



Guidelines

The 1st EoETALY Consensus on the Diagnosis and Management of Eosinophilic Esophagitis – Definition, Clinical Presentation and Diagnosis[☆]



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ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic type 2-mediated inflammatory disease of the esophagus that represents the most common eosinophilic gastrointestinal disease. Experts in the field of EoE across Italy (i.e., EoETALY Consensus Group) including gastroenterologists, endoscopists, allergologists/immunologists, and paediatricians conducted a Delphi process to develop updated consensus statements for the management of patients with EoE and update the previous position paper of the Italian Society of Gastroenterology (SIGE) in light of recent evidence. Grading of the strength and quality of the evidence of the recommendations was performed using accepted GRADE criteria. The guideline is divided in two documents: Part 1 includes three chapters, namely 1) definition, epidemiology, and pathogenesis; 2) clinical presentation and natural history, and 3) diagnosis, while Part 2 includes two chapters: 4) treatment and 5) monitoring and follow-up. This document has received the endorsement of three Italian national societies including the SIGE, the Italian Society of Neurogastroenterology and Motility (SINGEM), and the Italian Society of Allergology, Asthma, and Clinical Immunology (SIAAIC). With regards to patients' involvement, these guidelines involved the contribution of members of ESEO Italia, the Italian Association of Families Against EoE.

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1. Introduction

Eosinophilic esophagitis (EoE) is a chronic type 2-mediated inflammatory disease of the esophagus presenting with symptoms of esophageal dysfunction [1]. The disease is primarily led by an abnormal infiltration of eosinophils in the esophageal mucosa, although several different other type 2 inflammation mediators are involved in the pathogenesis [2,3]. The first descriptions of EoE date back to 1990, when Attwood and Straumann characterized the disease for the first time [4,5]. The epidemiology of EoE is still evolving, with incidence and prevalence rising worldwide at a rate that outpaces increased recognition [6,7]. In recent years, novel therapeutic strategies have been investigated [7], and drugs licenced specifically for EoE have become available [8]. These guidelines were developed to provide a practical and evidence-based guide for the management of patients with EoE and update the previous position paper of the Italian Society of Gastroenterology (SIGE) published in 2017 in light of recent evidence [1]. These guidelines were developed by 35 experts in the field of EoE (i.e., EoETALY Consensus Group) and included gastroenterologists, endoscopists, allergologists/immunologists, and paediatricians involved in the management of EoE at 20 tertiary referral centres across Italy. The aim of the EoETALY Consensus was:

- To update the diagnostic criteria of EoE, underlining the importance of recognizing clinically relevant symptoms, identifying endoscopic findings, and performing an adequate number of esophageal biopsies in case of suspected EoE.
- To provide a shared National strategy for the diagnosis, treatment, and follow-up of patients with EoE.
- To highlight knowledge gaps and identify future research priorities.

2. Methods

The EoETALY Consensus Group developed updated National consensus statements on relevant aspects of EoE divided in two different documents (i.e., Part 1 and Part 2). The present manuscript constitutes Part 1 and includes three chapters: (1) definition, epidemiology, and pathogenesis; (2) clinical presentation and natural history and (3) diagnosis (Table 1). The EoETALY Consensus Statements Part 2 includes two final chapters: (4) treatment and (5) monitoring and follow-up. The full methodology is reported in Supplementary Materials. This document has received the endorsement of the SIGE, the Italian Society of Neurogastroenterology and Motility (SINGEM), and the Italian Society of Allergol-

ogy, Asthma, and Clinical Immunology (SIAAIC). With regards to patients' involvement, these guidelines were reviewed and commented by members of ESEO Italia, the Italian Association of Families Against EoE, which provided useful insights into the perspective of families and patients dealing with eosinophilic esophagitis and who endorsed the guidelines.

