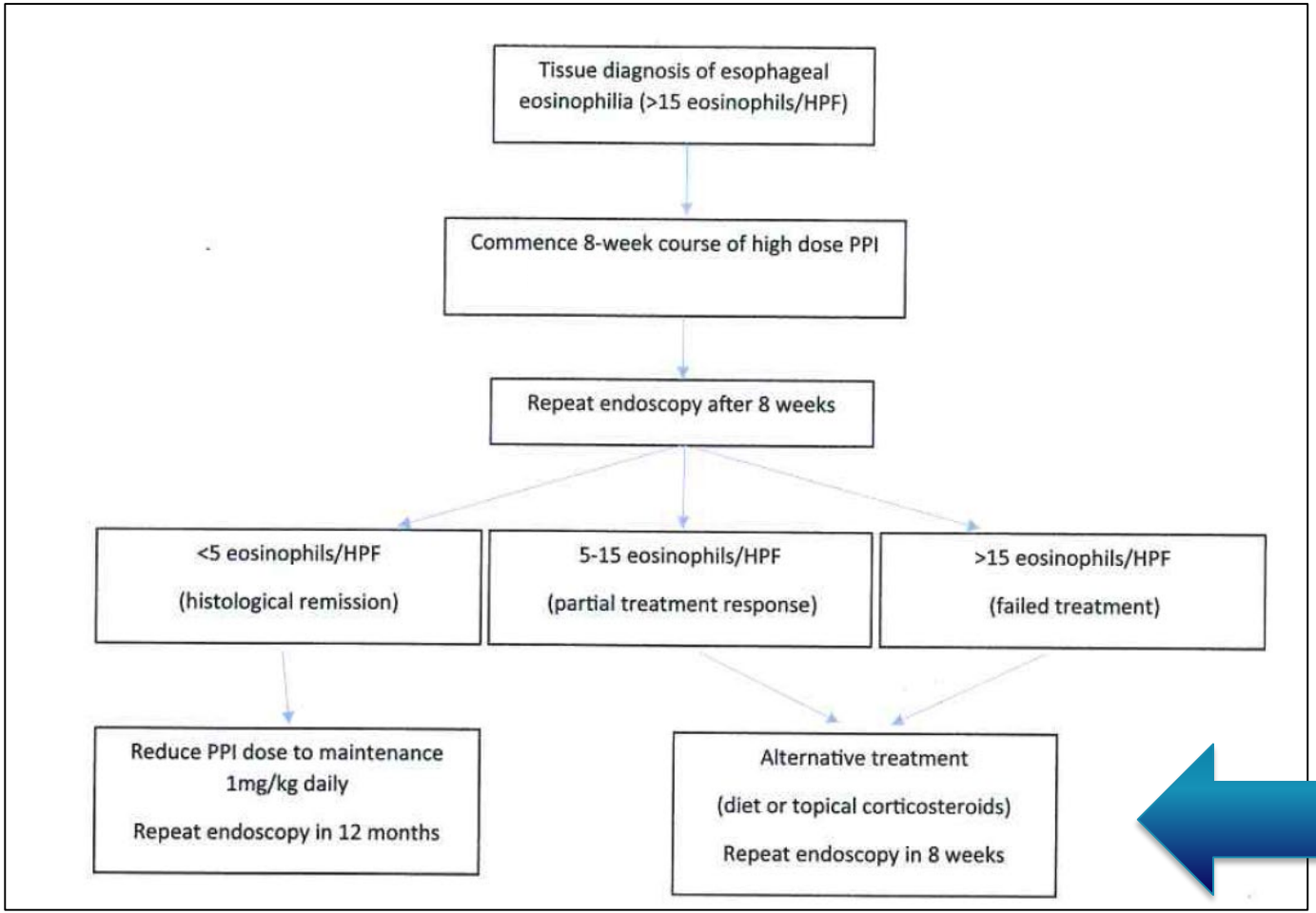


*Lucendo, 2017*

# 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 !!**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*JPGN; 2018*

# 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

**Avoid the ‘trigger ‘ food**

- Exclusive feeding with elemental diets
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- Allergy test-driven food elimination

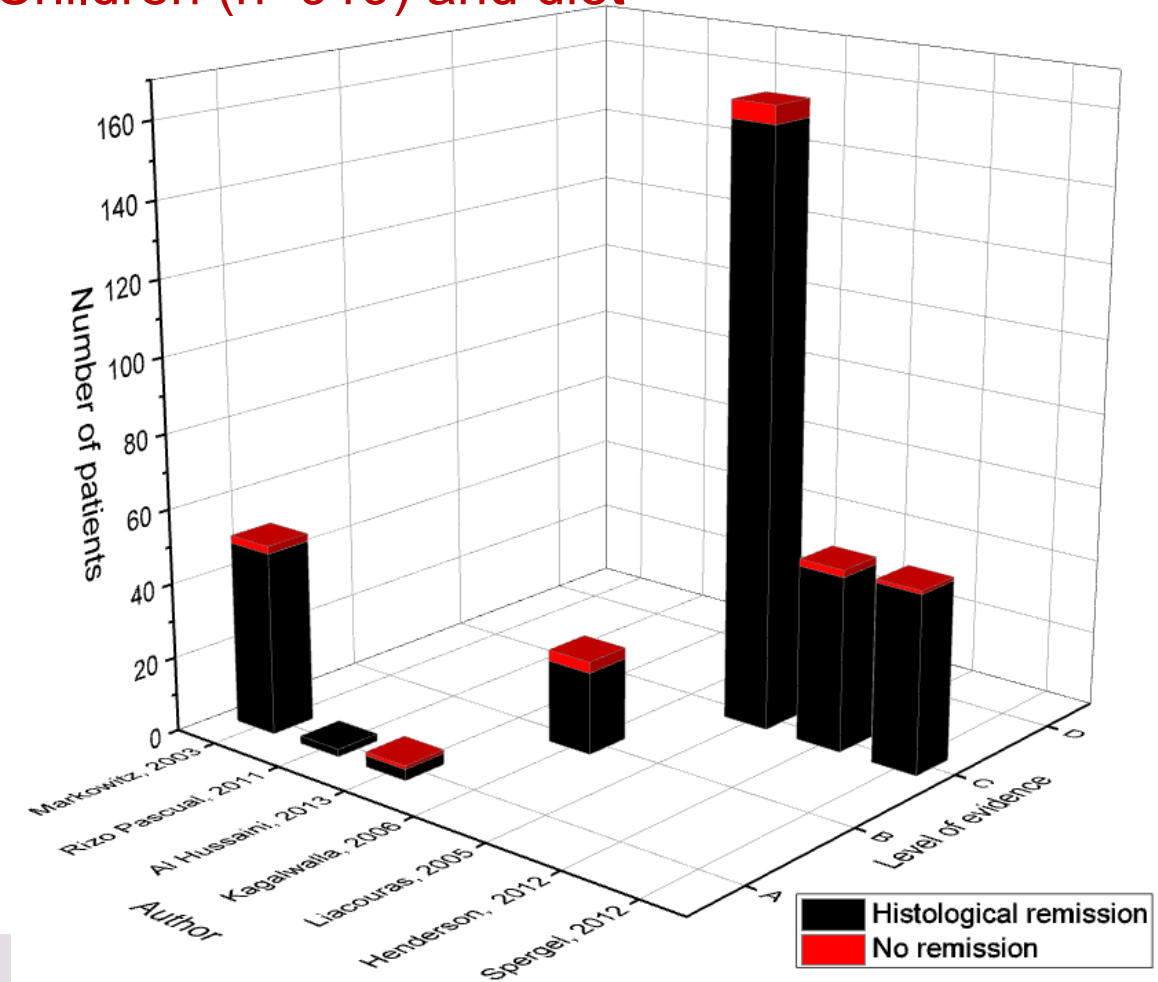
# Exclusive feeding with elemental diets

