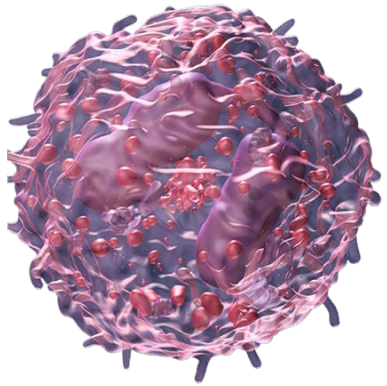


Eosinophilic Esophagitis(EoE)Panel

Mojgan Forootan MD
Ali Bahari MD
Iradj Maleki MD

Agenda

- Eosinophil in GI tract (including esophagus)
- Definition of eosinophilic esophagitis (EoE)
- Epidemiology
- Pathophysiology
- Clinical manifestations
- Diagnosis
- Differential Dx
- Management
- Prognosis

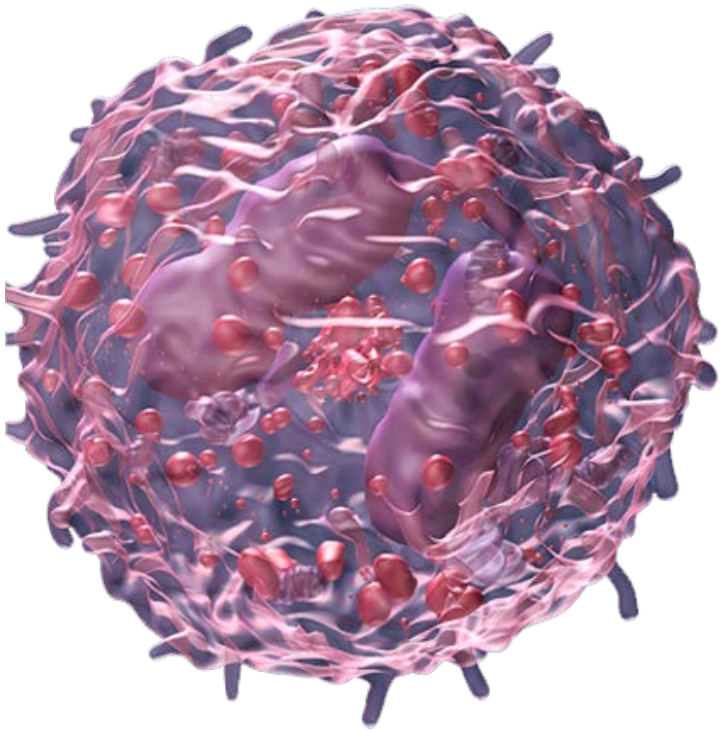
- A case based discussion

Eosinophils in GI Tract

- How many eosinophils per HPF are normal in esophagus?

- Zero
- Up to 5 per HPF
- Up to 10 per HPF
- Up to 15 per HPF

Eosinophils in GI Tract



- Normal eosinophil count / HPF

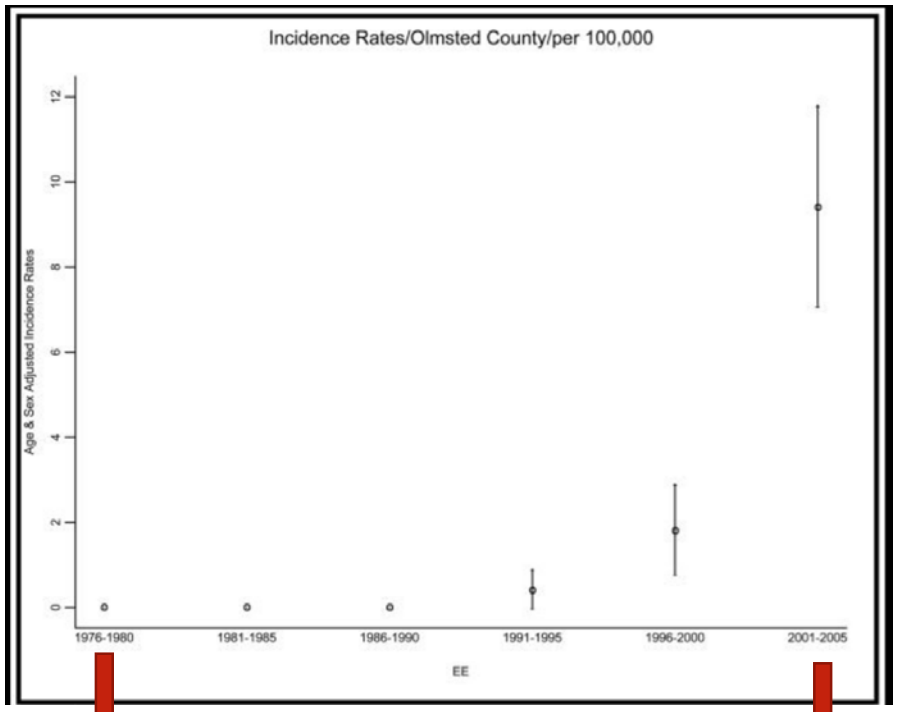
- Esophagus: 0
- Stomach: 30
- Duodenum: 30
- Ileum: 56
- Colon:
  - Right side: 100
  - Left side: 84
  - Rectosigmoid: 64

Epidemiology of EoE

- Reported cases from
  - North and South America
  - Europe
  - Asia
  - Australia
  - But not from Africa
- First cases of probable eosinophilic esophagitis (1960s to 1970s)
- Early1990s: patients with multiple esophageal rings

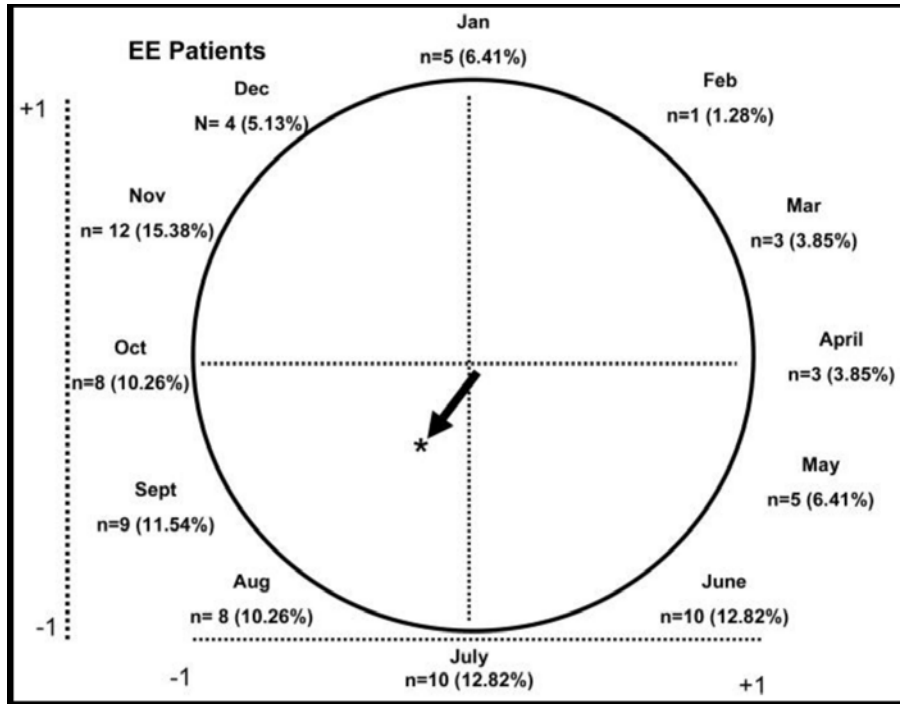
- Incidence of EoE is rising
- Most of the patients are male
- Most are in their 20s or 30s
- There is a seasonal variation in symptoms (Air pollution)
- More common in whites than other ethnic groups

Epidemiology of Eosinophilic Esophagitis over 3 Decades in Olmsted County, Minnesota

