Eosinophilic Esophagitis (EoE)

Aetiology/pathogenesis

EoE is a chronic, T-helper 2 (Th2)-mediated inflammatory disease:

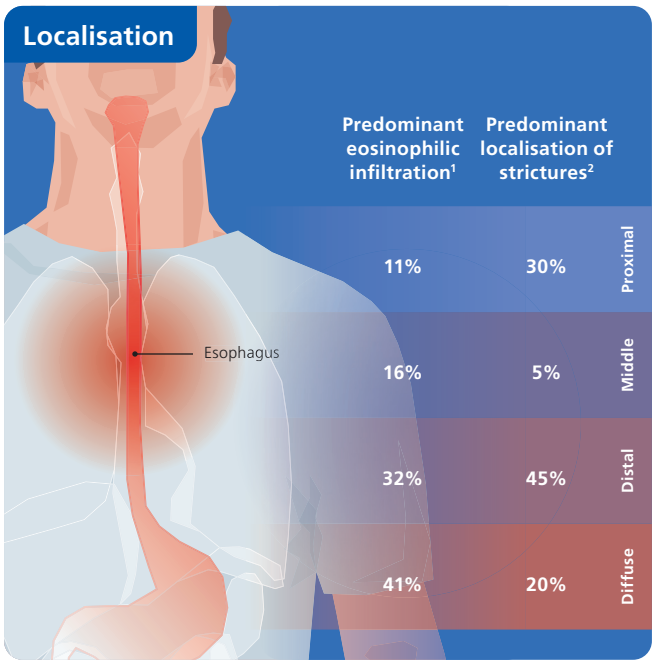
Food allergens trigger the release of pro-inflammatory cytokines such as IL-33 and TSLP from epithelial cells. This cytokine secretion leads to a Th2-dominated cellular response with increased secretion of IL-4, IL-5, and IL-13 as well as the pro-fibrotic cytokine TGF- . This results in epithelial barrier dysfunction and mucosal infiltration of mast cells and eosinophils attracted by eotaxin-3. Remodeling of connective tissue in the region of the lamina propria and the muscularis mucosae is the eventual outcome.

The following food groups are the primary allergens:

- Dairy products
- Eggs
- Soy/legumes
- Wheat and gluten
- Fish/seafood
- Nuts

Aeroallergens have also been proposed as aggravating factors or even as possible triggers of EoE.

Localisation



Epidemiology/genetics

Incidence: 10/100,000 person-years
Prevalence: 10–57/100,000 inhabitants (high regional variation)
The prevalence is currently assumed to be approx. 1:2000, with a high number of unrecorded cases.
Disease onset can occur at any age. However, a bimodal distribution of age at diagnosis has been observed (childhood and third to fifth decade of life).
Typically, young men are affected (median age at diagnosis is around 6–12 years of age in children and around 30 years of age in adults; wide range from 0–85 years of age).
Ratio men to women = 3 : 1

EoE has a hereditary component, with 7% of patients having a family history of EoE. Siblings of EoE patients have an 80-fold increased risk of also developing the disease.

Key susceptibility genes:

- TSLP (5q22.1)
- WDR36 (5q22.1)
- FLG (1q21.3)
- CRLF2 (Xp22.33)
- CCL26 (7q11.23)
- TGFB1 (19q13.1)

EoE often occurs with other Th2-mediated disorders: for example, 2/3 of patients have a history of atopic diseases (including allergic rhinitis, allergic asthma, atopic dermatitis).

Clinical manifestation

Most common symptom – dysphagia

- Sometimes only identifiable through a targeted review of medical history, slow progression (it is not uncommon for progression to be very gradual and to initially go undetected by the patient)
- Development of avoidance strategies (reduced speed of eating, avoidance of certain foods, not eating in public, increased fluid intake)
- High diagnostic delay (median: 4 years between first symptoms and diagnosis; > 10 years in approx. 1/3 of patients)[3]

Food impaction

- Persistent obstruction or partial obstruction (esophageal blockage for several seconds to a few minutes), possibly combined with need for endoscopic dilation

Chest pain

- Burning pain, sometimes indistinguishable from reflux, with or without association with food intake
- Sensation of pressure, constriction, choking; sometimes excercise-induced

Less common: regurgitation, nausea/vomiting, odynophagia, epigastric pain, sensation of lump in throat

Caution: Symptoms in children are less specific, and they often experience little to no dysphagia. Instead, signs in children include food refusal, failure to thrive, abdominal pain, and vomiting.