- 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, Puramino Junior)



# Children (n=919) and diet




# Amino-acid (AA) diet

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Masterproef 2017



- Induce remission
- Easy in young children
- Ultimate rescue therapy
- Temporary solution



- Palatability
- Delayed speech
- Cost of elemental formula
- Emotional cost

# Dietary assessment

**Avoid the ‘trigger ‘ food**

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



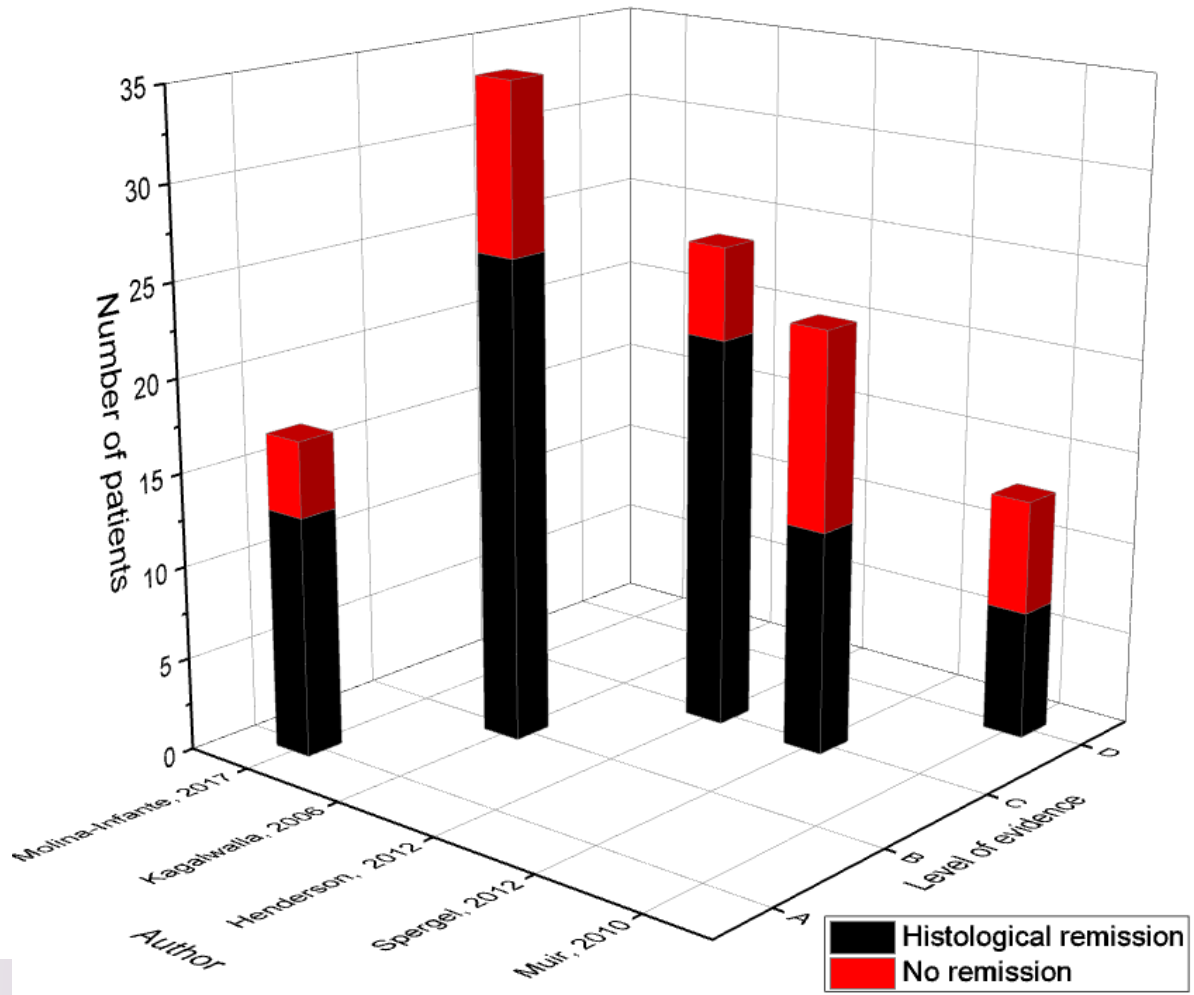
# Empiric elimination of common dietary antigens