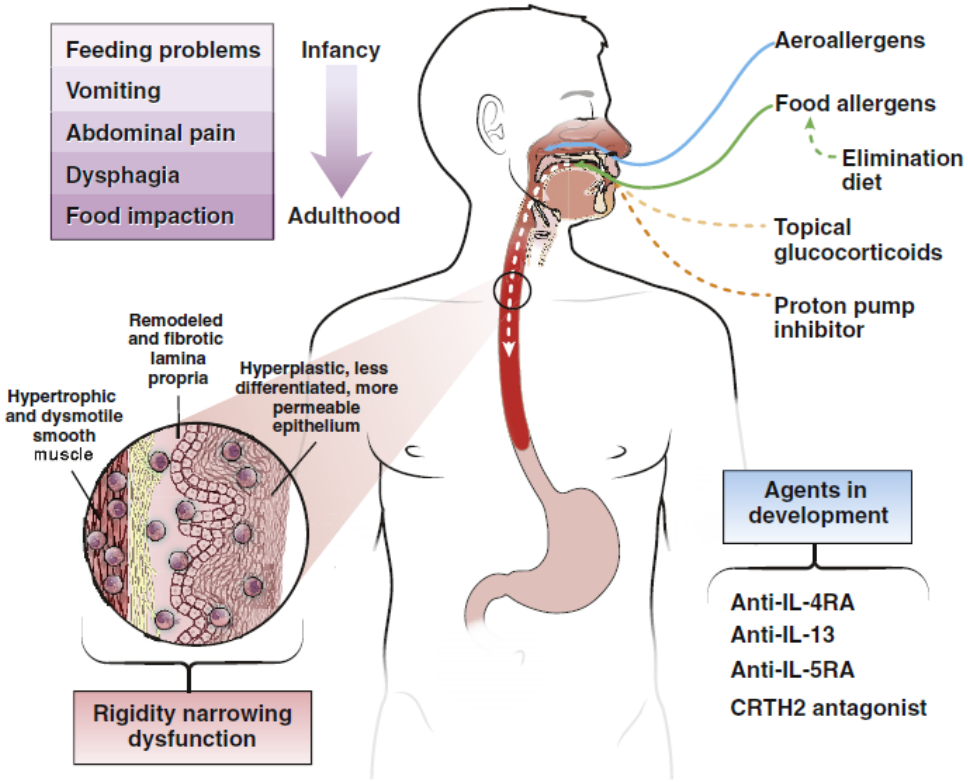


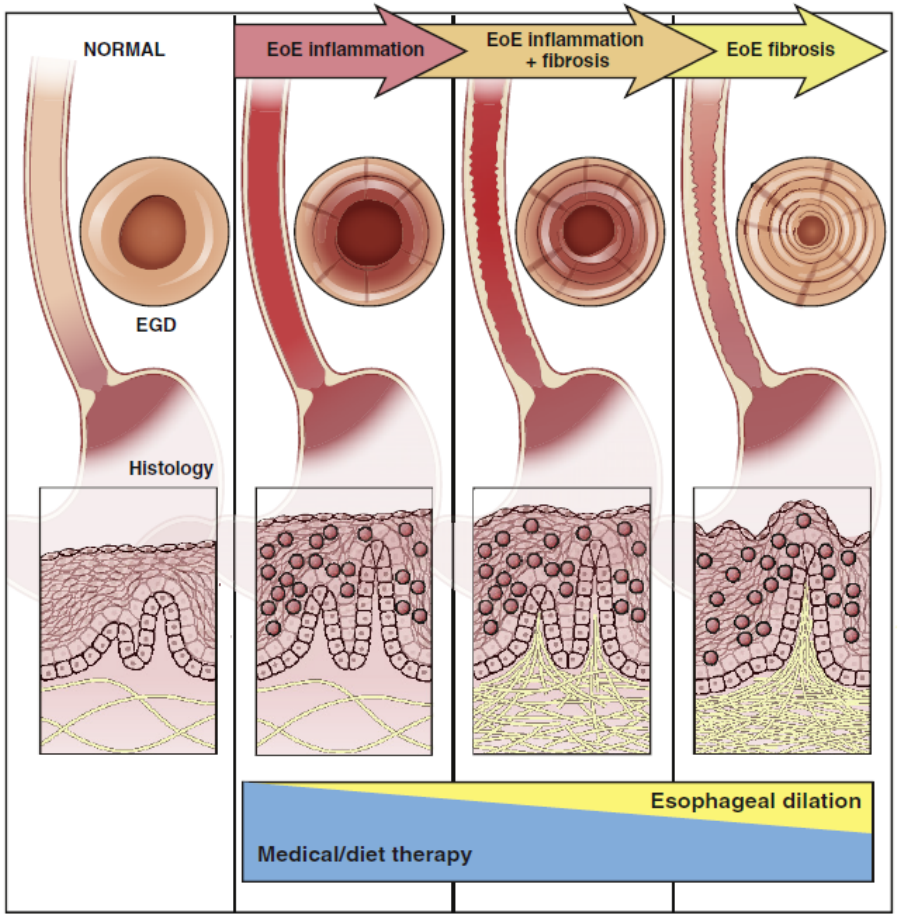
0.35 per 100,000

9.45 per 100,000

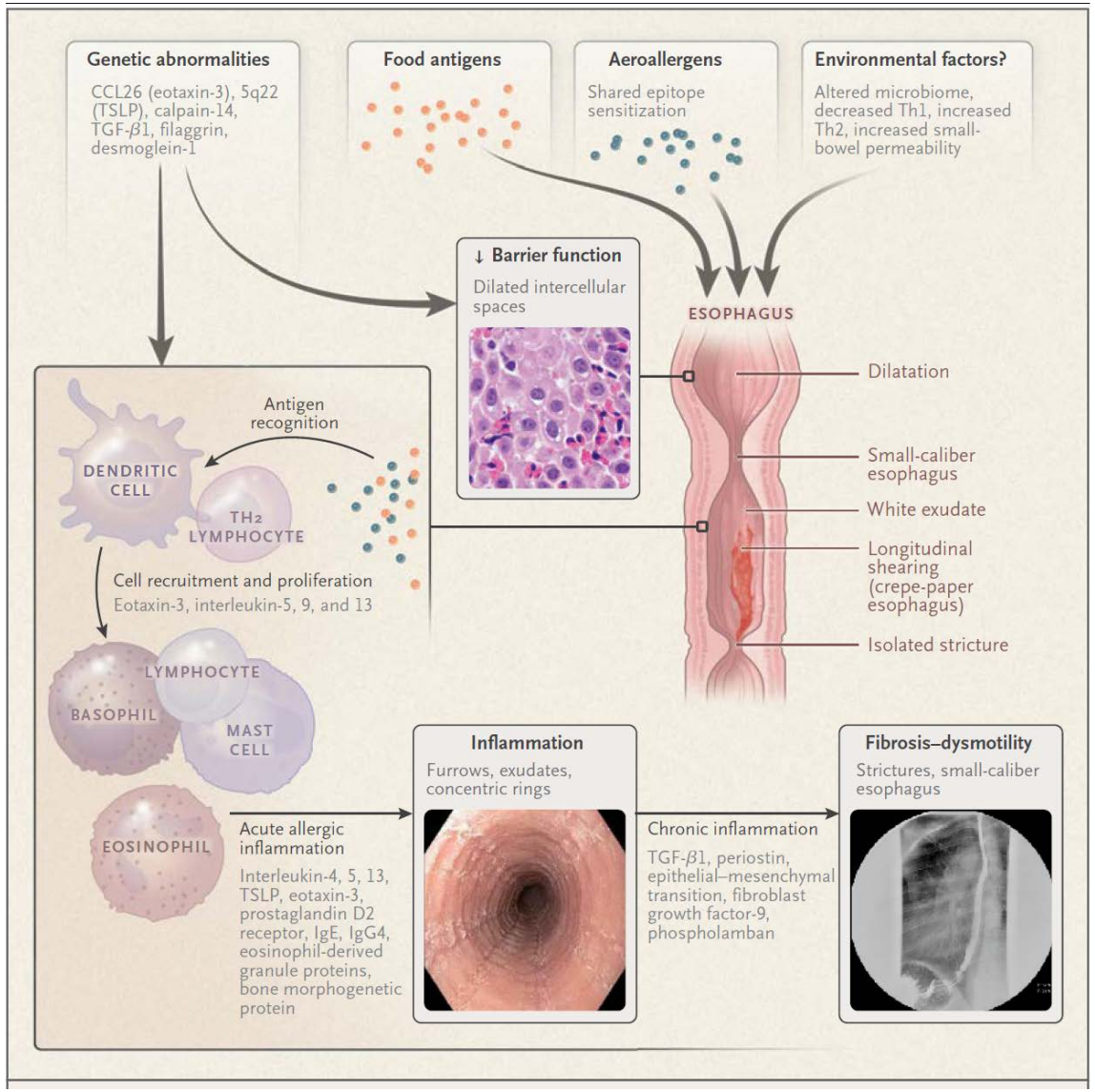


Pathophysiology Of EoE





Pathophysiology Of EoE



The Name of Eosinophilic Esophagitis

- Why EoE?
- Why not EE?

Case presentation

- A 22 years old male patient
- Complaining of retrosternal discomfort pain
- Recurrent food swallowing problem in chest during the few months
- Symptoms vanish in a few minutes, but recurs

- What is your plan?

Endoscopic finding

Can we diagnose EoE now?

- What are the clinical manifestation of EoE?

Clinical manifestations

Adults

- Dysphagia
- Food impaction
- Chest pain that is often centrally located and may not respond to antacids
- Gastroesophageal reflux disease-like symptoms/refractory heartburn
- Upper abdominal pain

Children

- Feeding dysfunction (median age 2.0 years)
- Vomiting (median age 8.1 years)
- Abdominal pain (median age 12.0 years)
- Dysphagia (median age 13.4 years)
- Food impaction (median age 16.8 years)

Clinical manifestations

- Adults and teenagers frequently present with dysphagia and food impactions
- younger children present with symptoms often include feeding difficulties, gastroesophageal reflux symptoms, and abdominal pain
- Eosinophilic esophagitis has been noted in 1 to 4 percent of patients with refractory reflux

Diagnosis of EoE

- The diagnosis of eosinophilic esophagitis is based upon symptoms, endoscopic appearance, and histological findings

- Diagnosis of EoE requires all of the following:
  1. Symptoms related to esophageal dysfunction
  2. Eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of ≥15 eosinophils per high power field (HPF) (or 60 eosinophils per mm^2
  3. Exclusion of other causes that may be responsible for or contributing to symptoms and esophageal eosinophilia

All causes of esophageal eosinophilia

Eosinophilic gastrointestinal diseases
PPI-responsive esophageal eosinophilia
Celiac disease
Crohn's disease
Infection
Hypereosinophilic syndrome
Achalasia
Drug hypersensitivity
Vasculitis
Pemphigus
Connective tissue diseases
Graft vs. host disease

Definition of EoE

- Chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil predominant inflammation

- ACG 2013
  - EoE is clinicopathologic disorder diagnosed by clinicians taking into consideration both clinical and pathologic
  - information without either of these parameters interpreted in isolation, and defi ned by the following criteria:
  - Symptoms related to esophageal dysfunction
  - Eosinophil-predominant inflammation on esophageal Bx, characteristically consisting of a peak value of 15 (Eos / HPF)
  - Mucosal eosinophilia is isolated to the esophagus and persists after a PPI trial
  - Secondary causes of esophageal eosinophilia excluded
  - A response to treatment (dietary elimination; topical corticosteroids) supports, but is not required for diagnosis

Definition of EoE

- **BSG (2021)**

- Eosinophilic oesophagitis is a condition characterized by
  - symptoms of dysphagia and/or food impaction in adults, and feeding problems, abdominal pain and/or vomiting in children,
  - with oesophageal histology showing a peak eosinophil count of ≥15 eosinophils/high power field (or ≥15 eosinophils/0.3 mm2 or >60 eosinophils/ mm2,
  - in the absence of other causes of oesophageal eosinophilia

Association with other diseases

Strong associations

- Allergic diseases
- Asthma
- Atopic dermatitis
- Environmental allergies
- Food allergies

- Celiac disease

Weak associations

- Inflammatory bowel disease
- Chronic rhinosinusitis
- Connective tissue disorders
- Caustic injury
- Antibiotic exposure in infancy
- Herpes simplex virus esophagitis
- Schatzki ring A

Back to the case

- What else do we need for the proper diagnosis of EoE in this patient?