3. Chapter 1: definition, epidemiology and pathogenesis

STATEMENT 1

Eosinophilic esophagitis is a chronic, immune-mediated esophageal disease characterized by symptoms of esophageal dysfunction and a peak eosinophil count of ≥ 15 eosinophils per high power field (around 60 eos/mm²) in at least one high-power field on esophageal biopsy, in the absence of other causes of esophageal eosinophilia.

Agreement: 100% [D + (0%); D (0%); D- (0%); A- (0%); A (10%); A + (90%)]

Level of evidence: High

Level of recommendation: Strong

3.1. Summary of evidence

In the first consensus recommendations published in 2007, EoE was considered as a primary clinicopathologic disorder of the esophagus, and the threshold of ≥ 15 intraepithelial eosinophils per high-power field (eos/HPF) in at least one biopsy specimen was considered adequate to establish a diagnosis of EoE in the proper clinical context [9]. Initially, the lack of clinical or histologic response to high-dose proton pump inhibitors (PPI) therapy or absence of proven gastroesophageal reflux disease (GERD) were considered criteria for the diagnosis of EoE [9]. Subsequently, in 2011, since PPI treatment demonstrated efficacy for the induction of remission in patients with esophageal eosinophilia and absence of GERD at ambulatory reflux monitoring, the term PPI-responsive esophageal eosinophilia (PPI-REE) was introduced as a distinct entity from EoE [10]. In those years, however, a body of evidence indicated the absence of a rational basis to make a distinction between patients with symptomatic esophageal eosinophilia based on a different response to PPI therapy since phenotypic, molecular, mechanistic, and therapeutic features could not segregate EoE from PPI-REE [11]. Accordingly, the European guidelines published in 2017 questioned the PPI-REE as independent clinical entity suggesting that PPI-REE and EoE were part of the same disease spectrum, with PPI considered a possible treatment for EoE [12]. In the Updated International Consensus Diagnostic Criteria for

Table 1
Summary of EoETALY Consensus Statements.