- 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

# Six Food elimination diet



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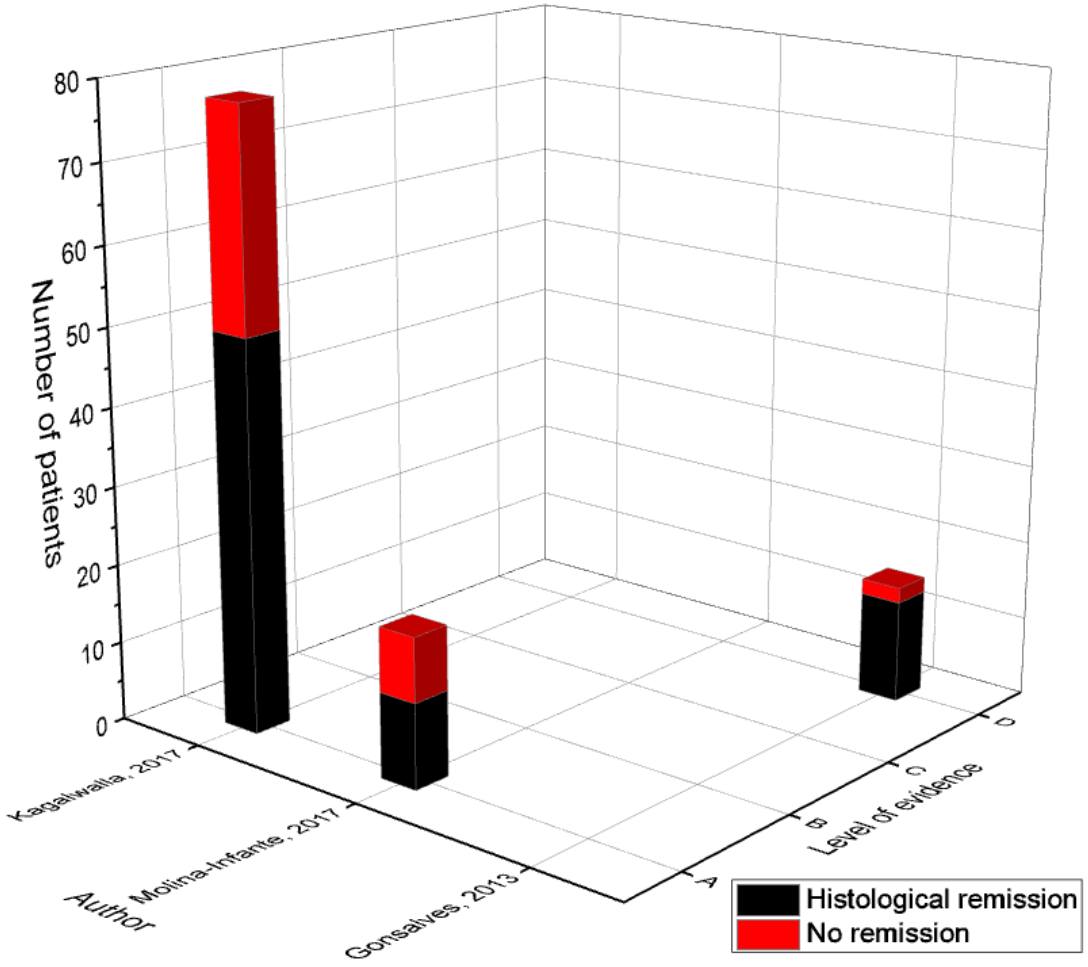
# Four Food elimination diet









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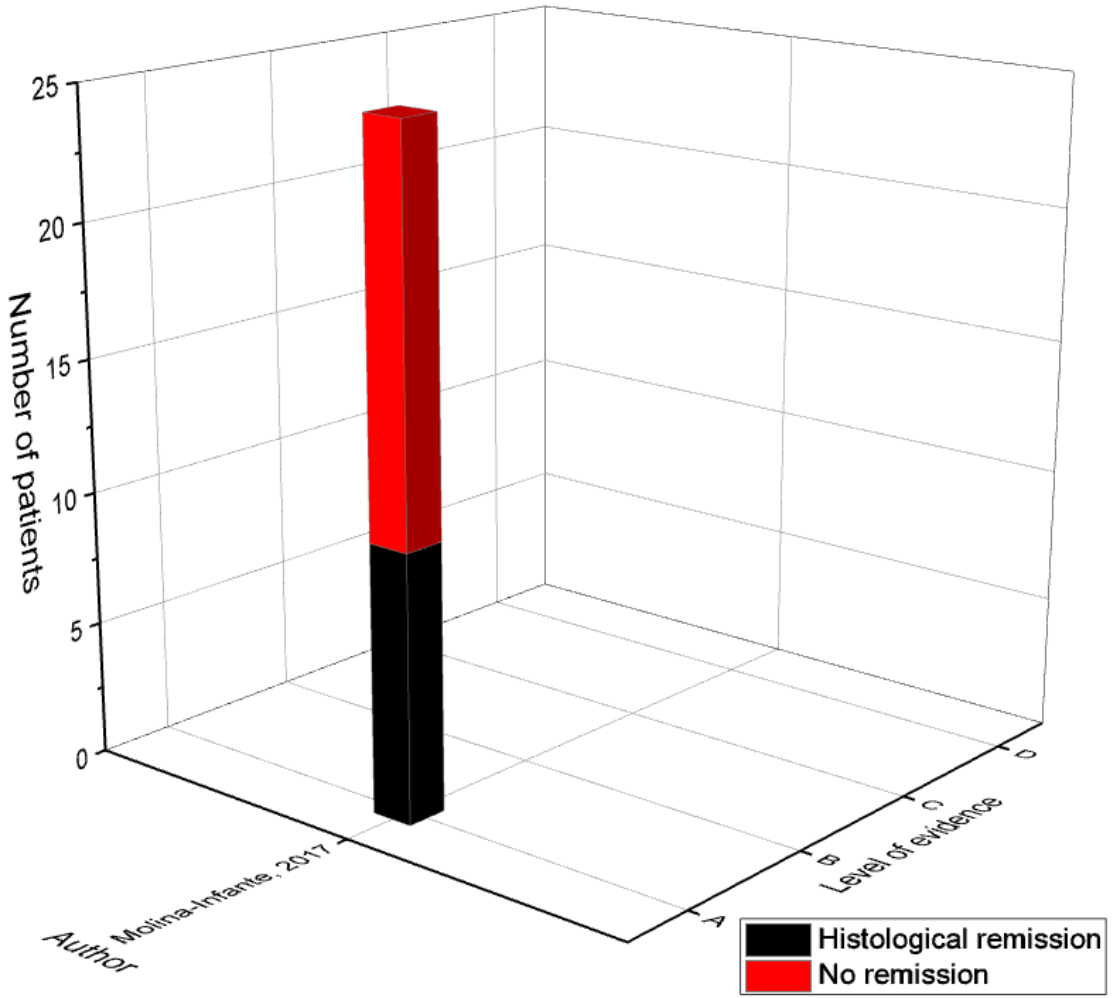