- Radiographic and laboratory findings may support the diagnosis and help establish baseline esophageal luminal integrity, but are not required to establish the diagnosis

Endoscopy in the diagnosis of EoE

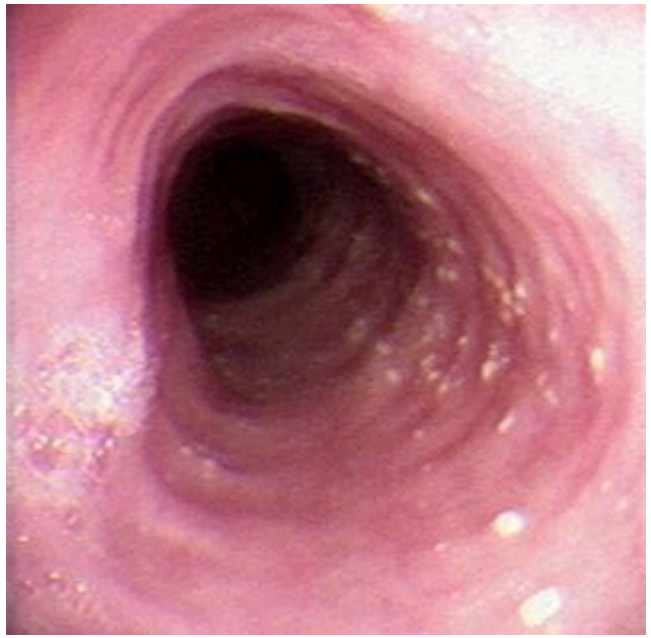
Endoscopy in the diagnosis of EoE

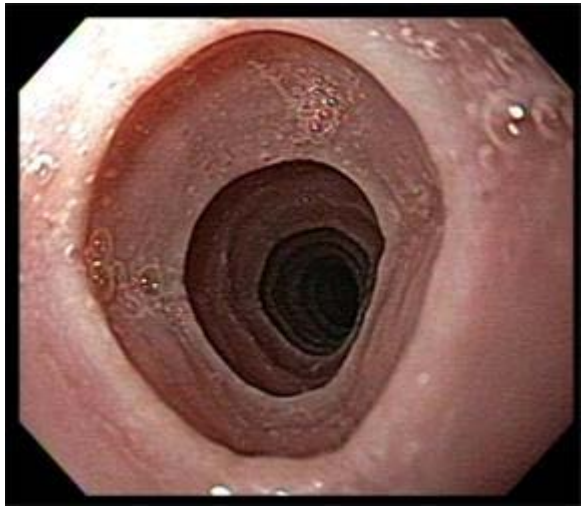
- What should we look after in the endoscopy
- Are the findings specific / sensitive?

Endoscopy in the diagnosis of EoE

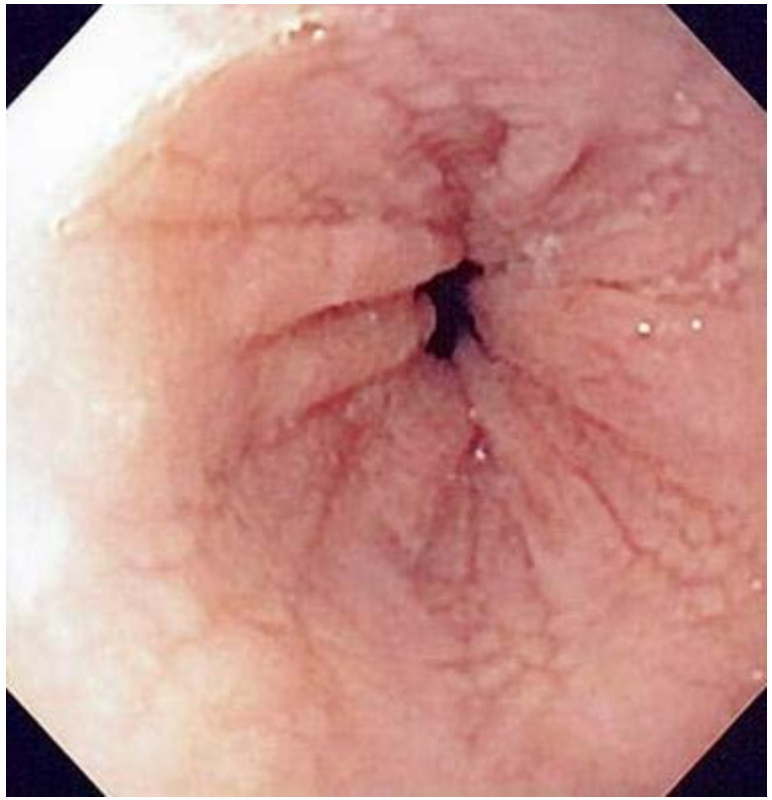
- Stacked circular rings ("feline" esophagus) (picture 1): 44 percent
- Strictures (particularly proximal strictures) (image 1): 21 percent
- Attenuation of the subepithelial vascular pattern: 41 percent
- Linear furrows (picture 2): 48 percent
- Whitish papules (representing eosinophil microabscesses) (picture 1): 27 percent
- Small caliber esophagus: 9 percent

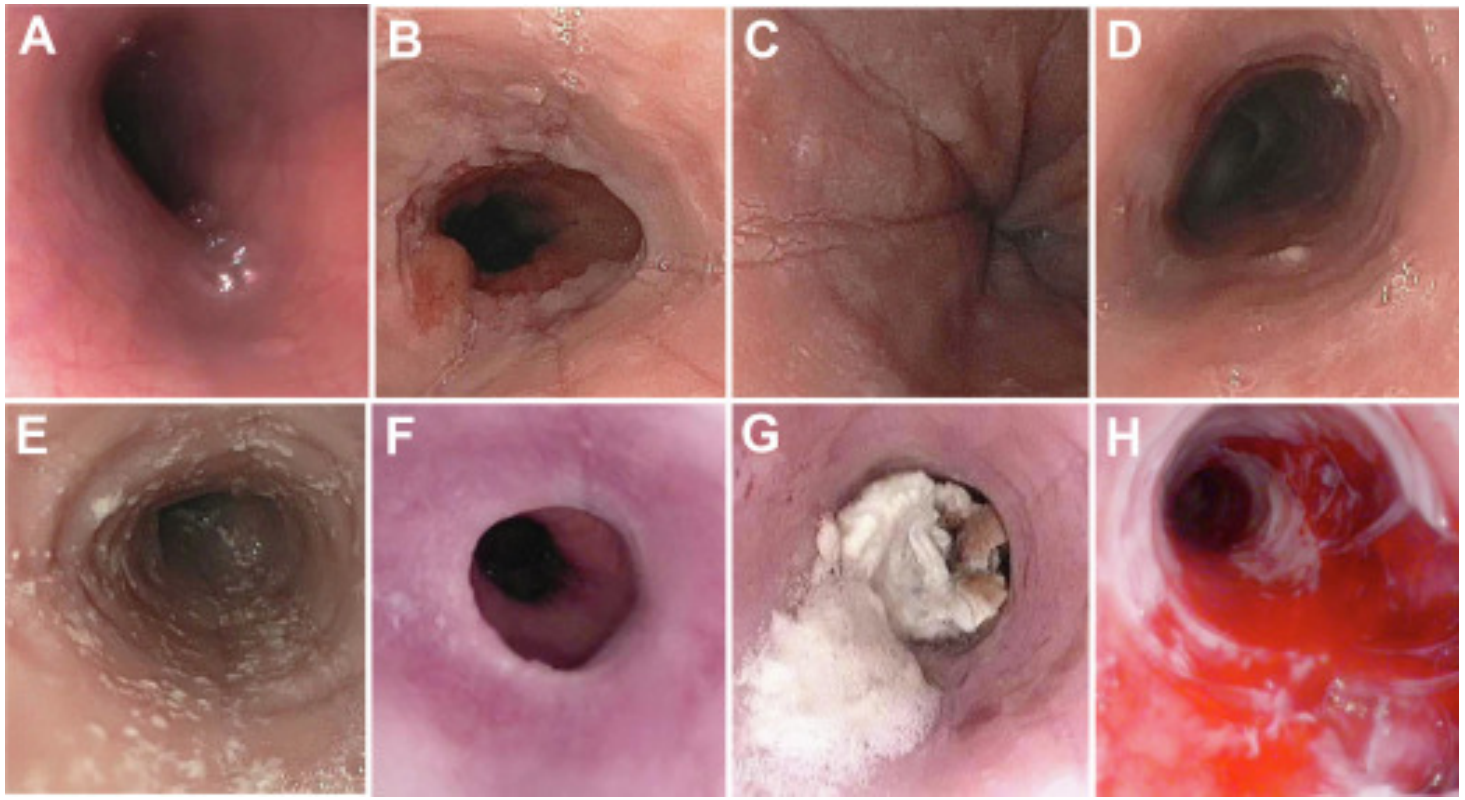
Endoscopy in the diagnosis of EoE





Endoscopy in the diagnosis of EoE





Endoscopy in the diagnosis of EoE

- Individual endoscopic features suggestive of EoE have:
  - Sensitivity: 15 - 48 %
  - Specificity: 90 - 95 %
  - Positive predictive value: 51 - 73 %
  - negative predictive value: 74 - 83 %

Histologic findings in EoE

Histologic findings in EoE

- Should we biopsy the esophagus during the EGD?
- Where should we biopsy at esophagus?
- Should we biopsy gastric mucosa during EGD?

