Eosinophilic Esophagitis (EoE)
EoE:

– immune-mediated disorder

– food or environmental antigens => Th2 inflammatory response.
  • Key cytokines: IL-4, IL-5, and IL-13 stimulate the production of eotaxin-3 in the esophageal mucosa
  • Eotaxin-3, a potent chemokine which is markedly upregulated in EoE, recruits eosinophils to the esophageal mucosa.
  • activated eosinophils secrete proinflammatory and profibrotic mediators, cause local tissue damage, and recruit additional inflammatory cells (mast cells and fibroblasts), perpetuating the inflammatory response and resulting in esophageal remodelling.

– interaction between environmental exposures and genetic susceptibility
Definition and causes of esophageal eosinophilia

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Diseases associated with 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
- PPI, proton-pump inhibitor.
Definition of eosinophilic esophagitis (EoE) and diagnostic criteria

- EoE is a clinicopathologic disorder diagnosed by clinicians taking into consideration both clinical and pathologic information without either of these parameters interpreted in isolation, and defined by the following criteria:
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• EoE is a clinicopathologic disorder diagnosed by clinicians taking into consideration both clinical and pathologic information without either of these parameters interpreted in isolation, and defined by the following criteria:

  – Symptoms related to esophageal dysfunction
  – Eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of ≥15 eosinophils per high-power field (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. (Strong recommendation, low evidence)
• Esophageal biopsies are required to diagnose EoE.

• At the time of initial diagnosis, biopsies should be obtained from the antrum and/or duodenum to rule out other causes of esophageal eosinophilia in all children and in adults with gastric or small intestinal symptoms or endoscopic abnormalities. (Recommendation strong, evidence low)
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  – 2–4 biopsies should be obtained from both the proximal and distal esophagus to maximize the likelihood of detecting esophageal eosinophilia in all patients in whom EoE is being considered. (Recommendation strong, evidence low)

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Clinical characteristics:

• none pathognomonic; the typical EoE patient:
  – atopic male (male to female ratio 3:1)
  – childhood or during the third or fourth decade of life
  – predominance in non-Hispanic Whites
Clinical manifestations:

- **In children** - nonspecific and vary by age:
  - infants and toddlers often present with feeding difficulties,
  - school-aged children are more likely to present with vomiting or pain. EoE is also commonly associated with other atopic diatheses (food allergy, asthma, eczema, chronic rhinitis, environmental allergies)

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Clinical manifestations:

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- **In adults:**
  - solid food dysphagia - the most common presenting symptom
  - food impaction necessitating endoscopic bolus removal occurs in 33–54 %
  - Other symptoms: chest pain, heartburn, and upper abdominal pain
• Physical examinations:
  
  – useful in children to identify normal growth patterns,
  
  – useful in both children and adults to identify comorbid allergic diseases;
  
  – **no features** on physical examination are specific in making the diagnosis of EoE.
Endoscopy?
Endoscopic and microscopic findings in eosinophilic esophagitis.
A: Esophageal rings; B: White exudates, longitudinal furrows and mucosal fragility; C and D: Esophageal mucosa infiltrated by several eosinophils (red cells)
Diagnostic challenges: PPI-responsive esophageal eosinophilia and GERD

• A clinical, endoscopic and/or histologic response to a PPI does not establish gastroesophageal reflux as the cause of esophageal eosinophilia. To determine whether reflux is contributing to esophageal eosinophilia, additional evaluation for GERD, as per standard clinical practice, is recommended. This may include ambulatory pH testing in selected cases. (Recommendation conditional, evidence low)
- Proton-pump inhibitor responsive esophageal eosinophilia (PPI-REE) should be diagnosed when patients have esophageal symptoms and histologic findings of esophageal eosinophilia, but demonstrate symptomatic and histologic response to proton-pump inhibition.

  - At this time, the entity is considered distinct from EoE, but not necessarily a manifestation of GERD. (Recommendation conditional, evidence low)

- To exclude PPI-REE, patients with suspected EoE should be given a 2-month course of a PPI followed by endoscopy with biopsies. (Recommendation strong, evidence low)

- more than one-third of all patients with esophageal eosinophilia on biopsy will respond to a PPI, and these patients should not be diagnosed with EoE.
Reason for PPI response - incompletely understood: => a complex interplay of multiple factors:

- **GERD:** the esophageal epithelium may have **damage to the tight junctions due to acid exposure** => **increased permeability** with dilation of intracellular spaces and **may allow for allergen penetration**, which triggers subsequent **recruitment of eosinophils** to the esophageal epithelium

- There may be a **direct anti-inflammatory effect of the PPI** on the esophageal epithelium. Exposure to omeprazole in oesophageal cells stimulated with cytokines such as IL-13 and Il-4 can block the secretion of **eotaxin-3**
• **PPI-REE** has **not** been shown to be **associated with an antigenic or immunologic cause** of esophageal eosinophilia and cannot be labeled as an EoE phenotype at this time.