# Two Food elimination diet





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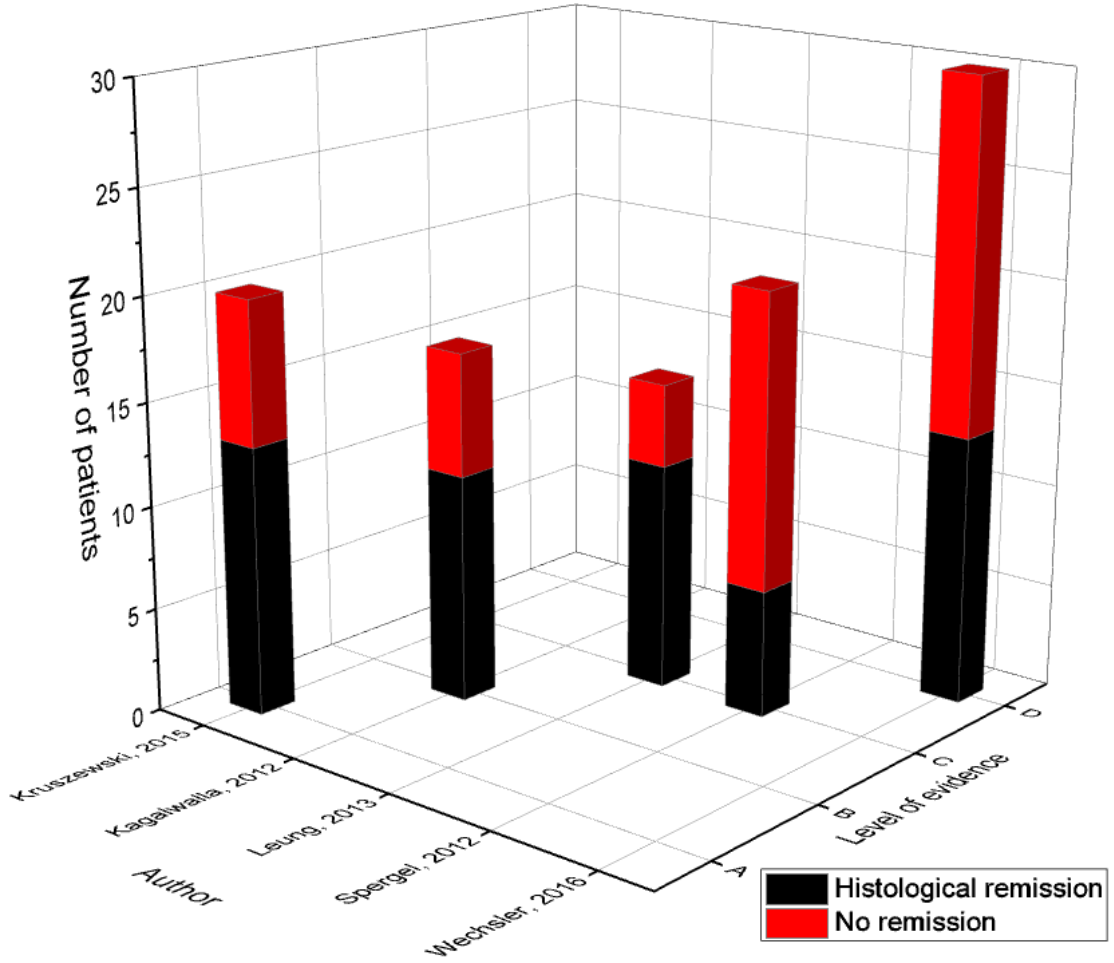
# Eliminating cow's milk



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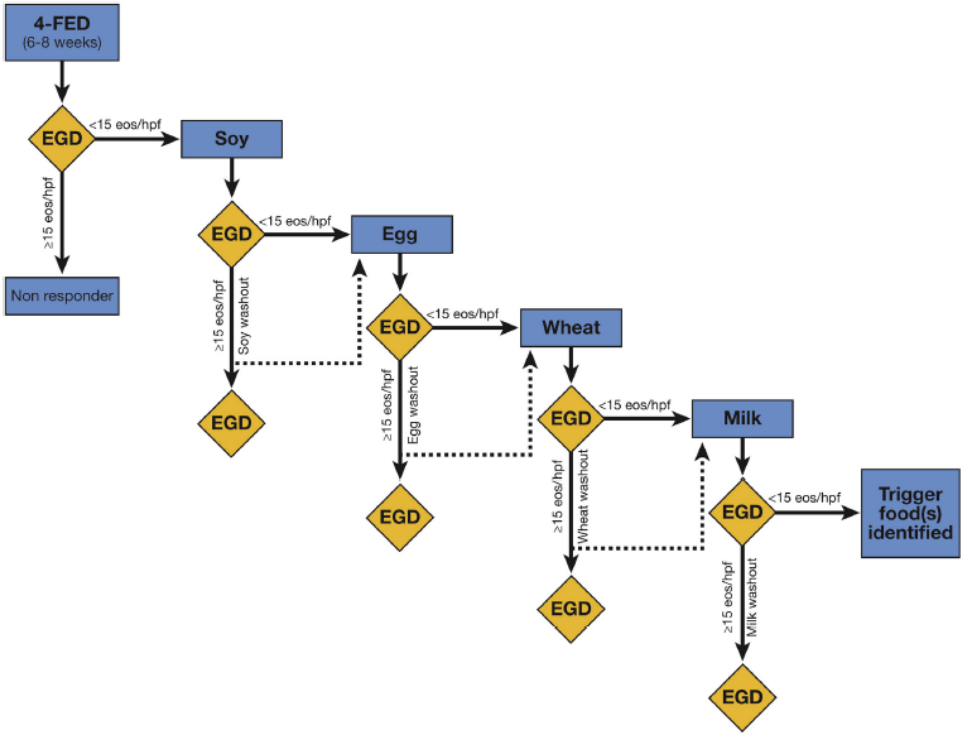
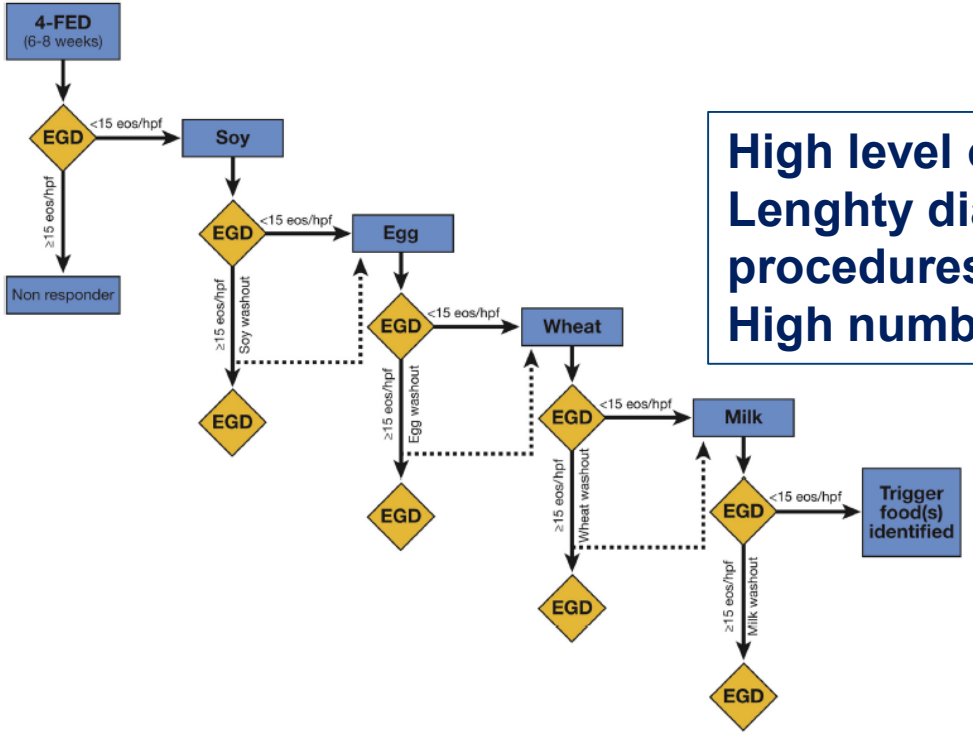
# STEP-DOWN elimination diet