Histologic findings in EoE

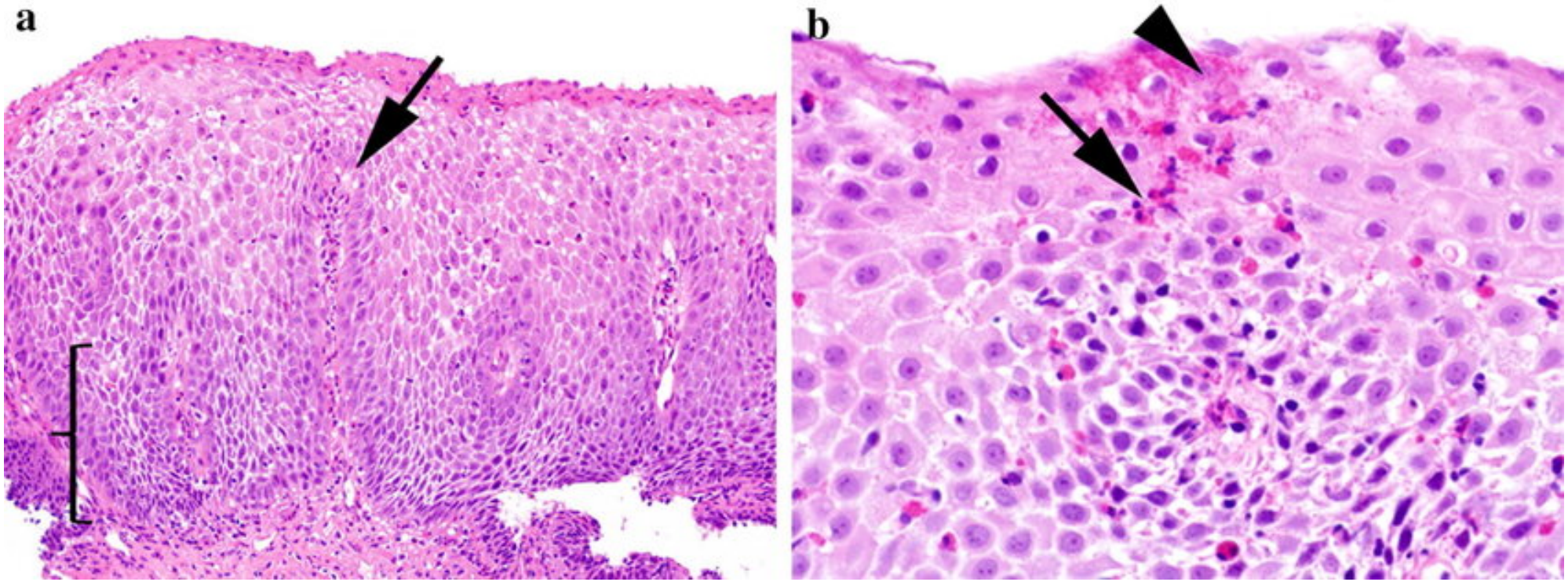
- Increased number of eosinophils
- At least 15 eosinophils per HPF in at least one biopsy specimen
- Esophageal eosinophilia & no clinical features → not sufficient for Dx of EoE
- Sensitivity of biopsies for Dx depends upon the number of biopsies obtained

- Probability of containing >15 eosinophils per HPF in biopsy fragments:
  - ❑ One → 0.63
  - ❑ Four → 0.98
  - ❑ Five → 0.99
  - ❑ Six → >0.99

Histologic findings in EoE

- Eosinophil micro-abscesses
- Superficial layering of eosinophils
- Sheets of eosinophils
- Extracellular eosinophil granules
- Subepithelial and lamina propria fibrosis and inflammation
- Basal cell hyperplasia
- Papillary lengthening
- Increased numbers of mast cells, B cells, and IgE-bearing cells

Histologic findings in EoE



Gastric biopsy in EoE

- Biopsies of the gastric antrum and duodenum should also be obtained:

1. Patients with symptoms suggestive of eosinophilic gastroenteritis
   - Abdominal pain
   - Nausea
   - Vomiting
   - Diarrhea
   - Weight loss
   - Ascites
2. Visible mucosal abnormalities
3. When there is a high index of suspicion of eosinophilic gastro-enteritis

Other para-clinical findings in EoE

Blood tests in the diagnosis of EoE

- Is there any place for blood tests in the Dx?

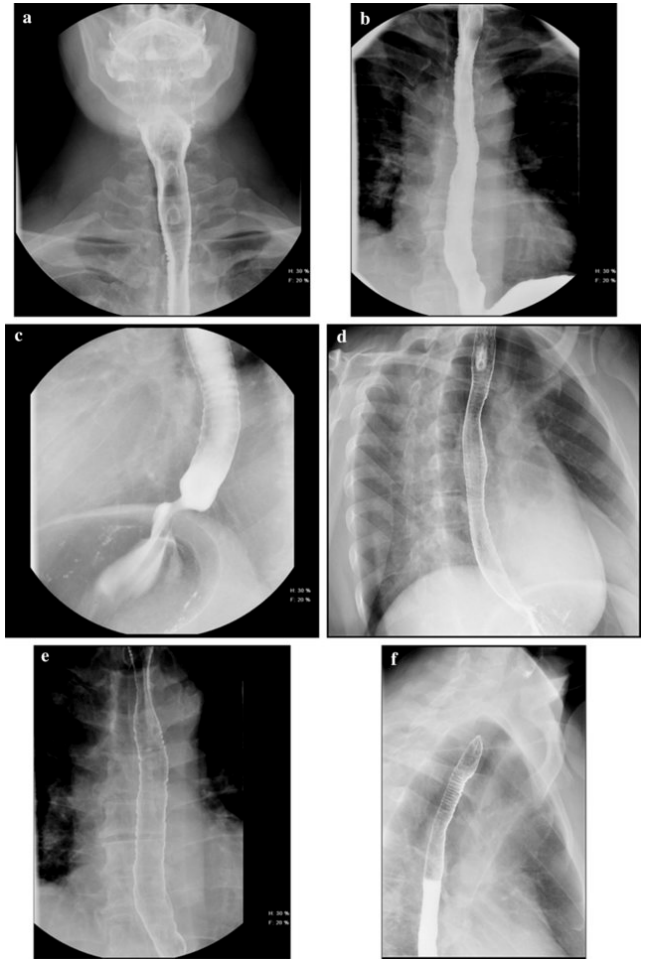
- CBC
- IgE
- Celiac tests?

- Blood eosinophilia
  - Usually mild
  - In about 40-50% of cases

- Elevated IgE
  - In about 50-60% of cases

Radiology findings in EoE

- Barium swallow in EoE
- Not sensitive
- Helpful in stricture Dx
- Luminal narrowing not seen in EGD
- R/O other diagnoses
- and anatomical status

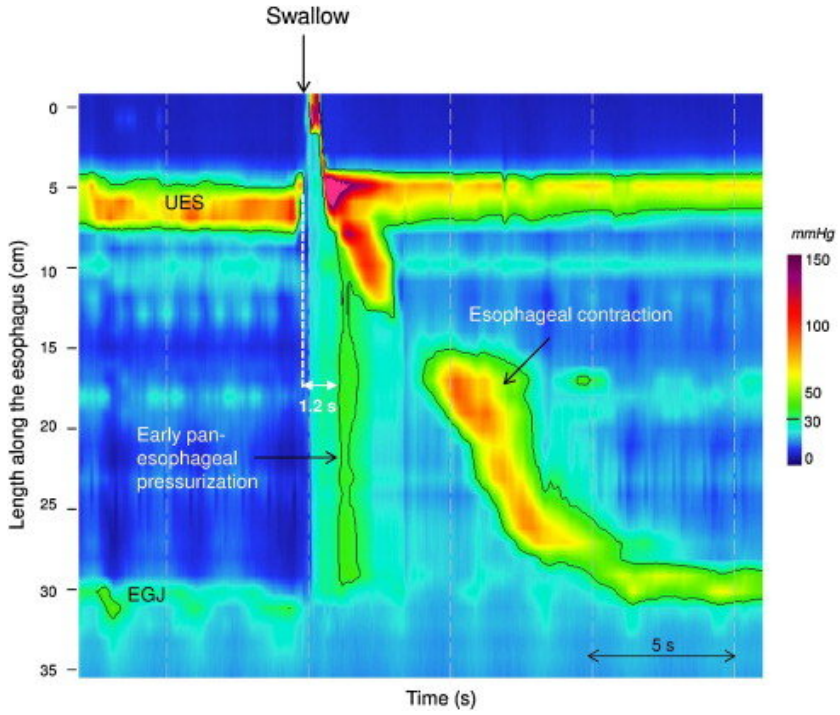


Allergy testing in the Dx of EoE?

- Allergy specialist consultation
- Guide for food elimination
- May help for atopic dermatitis therapy

Other tests

- EUS
- Impedance planimetry
- Mucosal impedance contour analysis
- Esophageal manometry
- Endoscopic confocal laser microscopy
- …



Severity of disease in EoE

Estimation of disease severity is crucial for the management of EoE

Severity of disease

- **EoEe1** – A mild subtype with normal-appearing esophagus, and mild histological, endoscopic, and molecular changes
- **EoEe2** – An inflammatory endotype with highest expression of inflammatory cytokines and steroid-responding genes and a steroid refractory phenotype
- **EoEe3** – A fibrostenotic endotype associated with a narrow-caliber esophagus, and characterized by the highest degree of endoscopic and histological severity and the lowest expression of epithelial differentiation genes

Severity of disease

- Symptoms and associated complications – Symptom frequency, food impaction, hospitalization
- Endoscopic features – Edema, furrows, exudates, rings, strictures
- Histology – Eosinophil burden per high power field

Severity of disease index - ISEE

Table 1. Eosinophilic Esophagitis Severity Index

To be assessed at initial diagnosis and then at each visit (with the recall being only between visits). The severity of EoE depends on an accurate diagnosis which includes an isolated esophageal eosinophilia with ≥15 eos/hpf and with other etiologies excluded. Select the box the patient fits for each row, and then calculate the number of points. For boxes with more than one element, each selected feature gets points.
Total Score: <1: Inactive EoE; 1–6: Mild Active EoE; 7–14: Moderate Active EoE; ≥15: Severe Active EoE