Chapter 1: Definition, Epidemiology and Pathogenesis		
Statement	Level of Agreement	Recommendation and quality of evidence
1. Eosinophilic esophagitis is a chronic, immune-mediated esophageal disease characterized by symptoms of esophageal dysfunction and a peak eosinophil count of ≥ 15 eosinophils per high power field (around 60 eos/mm ²) in at least one high-power field on esophageal biopsy, in the absence of other causes of esophageal eosinophilia.	100%	Strong recommendation – High quality of evidence
2. Research has shown a link between EoE and food allergy. Food allergens can trigger and maintain esophageal inflammation in patients with EoE.	100%	Recommendation not applicable – High quality of evidence
3. Genomics and transcriptomics studies have identified specific genetic loci predisposing to the development of EoE.	96.7%	Recommendation not applicable – Low quality of evidence
4. The incidence and prevalence of EoE are increasing in children and adults as a result of both increased awareness and a true increase in rates of the disease.	100%	Recommendation not applicable – High quality of evidence
5. EoE may present at any age. Disease incidence increases with age and peaks in early adulthood.	93.3%	Recommendation not applicable – High quality of evidence
6. Patients with EoE are more commonly males.	100%	Recommendation not applicable – High quality of evidence
7. EoE and GERD represent two distinct clinical entities that may coexist in the same patient and interact.	100%	Recommendation not applicable – Moderate quality of evidence
Chapter 2: Clinical presentation and Natural history		
Statement	Level of Agreement	Recommendation and quality of evidence
8. The main symptoms associated with EoE in adults are dysphagia and food bolus impaction. In children, symptoms are often non-specific and vary with age, including reflux-like symptoms, failure to thrive, dyspepsia, nausea, and vomiting.	100%	Recommendation not applicable – High quality of evidence
9. Persistent symptoms, social restrictions, and long-term treatments reduce quality of life in EoE patients. Anxiety and depression affect these patients and may be alleviated by specific therapy.	96.7%	Conditional recommendation – Low quality of evidence
10. There is a positive association between EoE and allergic comorbidities.	100%	Recommendation not applicable – High quality of evidence
11. The association of EoE with autoimmune diseases is still uncertain. Patients should undergo specific tests only in case of clinical suspicion.	93.3%	Recommendation not applicable – Low quality of evidence
12. Psychiatric comorbidities are not uncommon in patients with EoE. Disease-specific anxiety may account for increased dysphagia severity and should be evaluated and actioned when managing patients with EoE.	93.3%	Conditional recommendation – Low quality of evidence
13. EoE is a chronic esophageal inflammation with a possible progression from an inflammatory to a fibrostenotic phenotype and, when untreated, can be associated with persistent symptoms and strictures development. Effective therapy may limit disease progression.	100%	Conditional recommendation – Low quality of evidence
14. There is no evidence that EoE is a pre-malignant condition. However, the relationship between a chronic inflammatory condition like EoE with Barrett's esophagus and esophageal cancer remains unclear.	93.4%	Recommendation not applicable – Moderate quality of evidence
Chapter 3: Diagnosis		
Statement	Level of Agreement	Recommendation and quality of evidence
15. - A conclusive diagnosis of EoE requires a combination of symptoms of esophageal dysfunction and histology showing ≥ 15 eosinophils/high-power field in at least one esophageal biopsy while off drugs potentially interfering with esophageal eosinophil counts. - Proton pump inhibitors should be withdrawn at least 3–4 weeks prior to biopsy collection to achieve a conclusive diagnosis of EoE. - Alternative causes of esophageal eosinophilia should be excluded.	96.7%	Strong recommendation – High quality of evidence
16. The endoscopic features of EoE reflect its natural history, made of active inflammation (edema, exudates and longitudinal furrows), that leads to a fibrostenotic remodelling of the esophagus (rings, strictures, narrowing, and crêpe-paper mucosa).	96.7%	Recommendation not applicable – High quality of evidence
17. - All patients with dysphagia and/or episodes of food bolus impaction should undergo at least six esophageal biopsies to rule out EoE even when the esophagus appears normal at endoscopy. - All patients with endoscopic signs of EoE should undergo multiple esophageal biopsies to rule out EoE. - Esophageal biopsies should be obtained at index endoscopy following an episode of food bolus impaction.	93.3%	Strong recommendation – High quality of evidence
18. To diagnose EoE, at least six biopsies should be taken from no less than two different esophageal sites, preferably from areas with esophageal abnormalities.	96.6%	Strong recommendation – Moderate quality of evidence
19. The accepted diagnostic threshold for a diagnosis of EoE corresponds to a peak eosinophil count of 15 eosinophils/high-power field (about 60/mm ²) in at least one high-power field on esophageal biopsy.	100%	Strong recommendation – Moderate quality of evidence
20. Besides mucosal eosinophilia, additional histologic features of EoE should be assessed for an accurate diagnosis and monitoring of disease activity. These include basal zone hyperplasia, eosinophil micro abscesses, eosinophil surface layering, dilated intercellular spaces, lamina propria fibrosis and papillary elongation.	93.3%	Strong recommendation – Moderate quality of evidence

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Table 1
(continued)

21. Endoscopy has poor sensitivity for the detection of esophageal narrowing and subtle strictures when compared to a barium esophagogram. In case of suspicion, a barium study could be performed for a more accurate assessment of strictures in patients with EoE.	86.6%	Strong recommendation – Moderate quality of evidence
22. - High-resolution manometry should be performed to rule out motility disorders in patients with persistent symptoms despite proven histological remission of EoE and no evidence of esophageal stricture - pH-impedance should be considered in patients with persisting reflux symptoms despite proven histological remission of EoE	90%	Conditional recommendation – Very low quality of evidence
23. There are currently no validated non-invasive or minimally invasive biomarkers that can be used for the management of EoE in clinical practice.	100%	Strong recommendation – Very low quality of evidence

Eosinophilic Esophagitis published in 2018 this definition of EoE integrated the concept of PPI-REE [13]. Currently, there is no distinction between EoE and PPI-REE, and EoE is considered a chronic, immune-mediated esophageal disease characterized by symptoms of esophageal dysfunction and a peak eosinophil count of ≥ 15 eos/HPF (around 60 eos/mm²) in at least one HPF on esophageal biopsy, in the absence of other causes of esophageal eosinophilia (see statement 15), which may or may not respond to PPI treatment.