# STEP-DOWN elimination diet




**High level of restrictions**
**Lenghty diagnostic procedures**
**High number of endoscopies**

# 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



*Molina-infante, 2017*

# STEP-UP elimination diet

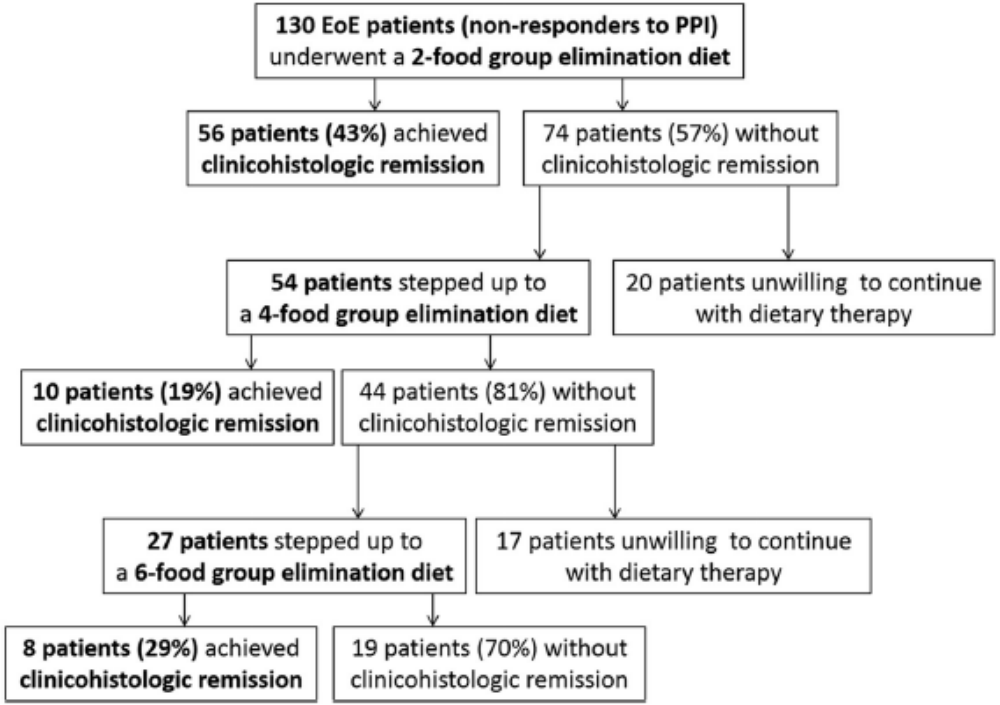



**FIG 1.** Flowchart of patients during the study.

*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 %
    - 1 food : cow's milk - remission rate in 33% in children and 13% in adults
  - Studies :
    - **Belgium : cow's milk, wheat and eggs**
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*Molina-infante, 2017*

# Dietary assessment

**Avoid the ‘trigger ‘ food**

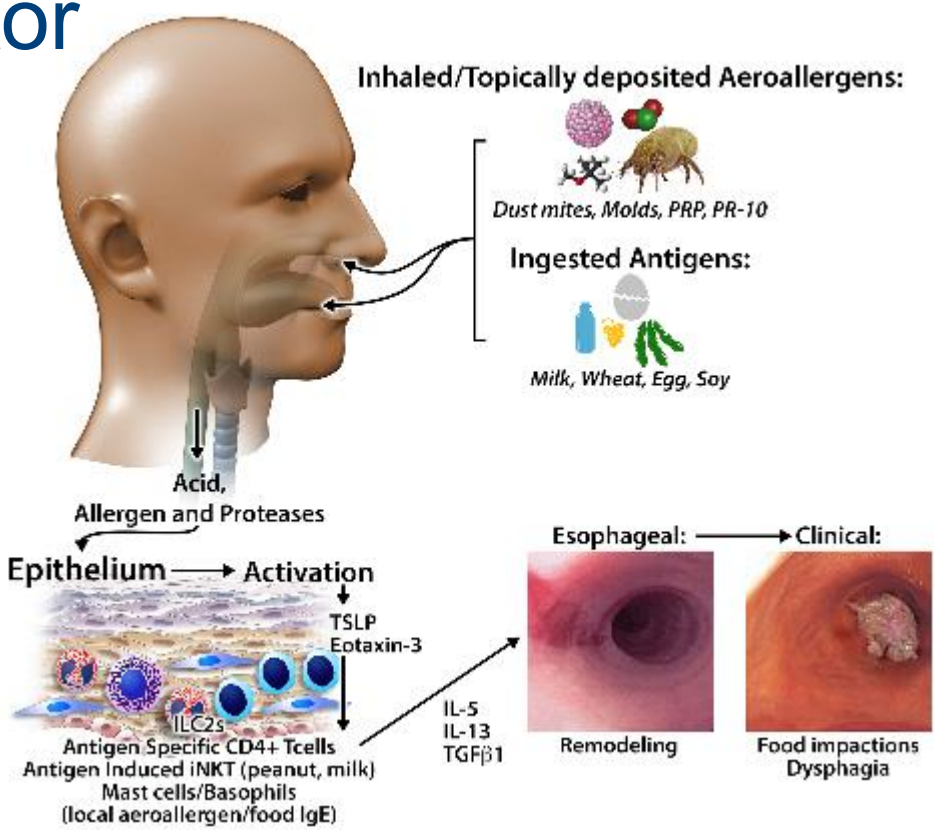
- Exclusive feeding with elemental diets
- Empiric elimination of common dietary antigens
- Allergy test-driven food elimination

