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Eosinophilic esophagitis—from definition to therapy

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Summary Eosinophilic esophagitis (EoE) is a chronic immune-mediated disorder that is characterized clinically by symptoms of esophageal dysfunction and histologically by a dense eosinophilic inflammation of the esophagus. This article provides an overview of the current knowledge in the field of EoE. EoE has seen significant progress in its understanding, including its definition, clinical presentation, diagnosis, and treatment. Consensus criteria have been established for diagnosing EoE, with symptoms commonly including dysphagia, food impaction, and reflux-like symptoms. Diagnosis involves clinical evaluation, endoscopy, and histological assessment. Therapeutic strategies for EoE aim to alleviate symptoms, induce and maintain remission, and prevent complications. These strategies include dietary modifications, pharmacotherapy, and endoscopic interventions. Treatment choice depends on disease severity, patient preferences, and comorbidities. Despite progress, challenges persist in EoE management. Long-term outcomes and optimal treatment duration are still under investigation. Research efforts focus on identifying predictive markers for treatment response and developing personalized approaches. In conclusion, EoE is a chronic, progressive and recurrent disease with various clinical manifestations and treatment options. Improved understanding has led to better diagnostic criteria and therapeutic strategies. However, further research is necessary to enhance our understanding of disease pathogenesis, refine treatment algorithms, and optimize long-term outcomes for individuals with EoE.

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Abbreviations

APT	Atopy patch test
CSACI	Canadian Society of Allergy and Clinical Immunology
EGD	Esophagogastroduodenoscopy
EoE	Eosinophilic esophagitis
EREFS	EoE endoscopic reference score
GERD	Gastroesophageal reflux disease
GvHD	Graft-versus-host disease
HE	Hematoxylin–eosin
HPF	High power field
OIT	Oral immunotherapy
PPI	Proton pump inhibitor
SFED	Studies on the 6-food elimination diet
TCS	Topical corticosteroids

Definition

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease of the esophagus characterized by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation. Other systemic and/or local causes of esophageal eosinophilia should be excluded [1, 2].

By definition, other systemic and local causes of esophageal eosinophilia must be taken into account and must be excluded (Table 1).

Epidemiology

Since its first description in the early 1990s [3, 4], EoE has evolved from a rare condition described only in individual cases to one of the most common inflammatory diseases of the esophagus.

Table 1 Differential diagnosis of esophageal eosinophilia [1, 2]

Gastroesophageal reflux disease (GERD)
Eosinophilic gastritis/gastroenteritis/colitis with esophageal involvement
Achalasia or other motility disorders of the esophagus
Hypereosinophilic syndrome
Crohn's disease with esophageal involvement
Infections (fungal, viral, parasitic)
Drug hypersensitivity
Pill esophagitis
Autoimmune disorders, vasculitis
Graft-versus-host disease (GvHD)
Skin diseases with esophageal involvement (pemphigus, lichen)
Pseudodiverticulosis

A recently published meta-analysis reported pooled incidence rates of 7.7 and 6.6 per 100,000 person–years for adults and children, respectively. The pooled prevalence was 34.4 per 100,000 population and was higher for adults than for children (42.2 versus 34).

EoE can manifest at any age and is most commonly diagnosed in the third and fourth decades of life. In children, the age of onset has a bimodal distribution. The first peak of onset is found in the first 3 years of life, while the second peak is in adolescence [5]. Males have a 2- to 3-fold increased risk of developing EoE [6].

Potential risk factors

Individuals with atopic pre-existing conditions have an increased risk of developing EoE. The prevalence of accompanying atopic diseases, such as allergic rhinitis, asthma, and atopic dermatitis, is more common in EoE patients than in the general population and ranges from 28–86% in adults and 42–96% in children [7]. It is postulated that EoE is mainly induced by food allergens, but also by airborne allergens, and is mediated by Th2 helper cells [8]. Furthermore, it has been shown that EoE, atopic dermatitis, and allergic bronchial asthma share a similar pattern of disease-specific transcripts, highlighting the common molecular etiology [9]. De novo occurrences of EoE after oral immunotherapy (OIT) in children and adults with atopic diathesis have been described [10, 11]. De novo EoE after OIT in children and adults with atopic diathesis was reported in a systematic literature review, which analyzed 15 publications and found a prevalence of 2.7% [12]. In current guidelines of the Canadian Society of Allergy and Clinical Immunology (CSACI), EoE was therefore listed as a relative contraindication for OIT [13]. A familial aggregation and a genetic predisposition have been described in EoE [14]. Thus, male first-degree relatives have up to a 64-fold increased risk of developing EoE. Monozygotic and dizygotic twins were affected in 41 and 22% of cases, respectively [14].