• **long-term follow-up?**
  
  – Case series (four pediatric patients with PPI-REE): Despite continued therapy with PPI, patients developed symptoms warranting repeat endoscopy, which ultimately **demonstrated recurrent esophageal eosinophilia consistent with EoE.**
• Duration and dosage of PPI-Therapy:
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  – It is recommended that doses should at least be similar to those used to treat GERD related erosive esophagitis, with a duration of 8 weeks continuing until the time of the follow-up endoscopy and biopsy.
Endpoints of treatment in EoE

• Symptoms are an important parameter of response in EoE, but cannot be used alone as a reliable determinant of disease activity and response to therapy, given that compensatory dietary and lifestyle factors can mask symptoms. (Recommendation conditional, evidence moderate)
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• The endpoints of therapy of EoE include improvements in clinical symptoms and esophageal eosinophilic inflammation. While complete resolution of symptoms and pathology is an ideal endpoint, acceptance of a range of reductions in symptoms and histology is a more realistic and practical goal in clinical practice. (Recommendation conditional, evidence low)

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Pharmacologic treatments
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- **Topical steroids** (i.e., fluticasone or budesonide, swallowed rather than inhaled, **for an initial duration of 8 weeks**) are a first-line pharmacologic therapy for treatment of EoE. (Recommendation strong, evidence high)
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- **Prednisone** may be useful to treat EoE if topical steroids are not effective or in patients who require rapid improvement in symptoms. (Recommendation conditional, evidence low)
• Patients without symptomatic and histologic improvement after topical steroids might benefit from:

• There are few data to support the use of mast cell stabilizers or leukotriene inhibitors and biologic therapies remain experimental at this time.
Patients without symptomatic and histologic improvement after topical steroids might benefit from:

- longer course of topical steroids,
- higher doses of topical steroids,
- systemic steroids,
- elimination diet,
- esophageal dilation

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Dietary treatments

• Dietary elimination can be considered as an initial therapy in the treatment of EoE in both children and adults. (Strong recommendation, evidence moderate)

• empiric six-food elimination diet removing the six most common known food groups that are triggers of EoE:

• The decision to use a specific dietary approach (elemental, empiric, or targeted elimination diet) should be tailored to individual patient needs and available resources. (Recommendation conditional, evidence moderate)
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• empiric six-food elimination diet removing the six most common known food groups that are triggers of EoE:
  - soy, egg, milk, wheat, nuts, and seafood

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• Assessment of response:

• Gastroenterologists should consider consultation with an allergist to identify and treat extraesophageal atopic conditions, assist with treatment of EoE, and to help guide elemental and elimination diets. (Recommendation conditional, evidence low)
• **Assessment of response:**

  • **Clinical improvement and endoscopy** with esophageal biopsy should be used to assess response to dietary treatment when food antigens are either being withdrawn from or reintroduced to the patient. (Recommendation conditional, evidence low)

  • Gastroenterologists should consider consultation with an allergist to identify and treat extraesophageal atopic conditions, assist with treatment of EoE, and to help guide elemental and elimination diets. (Recommendation conditional, evidence low)
Endoscopic treatment

• Patients should be well informed of the risks of esophageal dilation in EoE:
Endoscopic treatment

- Esophageal dilation, approached conservatively, may be used as an effective therapy in symptomatic patients with strictures that persist in spite of medical or dietary therapy. (Recommendation conditional, evidence moderate)

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Endoscopic treatment

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- Patients should be well informed of the risks of esophageal dilation in EoE:
  - post-dilation chest pain,
  - bleeding,
  - esophageal perforation. (Recommendation conditional, evidence moderate)
OUTCOMES

• Natural history of EoE:
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  – While knowledge of the natural history of EoE is limited, patients should be counseled about the high likelihood of symptom recurrence after discontinuing treatment due to the chronic nature of this disease. (Recommendation strong, moderate evidence)
Maintenance therapy:

– The overall goal of maintenance therapy is to minimize symptoms and prevent complications of EoE, preserve quality of life, with minimal long-term adverse effects of treatments. (Recommendation conditional, evidence low)

– Maintenance therapy with topical steroids and/or dietary restriction should be considered for all patients, but particularly in those with
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- The overall goal of maintenance therapy is to minimize symptoms and prevent complications of EoE, preserve quality of life, with minimal long-term adverse effects of treatments. (Recommendation conditional, evidence low)

- Maintenance therapy with topical steroids and/or dietary restriction should be considered for all patients, but particularly in those with
  - severe dysphagia or food impaction,
  - high-grade esophageal stricture
  - rapid symptomatic/histologic relapse following initial therapy. (Recommendation conditional, evidence low)
Einen schönen Arbeitstag!!!