STATEMENT 2

Research has shown a link between EoE and food allergy. Food allergens can trigger and maintain esophageal inflammation in patients with EoE.

Agreement: 100% [D + (0%); D (0%); D- (0%); A- (0%); A (23.3%); A + (76.6%)]

Level of evidence: High

Level of recommendation: Not applicable

3.2. Summary of evidence

There is data showing that the presence of a recognized food allergy in atopic patients is a predisposing condition for the development of EoE. EoE is a Th2 cell-mediated disease associated with a sensitization to airborne and/or food allergens, but not developing through an immunoglobulin (Ig) E-mediated mechanism [14,15]. Several studies on food allergy testing and elimination diets have supported a link between EoE and food allergy and, recently, food specific IgG4 were found in the esophageal epithelium of EoE patients [16,17]. Food antigens are currently considered the main triggers of EoE although the lack of an adequate response to dietary changes in a portion of EoE patients implies that other antigens, such as inhaled aeroallergens, can play a role in EoE pathophysiology [18–20]. In this regard, a recent study showed that the response to elimination diets is lower during the pollen season in patients with EoE sensitized to seasonal pollens, suggesting a role of inhaled allergens in the pathophysiology of the disease [18].

STATEMENT 3

Genomics and transcriptomics studies have identified specific genetic loci predisposing to the development of EoE.

Agreement: 96.7% [D + (0%); D (0%); D- (0%); A- (3.3%); A (46.7%); A + (50%)]

Level of evidence: Low

Level of recommendation: Not applicable

3.3. Summary of evidence

The aetiologic and pathogenetic role of genes in EoE is supported by evidence of heritability. In this regard, proband concor-

dance in monozygotic and dizygotic twins has been shown to be of 58% and 36%, respectively [21]. The frequency of EoE between non-twin siblings is 2.4%, which represents a 44-fold increase compared to general population [21]. Furthermore, the recurrence risk-ratio is higher if first-degree relatives are male rather than female, thus allowing both an autosomal and an X-linked inheritance pattern to be ruled out [3,21]. In the last decades, genome-wide association studies have identified a consistent number of specific genetic loci that may predispose to EoE, i.e., an EoE-identifying transcriptome [22]. One of the most induced gene within the EoE transcriptome is eotaxin-3, an eosinophil chemoattractant that also upregulates the expression of IL-13 [23]. A relevant group of clustered EoE-linked genes has been found on locus 1q21, that corresponds to the “Epidermal Differentiation Complex”, which encodes for several epithelial barrier components such as Filaggrin, Involucrin, Small Prolin-Rich Repeat and whose expression is downregulated by IL-13 [24,25]. Moreover, Thymic Stromal Lymphopoietin (TSLP) and Calpain-14 genes have shown to play a role in EoE susceptibility, as their overexpression leads to the stimulation of Th2 inflammatory response and the induction of disruptive changes of esophageal epithelium, respectively [26,27].

STATEMENT 4

The incidence and prevalence of EoE are increasing in children and adults as a result of both increased awareness and a true increase in rates of the disease.