Together, these symptoms cause a relevant reduction in health-related quality of life, often with psychosocial/psychological implications – especially in periods of high disease activity.

Diagnosis and diagnostic criteria

Four cornerstones of diagnosis – none of which is specific or conclusive by itself:

1. Medical history

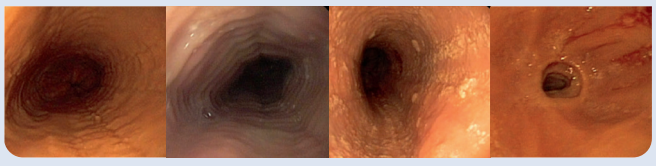
Symptoms of esophageal dysfunction, see above.

2. Endoscopy

The endoscopic reference score EREFS[4] is a standardized tool for identification and monitoring of disease progression (sufficient in modified form from 0–9).

- **Edema:** often mild with (slight) reduction of vascular pattern, loss of vascular markings in severe cases. Primary manifestation of inflammation (edema: 0 [absent] vs. 1 [present]).
- **Rings** (circular ridges; trachealization): subtle to moderately pronounced fixed, concentric rings that prevent passage of endoscope. Primary manifestation of fibrosis (0 [absent] vs. 1 [mild] vs. 2 [moderate; passage of standard endoscope possible] vs. 3 [severe; passage not possible]).
- **Exudates:** white plaques often in or along longitudinal furrows; frequently difficult to differentiate from Candida. Usually manifestation of pronounced inflammation (exudates: 0 [absent] vs. 1 [mild; < 10% surface] vs. 2 [severe > 10%]).
- **Furrows** (longitudinal): primary manifestation of inflammation. Usually easily definable even with full air insufflation (furrows: 0 [absent] vs. 1 [present]).
- **Stricture:** abnormal narrowing of the esophageal lumen, sometimes membranous. Primary manifestation of fibrosis (strictures: 0 [absent] vs. 1 [present]).

Sometimes crêpe-paper esophagus, mucosal fragility with lacerations after passage of endoscope (crêpe-paper sign 0 [absent] vs. 1 [present]).



Furrows and edema | Rings and edema | Exsudates | Stricture (severe)

3. Histology

Biopsies must be collected from all patients with suspected EoE regardless of endoscopic findings; endoscopic features may be (nearly) normal in up to 10% of patients even with an experienced clinician.

Collect at least 6 but preferably 8 biopsies (4 proximal, 4 distal; separate vials).
The pattern of inflammation may be heterogeneous, so biopsies must primarily be taken from areas with endoscopic mucosal abnormalities. Only 1 biopsy should be collected at a time; inclusion of subepithelial layers is desirable.

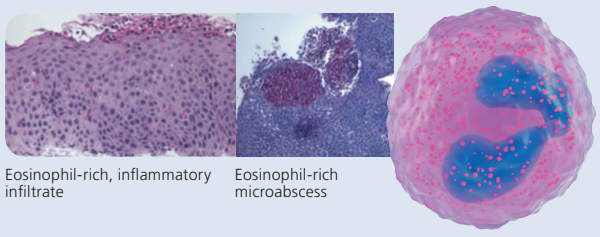
- The most important histological criterion for diagnosis and progression monitoring is the eosinophil count per high-power field (eos/hpf). The established diagnostic threshold is > 15 eos/hpf (60 eos/mm²).

For a diagnosis of EoE, the presence of elevated eosinophils should be restricted to the esophagus. Histological disease activity is most severe in proximal esophagus-predominant disease. In contrast, in GERD patients eosinophils are particularly found in the distal esophagus and at low frequency.

In itself, an elevated eosinophil count is not specific to EoE.
Other histological features with increasing significance (none are specific to EoE by themselves, but increased severity or a combination of multiple symptoms is suggestive of EoE):

- Eosinophilic microabscesses
- Surface layering of eosinophils on epithelia
- Basal cell hyperplasia
- Dilated intercellular spaces
- Elongation of vascular papillae
- Lamina propria fibrosis

Clinical symptoms are insufficient to assess disease activity. The absence of symptoms does not rule out persistent activity. For this reason, to date it is essential to perform an endoscopy/histology in order to monitor EoE and therapy effectiveness.