Points per feature	1 point	2 points	4 points	15 points
Symptoms and complications[a]				
Symptoms	Weekly	Daily	Multiple times per day or disrupting social functioning	–
Complications	–	Food impaction with ER visit or endoscopy (*patient ≥18 years*)	• Food impaction with ER visit or endoscopy (*patient <18 years*) • Hospitalization due to EoE	• Esophageal perforation • Malnutrition with body mass <5th percentile or decreased growth trajectory • Persistent inflammation requiring elemental formula, or systemic corticosteroid, or immunomodulatory[b] treatments
Inflammatory features				
Endoscopy (edema, furrows, and/or exudates)	Localized	Diffuse	–	–
Histology[c]	15–60 eos/hpf	>60 eos/hpf	–	–
Fibrostenotic features				
Endoscopy (rings, strictures)	Present, but endoscope passes easily	Present, but requires dilation or a snug fit when passing a standard endoscope[d]	–	Cannot pass standard upper endoscope; repeated dilations (*in an adult ≥18 years*); or any dilation (*in a child <18 years*)
Histology	–	BZH or LPF (or DEC/SEA if no LP)	–	–

Severity of disease index - ISEE

Points per feature	1 point	2 points	4 points	15 points
Symptoms and complications*				
Symptoms	Weekly	Daily	Multiple times per day or disrupting social functioning	--
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Inflammatory features				
Endoscopy (edema, furrows, and/or exudates)	Localized	Diffuse	--	--
Histology#	15-60 eos/hpf	>60 eos/hpf	--	--
Fibrostenotic features				
Endoscopy (rings, strictures)	Present, but endoscope passes easily	Present, but requires dilation or a snug fit when passing a standard endoscope##	--	Cannot pass standard upper endoscope; repeated dilations *(in an adult ≥18 years)*; or any dilation *(in a child < 18 years)*
Histology	--	BZH or LPF (or DEC/SEA if no LP)**	--	--

Management of EoE

Treatment goals in EoE

1. Elimination of symptoms
2. Endoscopic normalization
3. Normalization of inflammation

Management overview in EoE

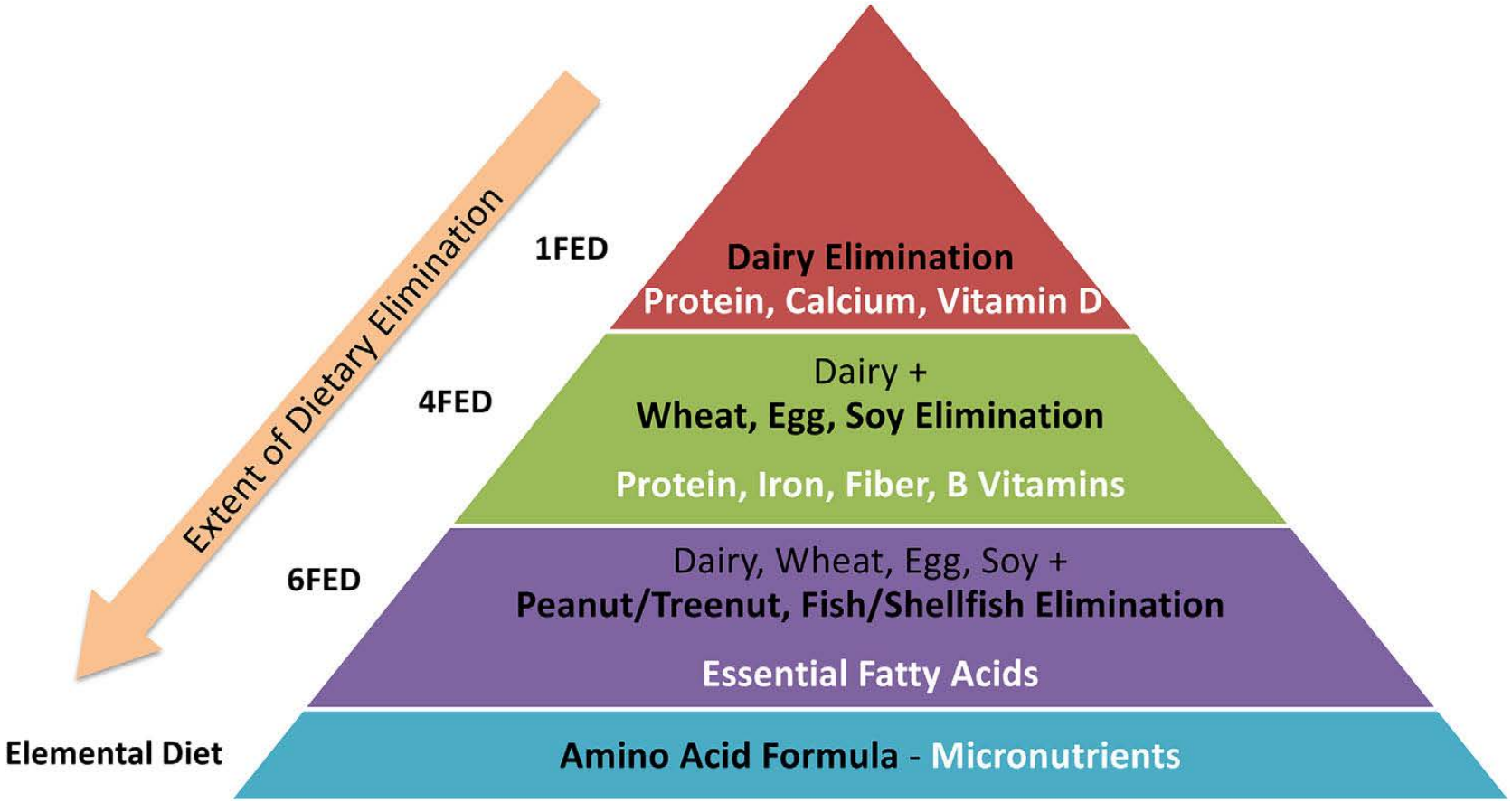
- There are three management options in the management of EoE

1. Dietary therapy/ Elimination diet
2. Topical/ systemic medicines
   a. Topical steroids
   b. PPIs
3. Endoscopic treatment (dilatation of strictures)

Elimination diet in EoE

- What to eliminate?
- How far should the elimination diet be?
- How long should it be taken?
- Can we re-introduce the eliminated foods later?

Elimination diet in EoE



Elimination diet in EoE

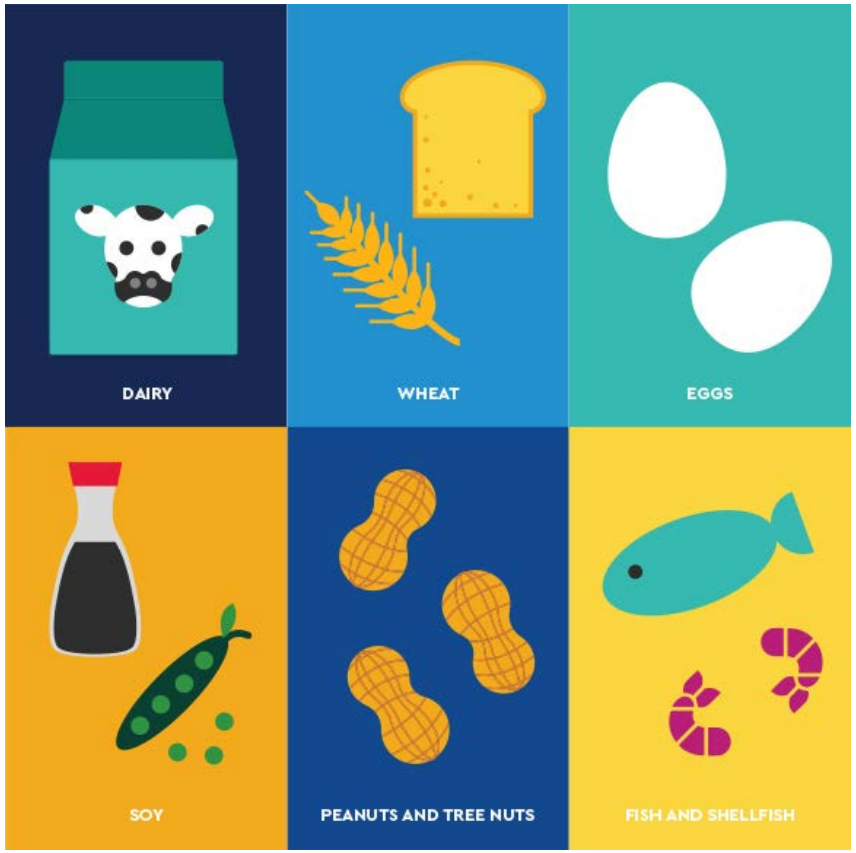
Dietary Management in EoE

Effectiveness

- Elemental Diet
- 6 Food Elimination Diet (6FED)
  cow's milk, wheat, egg, soy, seafood, nuts
- 4 Food Elimination Diet (4FED)
  cow's milk, wheat, egg, soy
- 2 Food Elimination Diet (2FED)
  cow's milk, wheat
- Single food, cow's milk

Ease

• Courtesy of Kirsten Wingate RD, Reference: Mundoz-Persy M, Lucendo AJ. Treatment of eosinophilic esophagitis in the pediatric patient: an evidence-based approach. Eur J pediatr. 2018;177:649-663.