Agreement: 100% [D + (0%); D (0%); D- (0%); A- (0%); A (20%); A + (80%)]

Level of evidence: High

Level of recommendation: Not applicable

3.4. Summary of evidence

The incidence and prevalence of the EoE have been constantly increasing over the past three decades as a result of both increased awareness and a true increase of the incidence [6]. In addition, esophageal biopsies have been consistently recommended in recent guidelines on dysphagia [1,12,13,28,29]. In this regard, several studies have investigated whether the change in rates of EoE over time was related to changes in rates of endoscopy with biopsy during the same time period and have found that the increase in EoE incidence outpaces the increase in rates of endoscopy with biopsy [30–32]. Current estimates report incidence rates of up to 20 per 100,000 people per year [33], similar to that of inflammatory bowel diseases [34–36]. The current estimated prevalence is more than 1 in 1000 people in Western Countries, and of 20 every 100,000 upper endoscopies in Asia [34]. Data coming from population-based studies suggest that the increase of the incidence may be higher in adults than in children [37], although this needs confirmation.

STATEMENT 5

EoE may present at any age. Disease incidence increases with age and peaks in early adulthood.

Agreement: 93.3% [*D* + (0%); *D* (0%); *D*- (0%); *A*- (6.7%); *A* (20%); *A* + (73.3%)]

Level of evidence: High

Level of recommendation: Not applicable

3.5. Summary of evidence

EoE has been reported throughout the lifespan, from infancy to almost 100 years of age [6,38,39]. A retrospective analysis of a large database including children and adults living in the United States showed that the prevalence of EoE increases with age, peaks in adulthood both in males and females aged 35–39 years, and then decreases after the age of 45 [32,40,41]. Other mostly retrospective studies provided similar results, and showed that most diagnoses of EoE are performed before the age of 50 [31,32,42].

STATEMENT 6

Patients with EoE are more commonly males.

Agreement: 100% [*D* + (0%); *D* (0%); *D*- (0%); *A*- (0%); *A* (10%); *A* + (90%)]

Level of evidence: High

Level of recommendation: Not applicable

3.6. Summary of evidence

EoE can be diagnosed both in males and females. However, males have an estimated three-fold higher risk of developing EoE. In this regard, several studies have shown that EoE occurs predominantly in male patients, with a 3:1 male to female ratio in all age groups [2,37,38]. It has been suggested that a single nucleotide polymorphisms in TSLP gene and receptor may be a possible mechanism for the male predilection of EoE [3,43].

STATEMENT 7

EoE and GERD represent two distinct clinical entities that may coexist in the same patient and interact.

Agreement: 100% [*D* + (0%); *D* (0%); *D*- (0%); *A*- (0%); *A* (30%); *A* + (70%)]

Level of evidence: Moderate

Level of recommendation: Not applicable

3.7. Summary of evidence

GERD and EoE represent two separate entities, that may coexist in a single patient [12,44]. GERD and EoE share similar clinical and histological features in children, making them hard to distinguish in the paediatric cohort. In adults, the most common clinical presentation of EoE is food impaction and recurrent dysphagia while the cardinal symptom of GERD is heartburn [45,46]. EoE and GERD may have a bidirectional relationship. EoE might cause GERD because of impaired esophageal clearance of physiological reflux, and GERD could cause EoE if reflux leads to a permeable epithelial barrier, through which environmental antigens may induce a type 2-driven immune response with cytokine-mediated recruitment of eosinophils.

It has been suggested that GERD may contribute to EoE development by increasing esophageal mucosal permeability and allowing transepithelial allergen infiltration, with subsequent immune activation and eosinophils migration [47]. In addition, it has been shown that higher impedance gradient between the mid and distal oesophagus [48], and improvement of chemical clearance [49] with higher efficacy of the esophago-salivary reflex [49] may predict PPI

responsiveness in EoE, suggesting an antireflux mechanism of action of PPIs and a pathogenic role of acid reflux in EoE patients responsive to PPIs.

4. Chapter 2: clinical presentation and natural history**STATEMENT 8**

The main symptoms associated with EoE in adults are dysphagia and food bolus impaction. In children, symptoms are often non-specific and vary with age, including reflux-like symptoms, failure to thrive, dyspepsia, nausea, and vomiting.