Diagnosis

The diagnosis of EoE is based on the clinical symptoms of esophageal dysfunction in combination with dense eosinophilic infiltration of the esophageal mucosa.

Symptoms

The clinical presentation of EoE is very different in children and adults. In adolescents and adults [15], solid food dysphagia (70–80%) and food bolus impaction (33–54%; Fig. 1) are the predominant symptoms [16]. In infants and young children, nonspecific symptoms are often present, such as reflux-like complaints with vomiting (27%), nausea (27%), food refusal (14%), or failure to thrive. Dysphagia (28%) and food bolus impaction (7%; Fig. 1) also occur [17]. During clinical evaluation, it is important to note that patients, especially adolescents and adults, often develop adaptive strategies and alter their eating behavior to avoid symptoms, which can lead to delayed diagnosis.

If the symptoms described above are present, it is indicated to perform an esophagogastroduodenoscopy (EGD).

Endoscopy

During EGD in patients with EoE structurally visible changes in the esophagus are very often detected. While whitish exudates, longitudinal furrows, and mucosal edema are signs of acute inflammation, fixed ring formation, narrow-caliber esophagus, and strictures reflect a chronic fibrotic stage of the disease (Fig. 2) [18]. These endoscopic findings of EoE are frequently described using the EoE endoscopic refer-

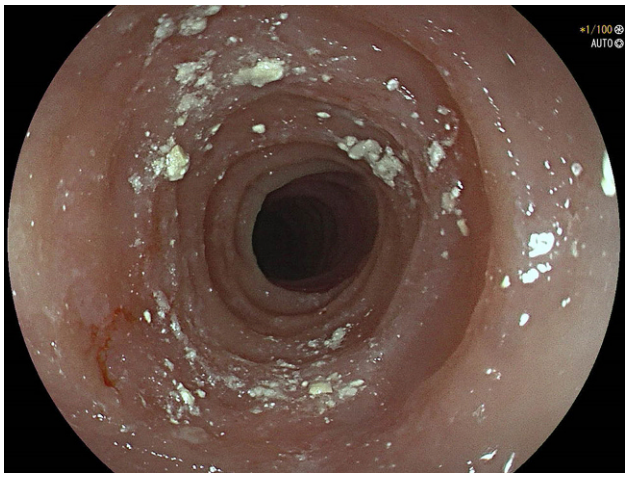

Fig. 1 Endoscopic aspect after food bolus removal (white tablet), esophageal stricture due to severe rings