Elimination diet in EoE

ADVANTAGES
- May lead to early identification of food triggers
- Short diagnostic process
- Avoid unnecessary diet restrictions

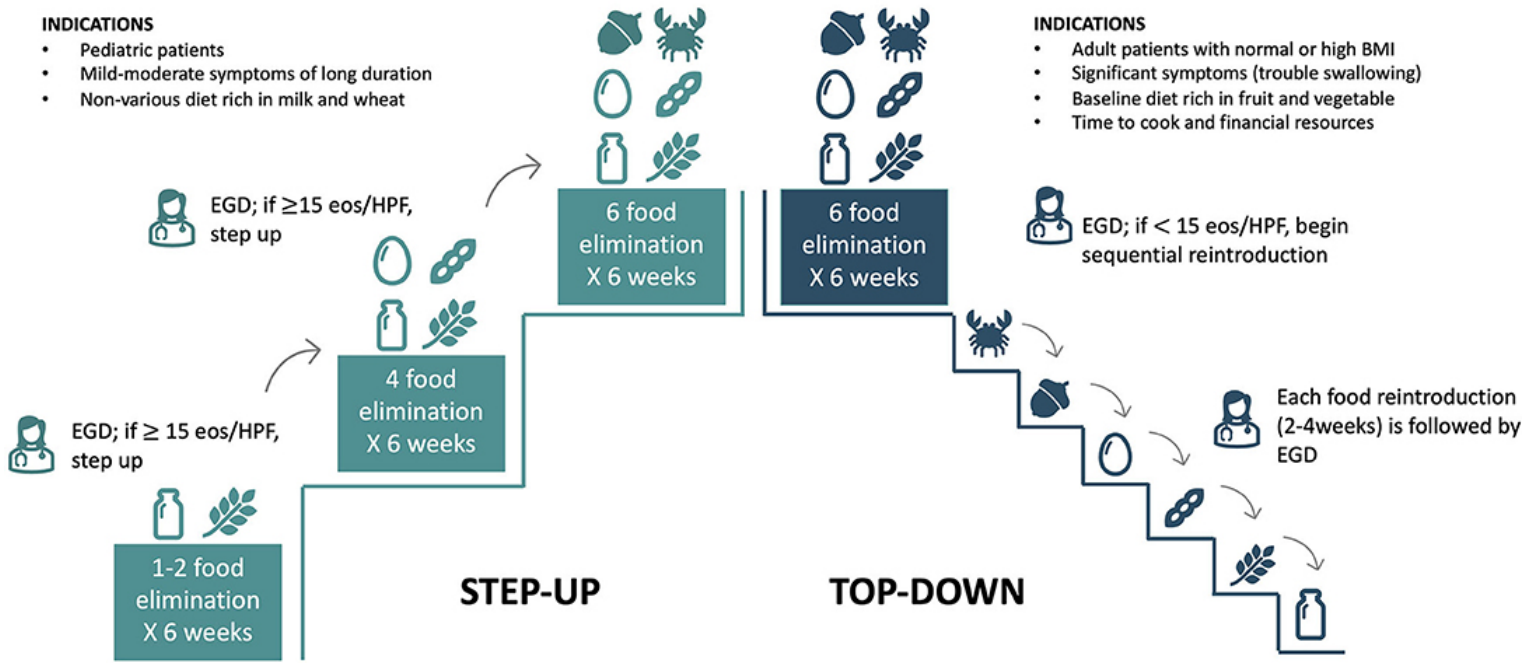
DISAVANTAGES
- Less effective

INDICATIONS
- Pediatric patients
- Mild-moderate symptoms of long duration
- Non-various diet rich in milk and wheat

ADVANTAGES
- Efficacy

DISAVANTAGES
- Up to 7 EGDs with single food reintroduction
- High diet restrictions → low compliance
- High risk of potential nutritional deficiencies

INDICATIONS
- Adult patients with normal or high BMI
- Significant symptoms (trouble swallowing)
- Baseline diet rich in fruit and vegetable
- Time to cook and financial resources



PPIs in the treatment of EoE

- First drug?
- Add-on treatment?
- Maintenance treatment?
- Which PPI?
- PPI dose?

PPIs in the treatment of EoE

- PPIs among the first drugs
- Begin with single daily dose
- If no response in 4 weeks → go for BID dosing
- Reducing acid production in patients with coexistent GERD
- They have anti-inflammatory mechanisms

- The relationship between GERD and EoE is unclear

Use of corticosteroids in EoE?

- Local or systemic?
- Which drugs?
- Form of drug to be prescribed?
- Are the drugs readily available?
- How long should the first course be given?
- Maintenance treatment?
- How long? Taper? Drug elimination?

Use of corticosteroids in EoE?

- Most patients with EoE respond to topical glucocorticoids
- Fluticasone and budesonide have been best studied
- Symptoms and histologic changes often recur when glucocorticoids are discontinued
- Endoscopic, symptomatic, and histologic improvement were noted in 71, 79, and 57 percent of patients who underwent a repeat endoscopy approximately eight weeks after treatment

Use of corticosteroids in EoE?

- **Fluticasone**
  - Metered dose inhaler
  - Sprayed into mouth
  - Swallowed
  - Then NPO for 30 min
  - 220 mcg/spray, four sprays daily in divided doses
  - Response is rapid (a few days)
  - Repeat EGD & Bx

- For non-responders
  - Dose increment
  - Change to Budesonide
  - Give PPI
  - Go for better elimination diet

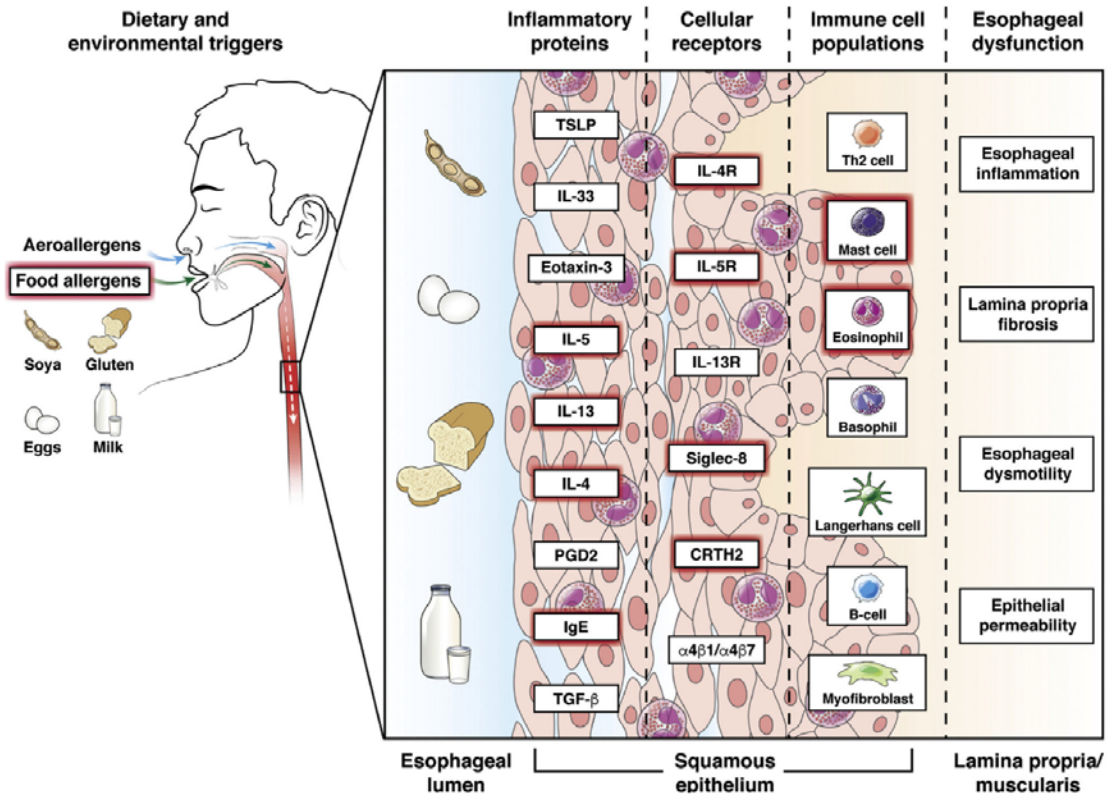
Use of corticosteroids in EoE?

- **Budesonide**
- Oral viscous slurry
- 2 mg twice daily (4 mg !)
- 2 mg twice daily
- Viscous budesonide can be compounded by mixing two or four 0.5 mg/2 mL Pulmicort Respules with sucralose
- Should be taken slowly (5 to 10 min)
- NPO for 30 min

Maintenance therapy

- Offered to all patients especially for:
  - Severe dysphagia
  - Food impaction
  - high-grade esophageal stricture
  - Rapid symptomatic/histologic relapse following initial therapy
- lack of symptoms does not reliably predict the absence of disease activity
- Optimal approaches ?

Experimental therapies



BSG recommendations (2022)

- Immunomodulators (eg, azathioprine, 6-mercaptopurine) are not recommended
- Monoclonal antibody therapies, such as anti-TNF and anti-integrin therapies, are not recommended
- Novel biologics used in other allergic conditions (such as dupilumab, cendakimab and benralizumab) have shown promise in the treatment of eosinophilic oesophagitis
- Sodium cromoglycate, montelukast and anti-histaminesare not recommended (they may be effective in concomitant atopic disease)

Endoscopic dilatation

- When?
- How? Balloon vs. bouginage?
- How to dilate? In how many sessions?
- Rule of three?
- Complication? Esophageal tearing or perforation?

Endoscopic dilatation

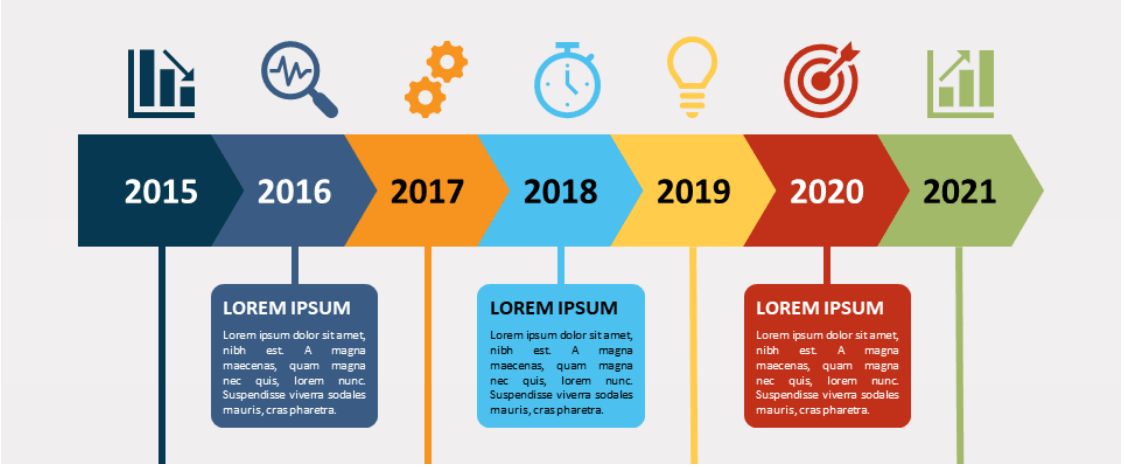
- Effective for relieving dysphagia
- No effect on underlying inflammation
- For failure of conservative therapy
- As initial therapy in patients with high-grade strictures
- Should be performed carefully
- Dilation per session be limited to 3 mm
- Multiple dilations sessions is needed