# 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



# Atopy as risk factor




Spergel J, Aceves SS. **J Allergy Clin Immunol**. **2018** Jul;**142**(1):1-8

| Food study | No. | Pediatric/adult | Milk | Egg | Wheat | Peanut/tree nuts | Soy/legumes | Fish/shellfish |
|---|---|---|---|---|---|---|---|---|
| Gonsalves et al[28] | 20 | Adult | 50% | 5% | 60% | 10% | 10% | |
| Kagalwalla et al[29] | 36 | Pediatric | 74% | 17% | 26% | 6% | 10% | |
| Lucendo et al[30] | 42 | Adult | 62% | 26% | 28.6%* | 16.7% | 23.8% | 19% |
| Henderson et al[31] | 26 | Pediatric | 65% | 40% | 37% | | | |
| Spergel et al[23] | 319 | Pediatric | 66% | 24.5% | 22.6% | 5% | | 0% |
| Molina-Infante et al[32] | 28 | Adult | 50% | 36% | 31%* | | 18% | |
| Rodriquez-Sanchez et al[33] | 46 | Adult | 64% | 21% | 28% | | 7% | |
| Wolf et al[34] | 11 | Adult | 44% | 44% | 22% | 11% | 11% | 11% |
| Molina-Infante et al[6] | 64 | Adult | 81% | 15% | 43%* | 1% | 9% | 6% |
| Kagalwalla et al[5] | 78 | Pediatric | 85% | 35% | 33% | | 19% | |
| Kruszewski et al[35] | 20 | Pediatric | 64% | | | | | |
| **Total of 702 patients** | | **Average** | **66%** | **24%** | **27%** | **4%** | **12%** | **2%** |

Spergel J, Aceves SS. **J Allergy Clin Immunol**. **2018** Jul;**142**(1):1-8



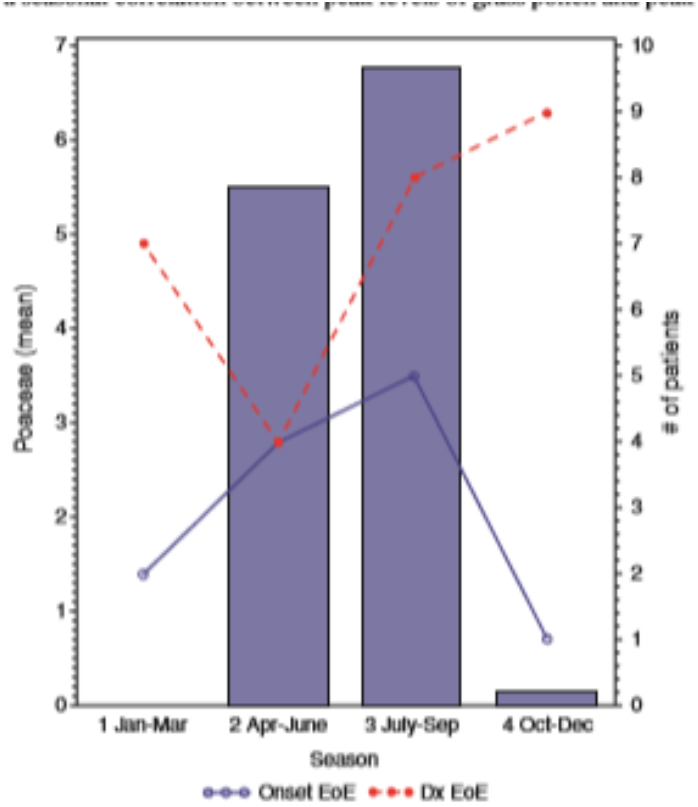
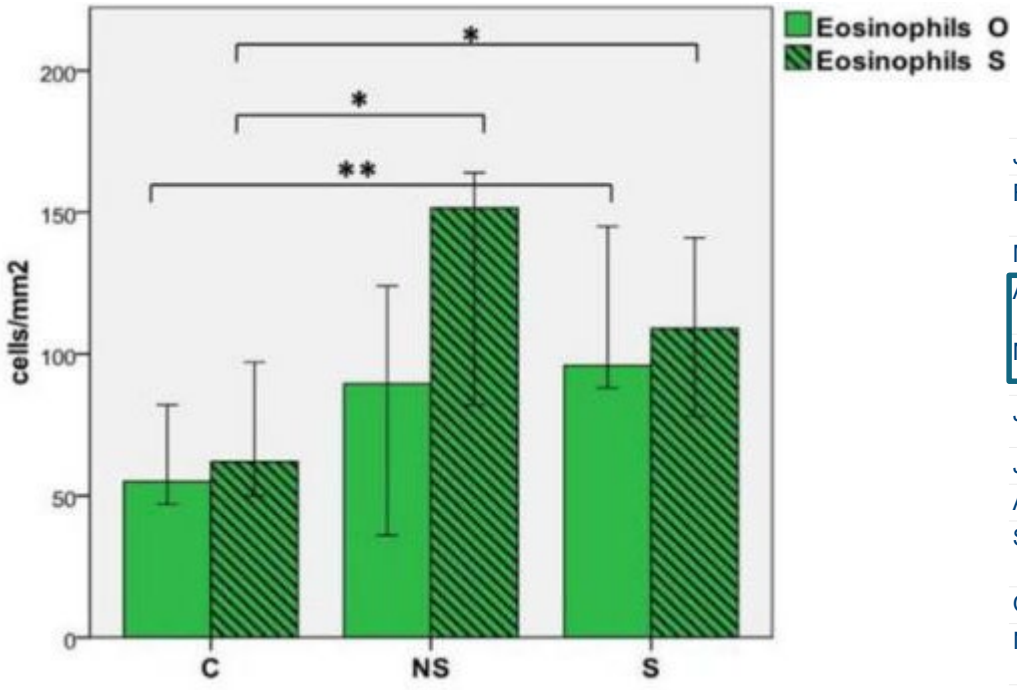



**FIGURE 1.** Seasonal correlation between Poaceae and symptom onset in newly diagnosed EoE. EoE indicates eosinophilic esophagitis.

Fahey L *et al* J Pediatr Gastroenterol Nutr. 2017 Jan;64(1):22-25.




| Month | Total cases | Daily pollen count (particles per $mm^3$, mean ± SD)[*] | Lamina propria eosinophils (mean ± SD)[a] | |
|---|---|---|---|---|
| | | | Ascending colon | Descending colon |
| January | 24 | N/A | 31 ± 14 | 22 ± 14 |
| February | 13 | N/A | 38 ± 12 | 14 ± 10 |
| March | 18 | N/A | 32 ± 10 | 12 ± 6 |
| April | 12 | 168 ± 50 | 45 ± 21 | 13 ± 11 |
| May | 16 | 363 ± 85 | 38 ± 13 | 12 ± 8 |
| June | 18 | 116 ± 42 | 32 ± 23 | 7 ± 4 |
| July | 17 | 11 ± 3 | 31 ± 20 | 10 ± 9 |
| August | 23 | 21 ± 9 | 30 ± 14 | 10 ± 8 |
| September | 14 | 31 ± 11 | 37 ± 20 | 7 ± 4 |
| October | 16 | N/A | 36 ± 11 | 8 ± 7 |
| November | 11 | N/A | 39 ± 19 | 13 ± 13 |
| December | 16 | N/A | 33 ± 15 | 7 ± 7 |

Abbreviation: N/A, not available.