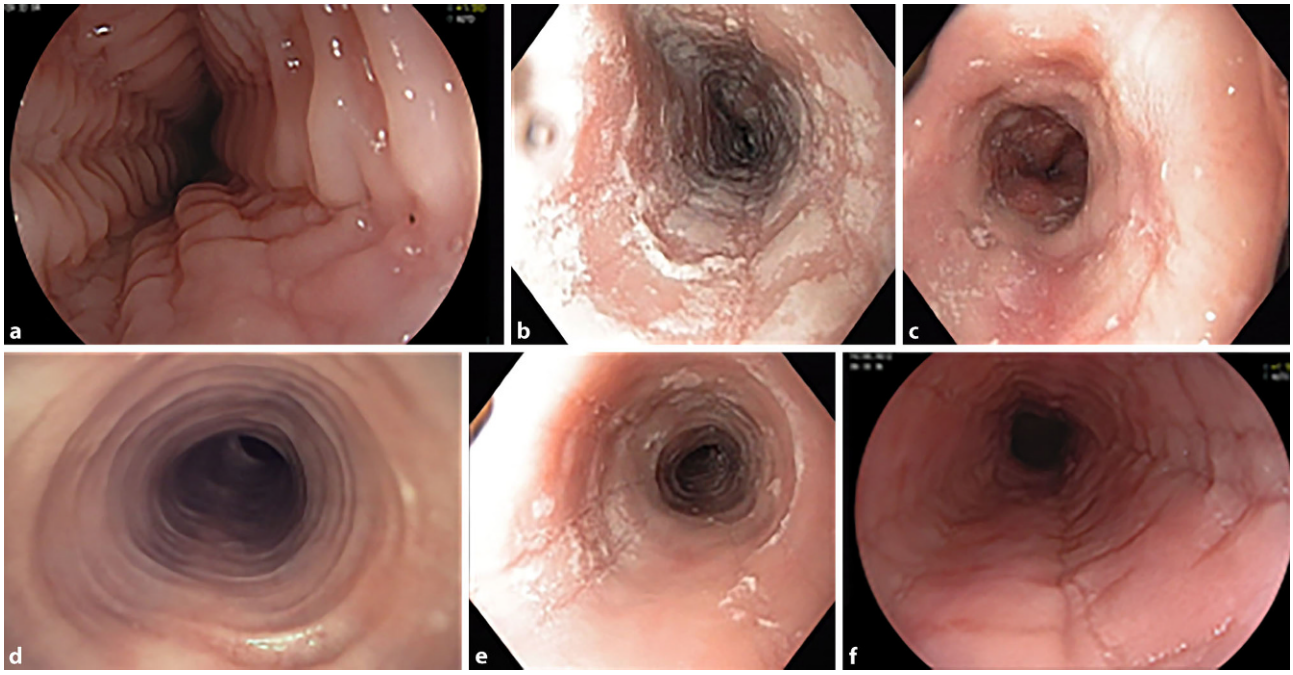

Fig. 2 Endoscopic findings in EoE manifest in various degrees (Image rights: Ulrike von Arnim) **a** Edema and rings, **b** whitish plaques or exsudates, **c** whitish plaques (distinct) or exsudate and edema, **d** severe rings **e** furrows, rings and whitish plaques or exsudates, **f** edema and furrows

ence score (EREFS), which stands for the five key findings: *E*dema, *R*ings, *E*xudates, *F*urrows, and *S*trictures [19]. This system provides greater uniformity in the description of findings, identifies, and discriminates between non-EoE and EoE patients, and correlates with treatment [20].

At least six biopsies should be taken from different locations, focusing on areas with endoscopic mucosal abnormalities. Because inflammatory changes in EoE are frequently patchy and may not be present in all biopsies. Diagnostic sensitivity increases with the number of biopsies and is maximized after taking at least 6 biopsies [1, 2].

Biopsies should also be taken despite a normal endoscopic appearance of the esophagus, which has been reported in up to 10% of adult and pediatric patients, respectively [21]. It is also indicated to obtain duodenal and gastric mucosal biopsies at the moment of initial diagnosis in order to exclude other causes of esophageal eosinophilia.

Histology

The diagnostic threshold of >15 per high power field (HPF) was arbitrarily chosen in the past to distinguish eosinophilic esophagitis (EoE) from other inflammatory esophageal diseases, particularly gastroesophageal reflux disease (GERD) [22]. Several studies have demonstrated high accuracy for this threshold in diagnosing EoE [23]. To ensure standardization, it is recommended to report the eosinophil count per 0.3 mm^2 of HPF, as the HPF can vary between microscopes [2]. The assessment of eosinophil counts and other parameters can be adequately performed using the hematoxylin–eosin (HE) staining method (Fig. 3 normal esophageal mucosa, Fig. 4 esophageal mucosa infiltration with eosnophils).

Allergy testing

In the initial studies on the 6-food elimination diet (SFED) in adult EoE patients, it was already demonstrated that allergological diagnostics (skin prick test, serum IgE) performed prior to the initiation of the elimination diet were not able to reliably identify the allergen responsible for EoE [24, 25]. In the study by Gonsalves et al. involving 50 adult EoE patients, the

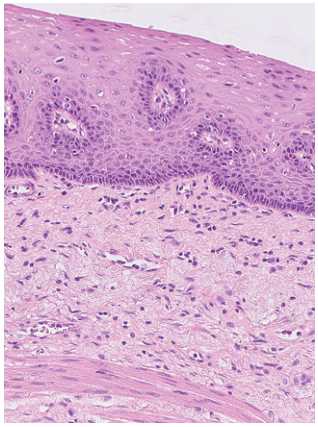

Fig. 3 Histology normal esophageal mucosa (HE staining)

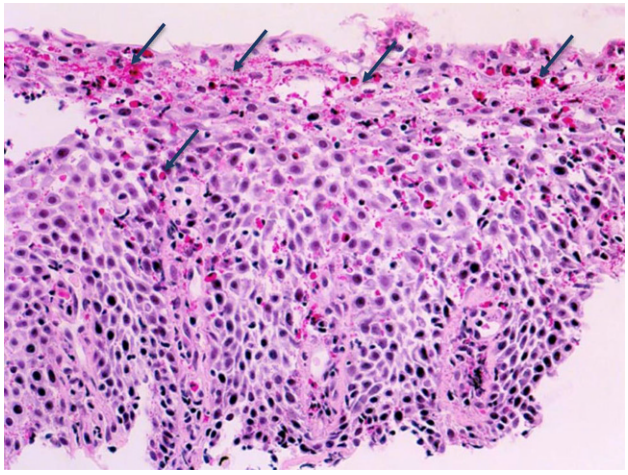

Fig. 4 Esophageal mucosa with an infiltrate of up to 63 eosinophils/HPF, consistent with esophageal eosinophilia (*arrows*)