- Goal is esophageal diameter of 15 to 18 mm

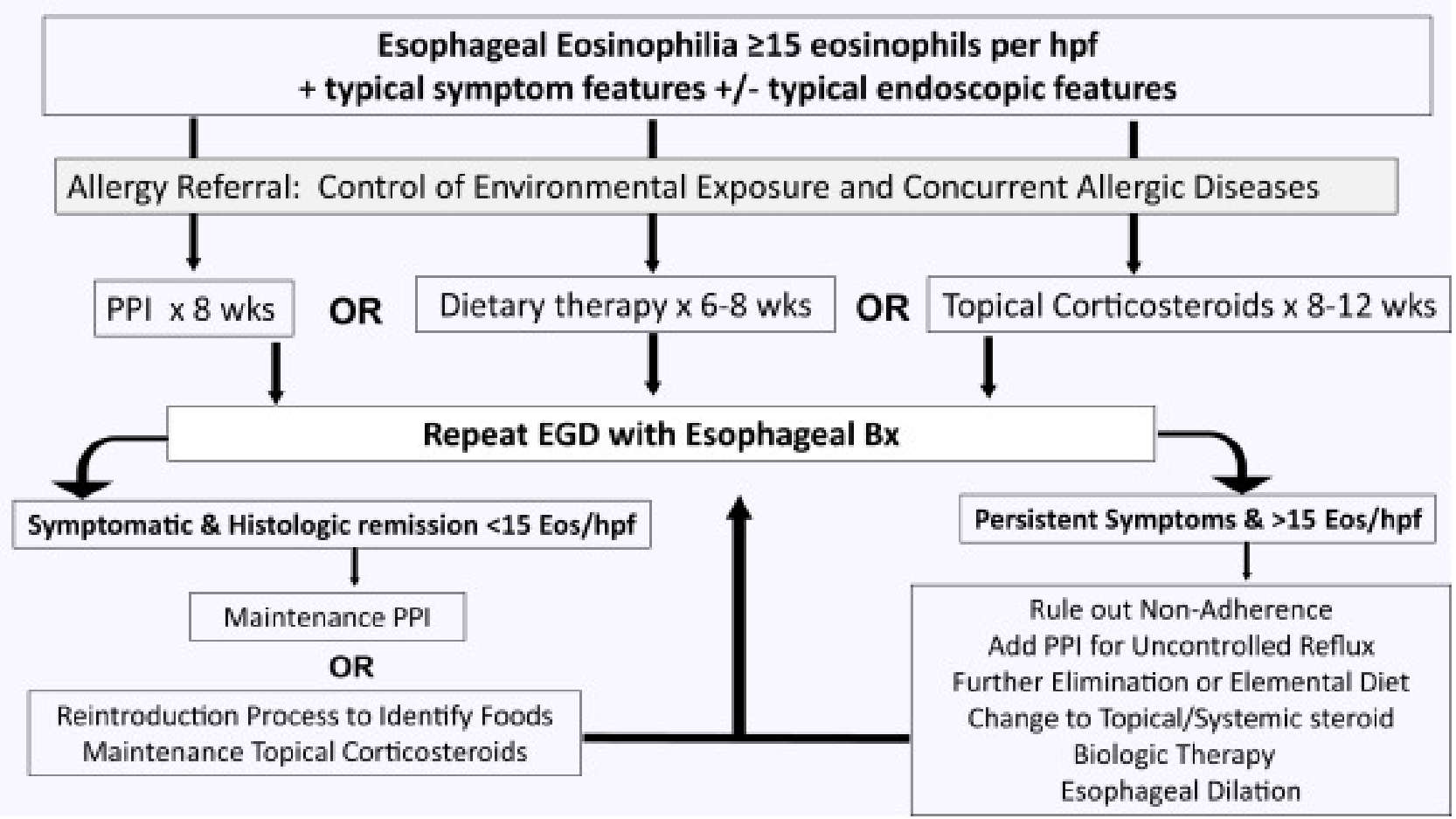
- Complications of dilatation are
  - Chest pain
  - Bleeding
  - Esophageal perforation