Rentzos G *et al*.Clin Transl Allergy. 2014 May 30;4:19.

Polydorides AD *et a*l,Hum Pathol. 2008 Jun;39(6):832-6.

**TABLE II.** Specific and total serum IgE levels, $IgG_4$ levels to rBet v 1, peripheral blood eosinophil counts, eosinophil cationic protein levels in stools, and medication at different ages

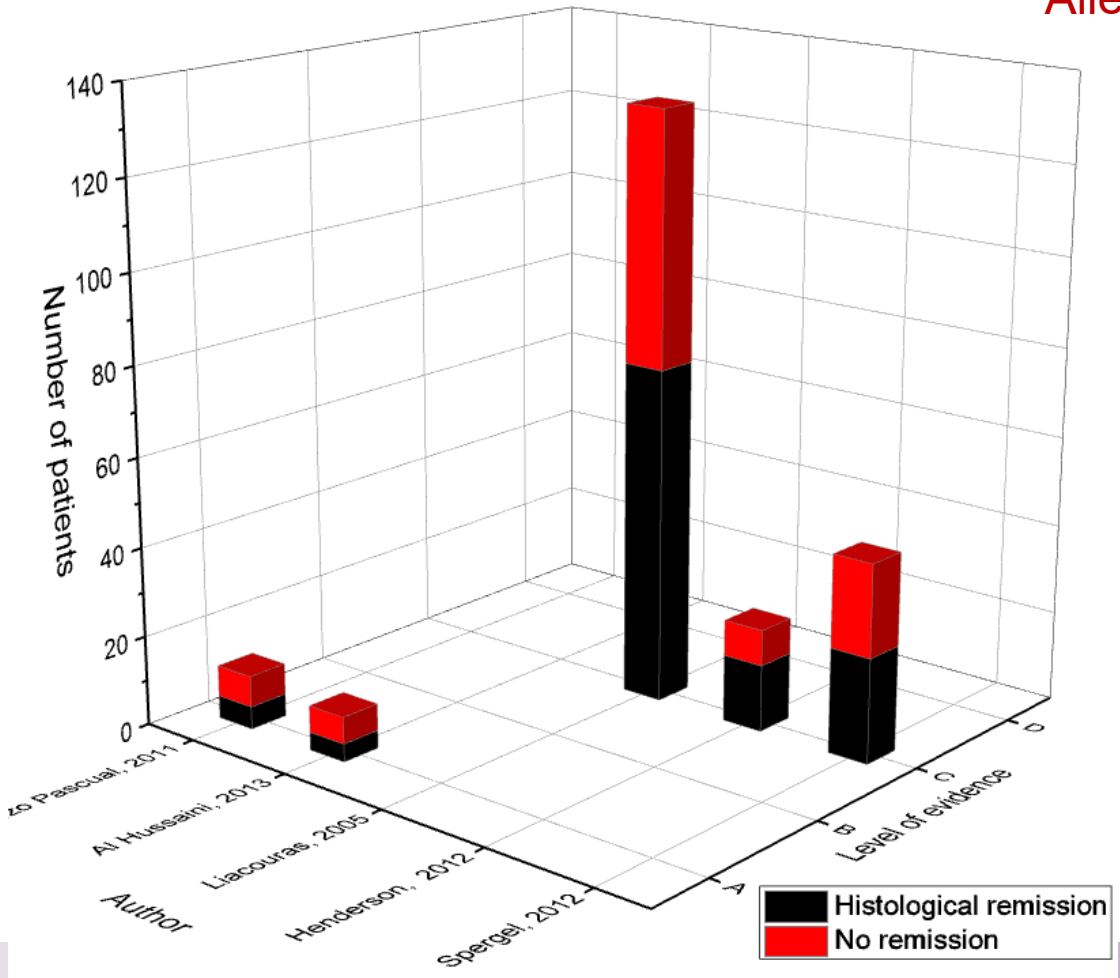
| Age (y) | | | 10.2 | 11.2 | 12.5 | 13.5 | 14.5 | 15.5 | 16.5 |
|---|---|---|---|---|---|---|---|---|---|
| Blood | | | | | | | | | |
| CAP (kU/L) | Birch | | >100 | >100 | >100 | | 27.0 | 22.2 | 33.90 |
| | rBet v 1 | | | | >100 | 56.4 | 21.4 | 14.8 | 27.30 |
| | rBet v 2 | | | | | | 0.10 | <0.10 | 0.77 |
| | Apple | | 0.92 | | 2.16 | | | 0.66 | 1.35 |
| | rCor a 1 | | | | | | | | 15.10 |
| | rPru p 1 | | | | 40.2 | | | | |
| | rPru p 3 | | | | <0.10 | | | | |
| | Bromelaine | | 0.11 | | | | 0.11 | | |
| Total IgE (kU/L) | | | 292 | 1143 | 405 | | 115 | 60 | 191 |
| $IgG_4$ (mg/L) | rBet v 1 | | | | 2.5 | 8.3 | | 9.8 | |
| Eosinophils (no./μL) | | | 440 | 477 | 251 | | 235 | 100 | 221 |
| Stools: ECP* | μg/g | | 5/3/16.2 | | | | | | 1.4/2/2.4 |
| | | Administration | Daily dose | | | | | | |
| Medication | | | | | | | | | |
| Loratadine | | PO | 5 mg ×1 | † | | | | | |
| Fluticasone | | Sw | 250 μg ×4 | † | | | | | |
| | | | 250 μg ×2 | | † | | | | |
| | | IH | 100 μg ×2 | | | † | † | † | |
| Ranitidine | | PO | 100 mg ×2 | † | † | | | | |
| | | | 150 mg ×2 | | | † | † | † | † |
| Levocetirizine | | PO | 5 mg ×1 | | † | † | † | † | † |
| DSCG | | PO | 60 mg ×4 | | † | † | † | | |
| Methylprednisolone | | PO | 8 mg for 5 d | | † | | | | |
| Desensitization | | | | | | | | | |
| Tree/grass pollen allergen | | SC | | | | † | † | † | † |

The *arrows* indicate the period during which a specific medication or medical treatment is given.
*DSCG*, Disodium cromoglycate; *IH*, inhaled; *PO*, oral ingestion; *SC*, subcutaneously; *Sw*, swallowed.
*Eosinophil cationic protein in stools collected just before provocation/immediately after provocation/10 days later, respectively.