Eosinophil-rich, inflammatory infiltrate | Eosinophil-rich microabscess

4. Differential diagnosis

Important differential diagnoses of eosinophilic esophagitis (selection):
GERD, eosinophilic gastroenteritis, achalasia, hypereosinophilic syndrome, Crohn's disease, collagenosis/vasculitis, infections (viral, fungal, parasitosis)

Treatment

The treatment options for EoE can be divided into the following three subgroups (3 Ds):

1. **D**rugs
   - **a.** Topical corticosteroids (TCS)
   - **b.** Proton pump inhibitors (PPI)
   - **c.** Antibody against IL-4/IL-13
2. **D**iet (elimination diet)
3. **D**ilation (endoscopic dilation)

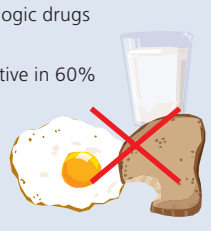
DDD

For remission induction in adults, TCS is recommended as the first-line therapy.[5] However, to date approval has only been granted for one special topical formulation.[6] Alternatively, high dosages of PPIs can be administered. However, these are not specifically approved for treatment of EoE. In addition, a biologic drug is also available (antibody against IL-4 / IL-13), which can be used after failure of conventional therapy and/or therapy intolerance. Dietary treatment is the only causal therapy option. Endoscopic dilation should never be used as the sole treatment, but as an add-on if fibrosis cannot be treated by other means.

Potential initial treatment regimens:

- Topical corticosteroids (TCS)
- High dosage of PPI
- In the case of intolerance to PPI/steroids: Biologic drugs

Possible diet strategies:



- Exclusive elimination of dairy products (effective in 60% of children[7]) (in some cases, the first option can also be the sole exclusion of wheat or products containing gluten)
- Step-up elimination diet with exclusion of 2, 4, or 6 food groups
- 6-food elimination diet

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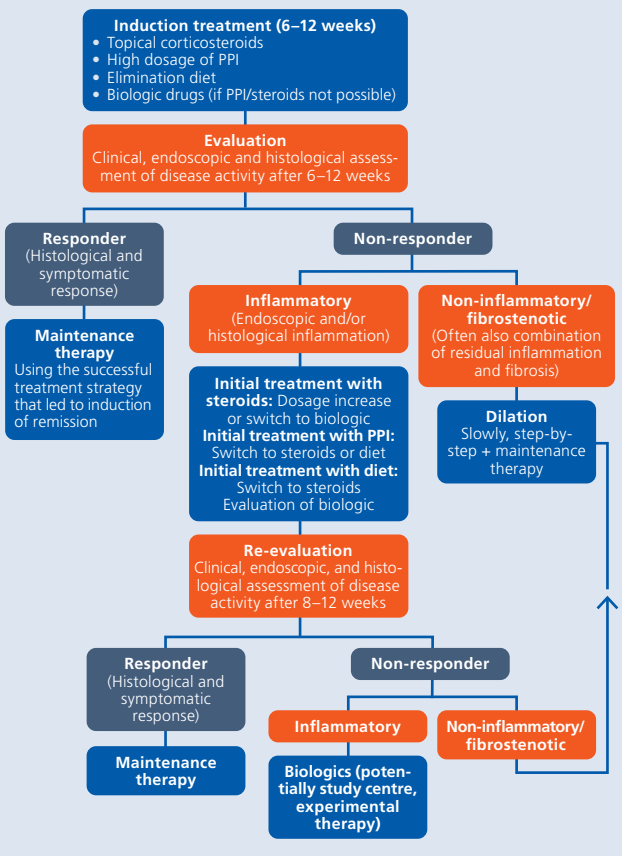
Therapy algorithm[5]



Long-term outcome, long-term treatment, and follow-up

EoE is a chronic, recurrent, inflammatory disease which likely progresses, if left untreated: Dysfunction resulting from fibrosis and strictures, increased risk of food impaction, and scarring with inadequate response to anti-inflammatory therapy.

Long-term maintenance therapy is therefore essential to modern treatment strategies.
The rationale and goals of long-term maintenance therapy are:

- Control/reduction of symptoms; increased quality of life
- Prevention/delay of fibrosis/strictures
- Food impaction: prevention and/or risk reduction

To date, there is no evidence of an increased long-term risk of esophageal neoplasia.

The majority of patients require long-term treatment.
Even in patients with complete remission (i.e. endoscopic, histological and clinical = deep remission), > 80% of patients experience relapse within 6 months of discontinuing their treatment.
There is currently only limited experience of long-term EoE outcomes, and no established surveillance criteria are available.

Regular clinical and endoscopic/histological follow-up is recommended every 1–2 years[5]:

- Relevant residual inflammation (even in the absence of symptoms) may require treatment modification
- Adequate monitoring of inflammation may reduce/prevent progression to fibrosis/stenosis/motility disorder

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