Esophageal strictures

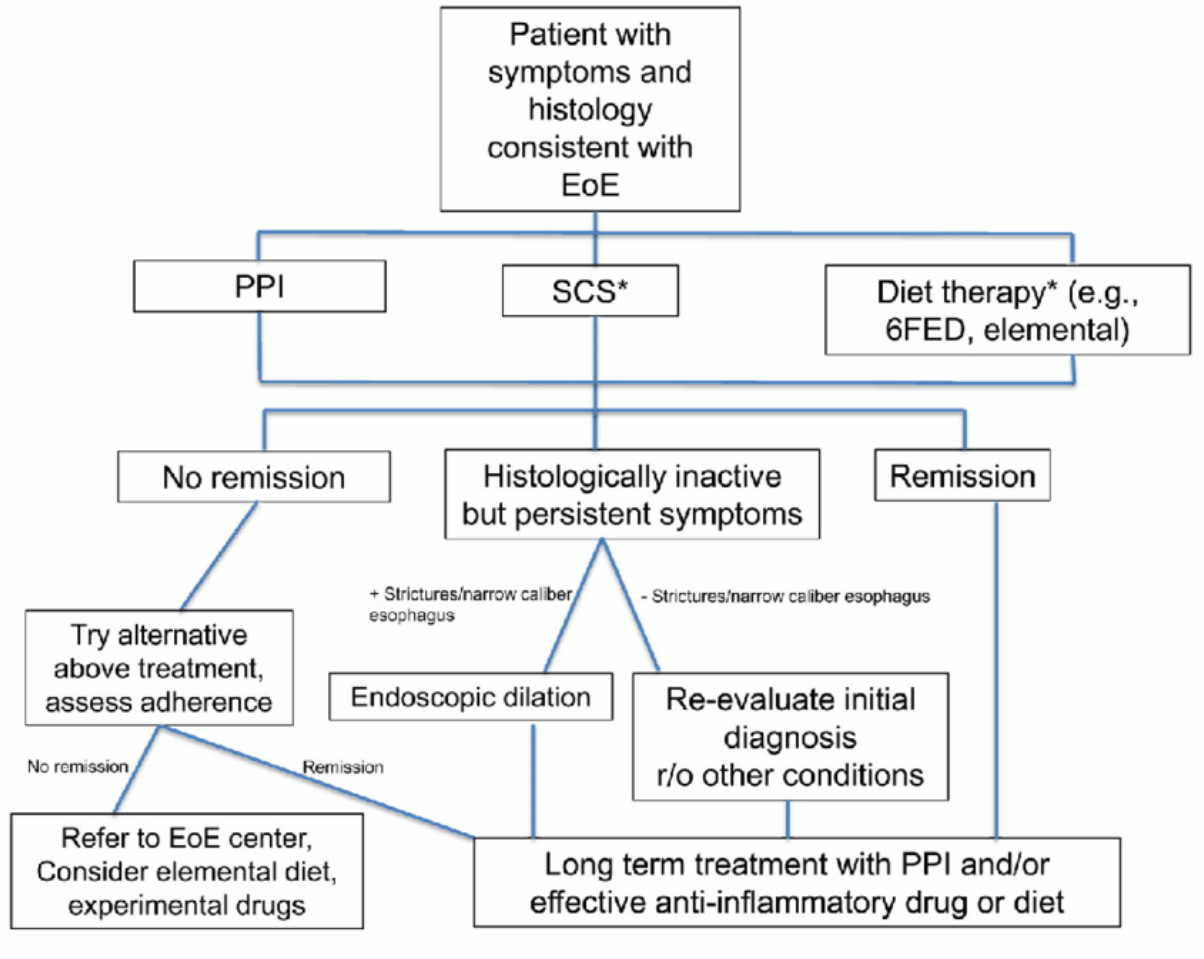
- Early diagnosis is the key



Algorithmic approach



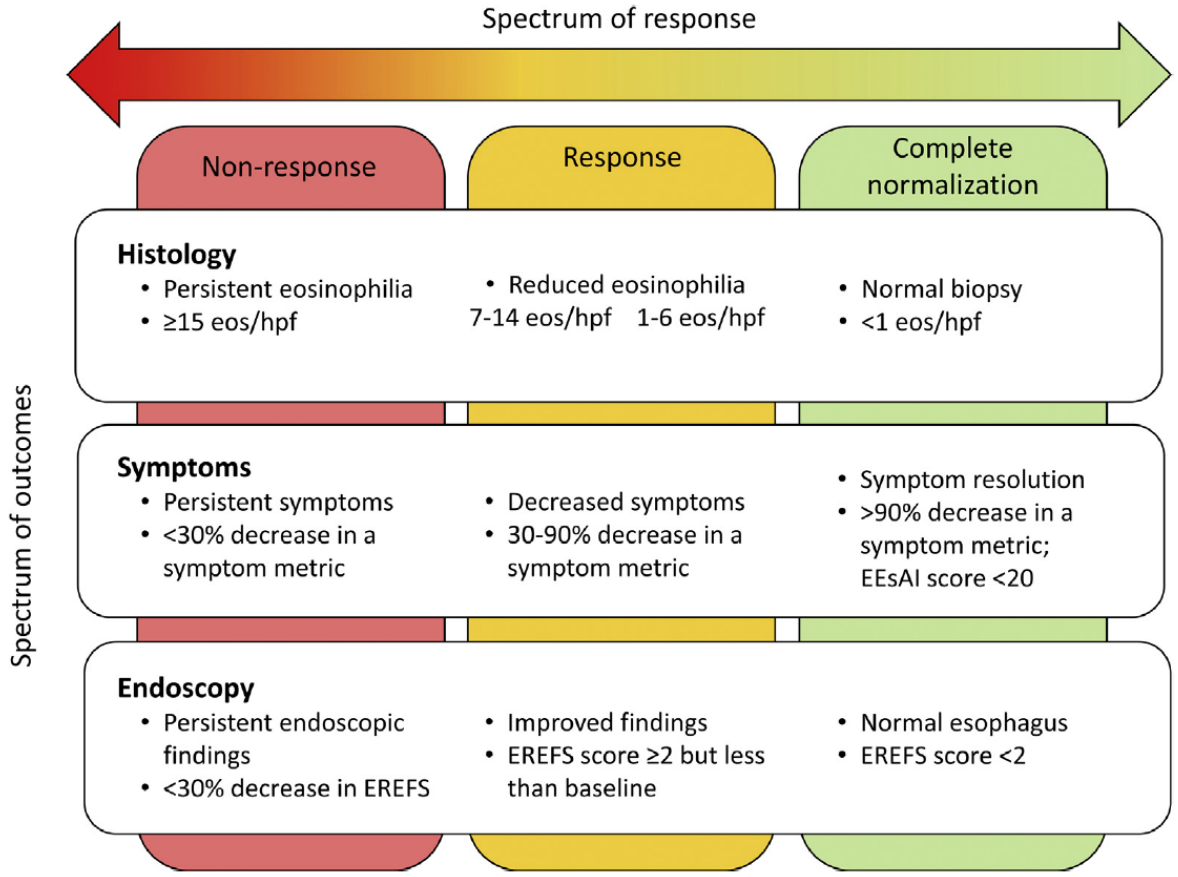
Algorithmic approach



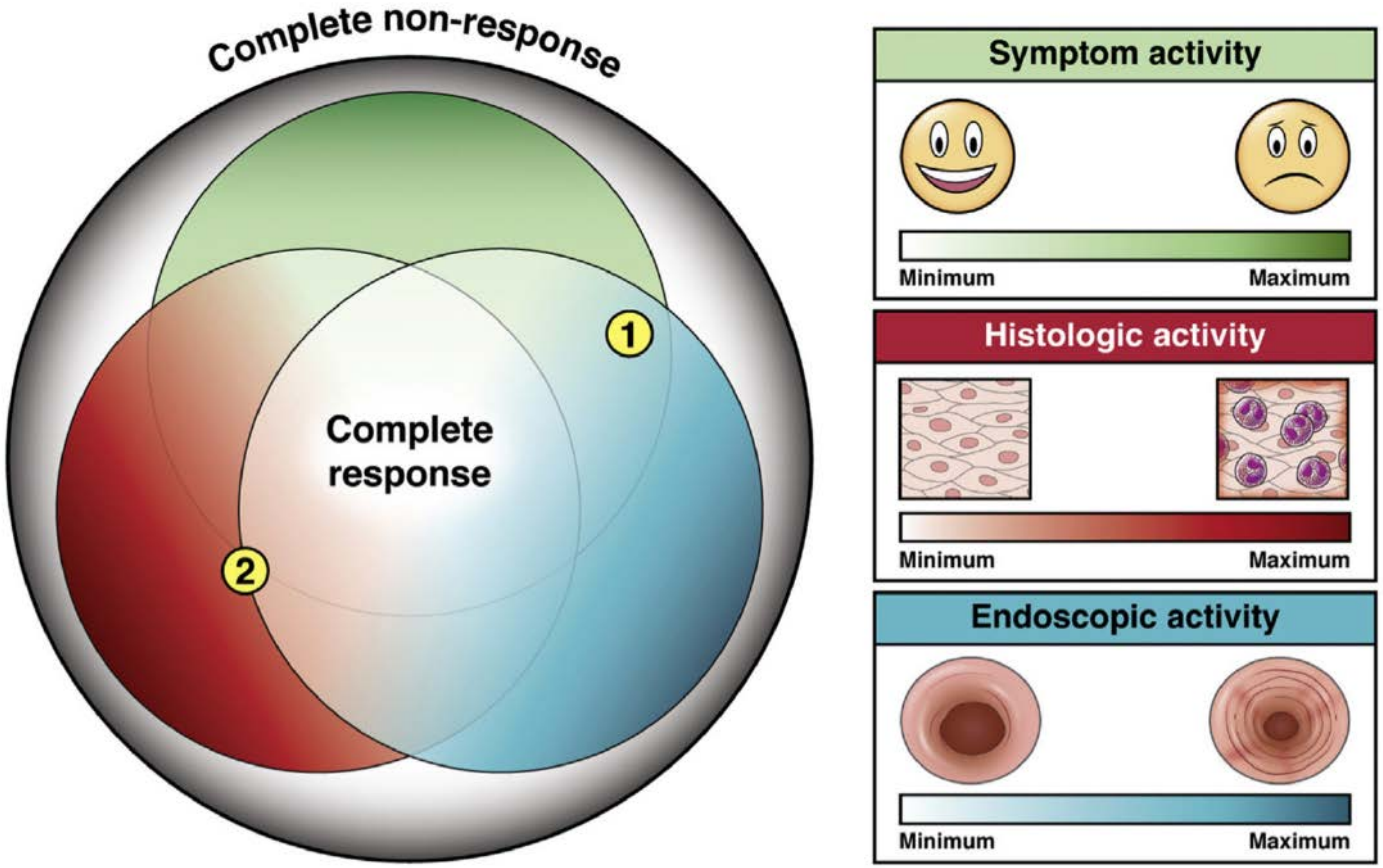
Prognosis in EoE

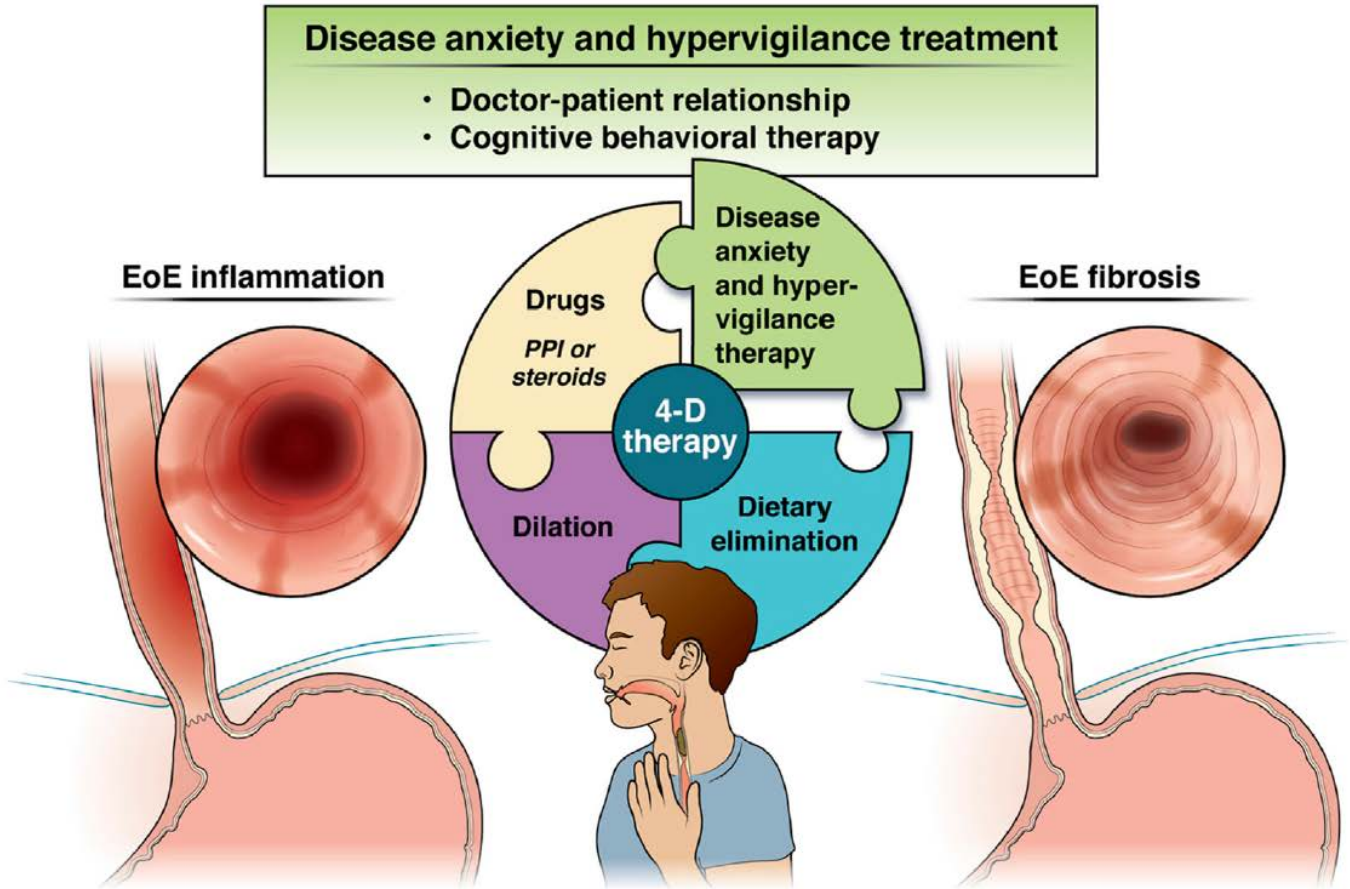
- Natural history is unclear
- Is a chronic disease
- No effect on life expectancy
- high likelihood of symptom recurrence after discontinuing treatment

Prognosis in EoE



Prognosis in EoE




Disease anxiety and hypervigilance treatment
• Doctor-patient relationship
• Cognitive behavioral therapy
EoE inflammation
EoE fibrosis
Drugs
PPI or steroids
Disease anxiety and hyper-vigilance therapy
4-D therapy
Dilation
Dietary elimination

Take home message

- EoE is a uncommon disease
- Incidence and prevalence are rising
- It is induced by food allergens
- Diagnosis needs high index of suspicion
- Dx is based on symptoms, EGD and histology findings
- Esophageal eosinophilia is crucial component for the Dx
- Early diagnosis is the key
- Severity of disease is related to symptoms, endoscopy and histology findings and dictates the management course and prognosis

Take home message

- Treatment of EoE is based on elimination diets, PPIs, superficial corticosteroin ingestion & esophageal endoscopic dilatation
- Prognosis and natural history is yet unclear
- Early diagnosis is the key

Thanks for your attention