**De Swert** L et al, J Allergy Clin Immunol. 2013 Feb;131(2):600-2.e1-3.

# Allergy-test-driven elimination diet

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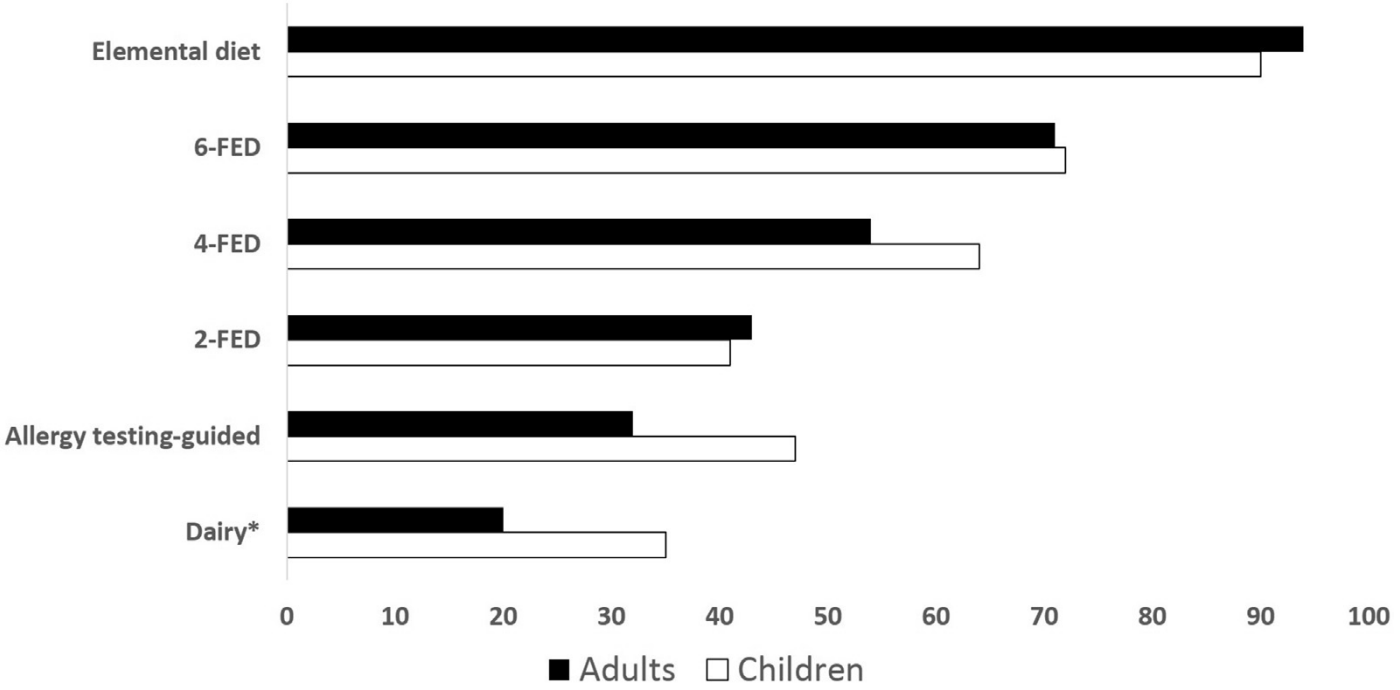
# Success rate




*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 UZ LEUVEN if PPI treatment is not succesful :

**Nutrition therapy**

**OR**

**Topical steroids**

If unsuccessful

Elimination of milk in infants & small children

If unsuccessful step-up to 3 food elimination diet – milk + egg + wheat

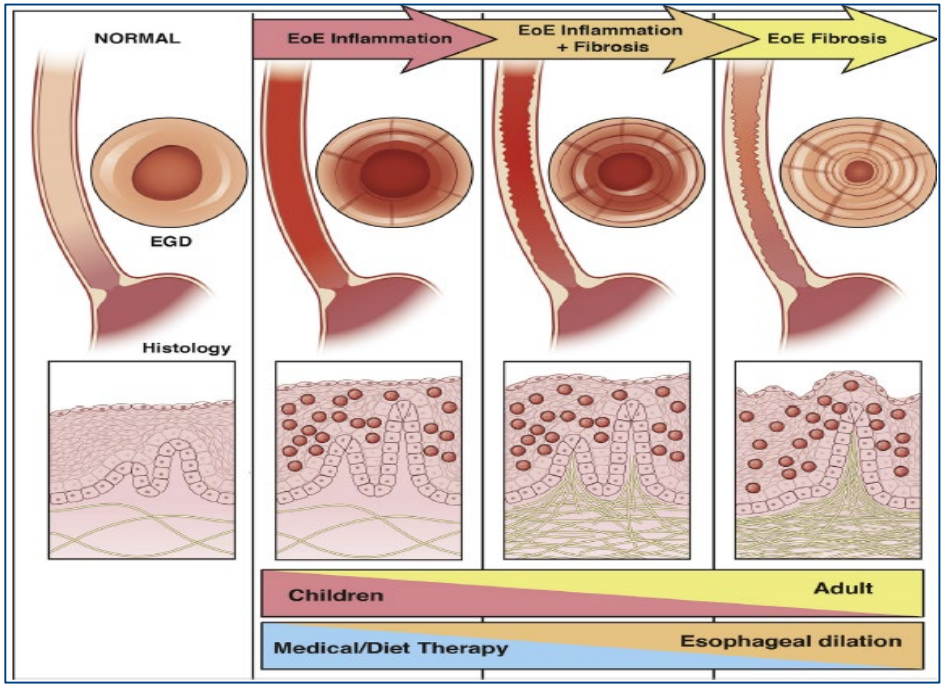
Elimination of 2 (or 3) foods in school children, adolescents & adults milk, egg, wheat

If unsuccesful, step-up to 6 food elimination diet

If successful continue long-term lowest possible dose

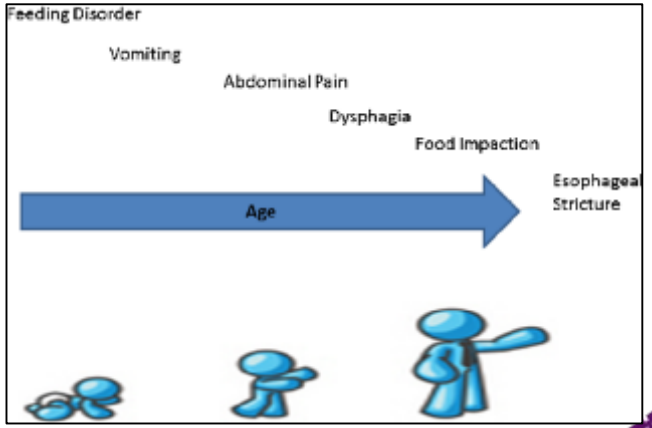
Whichever successful, continue long-term (!?)

# 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 topic steroids and dietary treatment to reverse esophageal remodeling in children




*Straumann, 2018*

# 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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