responsible allergen could only be identified through skin prick testing in 13% of cases [24]. In the study by Lucendo et al., sensitivities of 32% for food-specific serum IgEs and 22.8% for skin prick testing were determined among 77 patients [25]. In another prospective study involving adult EoE patients, an atopy patch test (APT) was conducted before initiating a 6-food elimination diet. The APT yielded positive results in 50% of the patients, but histological confirmation was only observed in 16% of the cases [26]. The sensitivity of the atopy patch test (APT) in identifying the responsible trigger was only 5.9% [26]. In a prospective study conducted in Australia, multiple allergological tests (skin prick test, skin patch test, allergen-specific serum IgE, basophil activation test, food-specific serum IgG) were examined in 82 adult EoE patients. The results showed that none of the tested tests were able to reliably predict the responsible allergen [27]. The main reasons for the lack of reliability in allergological diagnostics are twofold. First, there are test-specific limitations that can affect the accuracy of the results. Second, EoE is primarily considered a non-IgE-mediated disease, meaning that traditional allergological tests, which primarily focus on IgE-mediated allergies, may not be suitable for identifying the responsible allergen in EoE. Due to these reasons, the 2017 European guidelines strongly recommend *against* allergological diagnostics, especially in adult EoE patients. These guidelines acknowledge the limitations of such tests in reliably identifying the responsible allergen in EoE and suggest focusing on other diagnostic approaches instead [2].

Principles and management of eosinophilic esophagitis

Active EoE is characterized by chronic eosinophil-predominant inflammation of the esophagus, chronic-recurrent esophageal symptoms, and a significantly reduced quality of life. If left untreated, the disease carries a high risk of esophageal fibrosis, strictures, and food bolus obstructions (Fig. 1) [28]. For these reasons, current European and US guidelines recommend initiating an induction therapy upon the detection of active EoE, with the goal of achieving clinical and histological remission [2, 29]. This should be assessed through clinical and endoscopic–histological evaluation after 8–12 weeks. Once clinical and histological remission is achieved, maintenance therapy should be continued to maintain remission.

The therapeutic management of EoE is often referred to as the "three D's," which stand for drugs, dietary interventions, and endoscopic therapy (dilation).

Drugs (medical therapy)

Topical corticosteroids

For remission-inducing therapy of EoE with topical corticosteroids (TCS) in adults and children, there are currently 11 placebo-controlled double-blind studies available, including 7 studies with budesonide and 4 studies with fluticasone [30].

An esophageal-specific formulation of budesonide is a budesonide orally disintegrating tablet (BUD ODT), which has been highly effective in inducing clinical–histological remission in a phase III study [31]. BUD ODT received EU approval in the summer of 2018 for induction therapy in EoE over an 8-week period, with a dosage of 2×1 mg daily. It is important to note that this medication should be taken after breakfast and before bedtime. After taking the tablet, one should refrain from eating or drinking for at least half an hour. The BUD ODT has also proven to be highly effective in maintenance therapy. In a European phase III study, patients who had previously achieved clinical and histological remission through induction therapy were randomized to receive treatment with 2×1 mg/day or 2×0.5 mg/day of budesonide or placebo over 48 weeks. The primary endpoint of clinical and histological remission was achieved in 75 and 73.5% of patients treated with budesonide, respectively [32]. The rate of suspected symptomatic candidiasis in this study was 14% (histologically confirmed candidiasis was 5%). Regarding morning serum cortisol levels, there was no significant difference between budesonide and placebo after 48 weeks [32]. Currently, in Germany and Europe, the orodispersible budesonide tablet is approved for the treatment of active EoE in adults. In the current German guidelines, topical corticosteroid therapy for active EoE is recommended with the term "should."

Proton pump inhibitors

In comparison to topical corticosteroids (TCS), the scientific evidence for the efficacy of proton pump inhibitors (PPIs) in the treatment of EoE is significantly weaker [33]. There are no placebo-controlled studies available for PPIs in EoE.

A meta-analysis found a pooled histological remission rate (<15 eosinophils/hpf) of 50%. The meta-analysis indicated significant heterogeneity and also suggested a significant publication bias [34]. A prospective study including adult EoE patients reported a clinical–histological remission rate of 33% after 8 weeks of high-dose PPI therapy [35]. The role of PPIs in long-term therapy for EoE is still unclear as no controlled long-term studies are available [33]. Furthermore, PPIs are not approved for the treatment of EoE, which is particularly problematic in the long-term management of a chronic condition with potential progression and significant complications. In the current German guidelines, PPI therapy for active EoE is recommended with the term "may."

Biologics

For a long time, the search for effective biologics for the treatment of EoE was frustrating. Substances that seemed to be pathophysiologically relevant, such as anti-IL5 antibodies (mepolizumab, reslizumab), or anti-IgE antibodies (omalizumab), showed no or insufficient efficacy in phase II studies [36].

Dupilumab is a monoclonal antibody that binds to the shared alpha subunit of the IL-4 receptor and IL-13 receptor, thereby antagonizing both the IL-4 and IL-13 signaling pathways. This antibody has already demonstrated its efficacy in other atopic diseases and is approved for multiple indications (atopic dermatitis, eosinophilic asthma, nasal polyps) [37]. Dupilumab has demonstrated significant superiority in achieving clinical–histological remission compared to placebo in both phase II and phase III studies in patients with active EoE [38, 39]. Since early 2023, this antibody has been approved for the treatment of EoE in Europe.

Diets/dietary interventions

Elemental diet

The initial evidence that dietary adherence can lead to remission comes from a pediatric study in which a strict amino acid-based diet was used, resulting in a clinical and histological remission rate of 80% [40]. Randomized controlled studies regarding the effectiveness of an elemental diet are lacking, but a meta-analysis of all observational studies estimated an overall histological remission rate of approximately 90% [41]. This dietary intervention has limitations in everyday life, including significant taste impairments, which restrict its applicability in adult EoE patients.

Elimination diets

In a pediatric study in 2006, adherence to a 6 food elimination diet (SFED) demonstrated that 74% of children achieved histological and symptomatic remission [42]. The following food components had to be avoided in this diet: cow's milk, wheat, eggs, soy, peanuts/tree nuts, and fish/seafood. Similar results regarding the effectiveness of remission induction through an elimination diet have been shown in further studies in EoE patients of all age groups [24, 25, 43].

After remission induction, the individual components of the diet were gradually reintroduced, and an esophagogastroduodenoscopy (EGD) was performed to assess histological activity. This approach allowed for the identification of causative food allergens. In descending order, these allergens were cow's milk, wheat, eggs, and to a lesser extent, soy, nuts, and fish/seafood. In 65–85% of patients who responded to SFED, one or two causative food components could be identified. Adhering to dietary restrictions in daily life poses a challenge. Furthermore, multiple gastroscopies are necessary when reintroducing the individual components of the diet. Despite the positive results mentioned above, this dietary intervention has drawbacks in terms of palatability, practicality, patient compliance, and adherence. However, it is important to note that this type of treatment is medication-free and can be considered a causal therapy.

Endoscopic therapy (dilation)

Esophageal strictures are often responsible for dysphagia and are the main risk factor for food impactions in EoE [44]. Endoscopic dilation, which can be performed using either "through the scope" balloons or wire-guided Savary bougies, is therefore a valuable treatment option [45]. However, it does not affect the underlying eosinophilic inflammation. A meta-analysis of 525 adult EoE patients and a total of 992 dilations demonstrated clinical improvement in 75% of the patients. The occurrence of perforation was reported to be 0.3% [46]. There were no differences in the complication rates based on the different dilation techniques [46, 47].

Concluding remarks and future perspectives

Eosinophilic esophagitis (EoE) is a chronic, progressive, and recurrent disease with increased recognition over the last past two decades. Over the years, significant progress has been made in understanding the pathophysiology, diagnosis, and treatment options for EoE. However, there are still several challenges and

unanswered questions that need to be addressed in the future.

One important aspect is the development of more targeted and personalized therapies for EoE. While corticosteroids and dietary modifications have shown efficacy, there is a need for novel treatment options that can specifically target the underlying inflammatory pathways involved in EoE. The recent approval of dupilumab is a promising step in this direction, but further research is required to explore additional therapeutic options.

Furthermore, long-term outcomes and the natural history of EoE need to be better understood. Prospective studies with long-term follow-up are necessary to assess the progression of the disease, the risk of complications, and the impact of various treatment approaches on patient outcomes.

Lastly, improving patient education and awareness about EoE is crucial. Increased recognition of symptoms, early diagnosis, and timely intervention can lead to better management and improved quality of life for affected individuals.

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