Agreement: 100% [*D* + (0%); *D* (0%); *D*- (0%); *A*- (0%); *A* (16.7%); *A* + (83.3%)]

Level of evidence: High

Level of recommendation: Not Applicable

4.1. Summary of evidence

In adults, intermittent dysphagia for solids is a typical symptom for EoE. A retrospective study evaluated 117 patients (108 adults) with EoE found dysphagia as the common symptom in 70% of patients [50]. A prospective study of 100 adult patients with non-obstructive dysphagia reported that 22% had EoE [51]. Food bolus obstruction is also a common presentation of EoE [52]. In a retrospective study of 546 patients presenting with food bolus obstruction, 46% had histological evidence of EoE. EoE was also the strongest predictor of multiple presentations with bolus obstruction [53]. It is estimated that food impaction necessitating endoscopic bolus removal occurs in 33 – 54% of adult EoE patients [54]. On rare occasions, impaction can lead to esophageal perforation (Boerhaave's syndrome) [55]. A retrospective study of 353 patients with reflux symptoms reported that 7.7% of those biopsied at endoscopy had EoE [56]. A retrospective review of 161 patients having endoscopy for noncardiac chest pain reported that 6% had EoE [57]. While heartburn and chest pain may be present in EoE, they are characteristically not the dominant complaints reported by adult patients and if present, usually accompany dysphagia [11]. However, non-specific upper gastrointestinal symptoms including abdominal pain, nausea, vomiting, dyspepsia, and failure to thrive may be common in childhood [2]. The presence of diarrhoea, gastrointestinal bleeding, and weight loss are not typical in patients with EoE, especially adults, and alternative causes, including non-esophageal eosinophilic gastrointestinal disorders (EGIDs) should be investigated when these features predominate [58,59].

STATEMENT 9

Persistent symptoms, social restrictions, and long-term treatments reduce quality of life in EoE patients. Anxiety and depression affect these patients and may be alleviated by specific therapy.

Agreement: 96.7% [*D* + (0%); *D* (0%); *D*- (0%); *A*- (3.3%); *A* (36.7%); *A* + (60%)]

Level of evidence: Low

Level of recommendation: Conditional

4.2. Summary of evidence

Esophageal hypervigilance and anxiety are emerging as important considerations in understanding symptom reporting especially in patients with refractory symptoms and a poor quality of life (QoL) [60,61]. In this regard, a prospective cross-sectional observational study from the United Kingdom using several validated questionnaires, compared the QoL and dysphagia severity of EoE patients to healthy subjects. EoE patients reported a statistically significant lower mental QoL, probably due to symptoms and medication use. In addition, EoE patients had higher dysphagia scores,

which negatively correlated with both physical and mental QoL. This study demonstrated that EoE may have an impact on patient's mental health and that education and reassurance are fundamental for all patients at diagnosis [62]. Of note, Klinnert et al. demonstrated that a year-long treatment reduced symptoms and improved QoL in children with EoE [63].

STATEMENT 10

There is a positive association between EoE and allergic comorbidities.

Agreement: 100% [D + (0%); D (0%); D- (0%); A- (0%); A (10%); A + (90%)]

Level of evidence: High

Level of recommendation: Not Applicable

4.3. Summary of evidence

There is an established association between EoE and atopic disorders [64]. Most EoE patients have at least one atopic comorbidity [65]. Bronchial asthma, allergic rhinitis, and atopic dermatitis are more frequently described in patients with EoE than in the general population regardless of the age [66]. Hill et al. suggested that EoE is a late manifestation of the atopic march. Using a primary care birth cohort of 130,435 children, they observed that the presence of allergic rhinitis, atopic dermatitis, IgE-mediated food allergy and asthma was associated with subsequent EoE diagnosis, with a cumulative effect of multiple preceding allergic conditions [67]. Finally, seasonal exacerbations and lower treatment response during the pollen season suggest a role of aeroallergens in the pathogenesis of eosinophilic esophagitis in some patients [18,68]. Considering the abovementioned, referring EoE patients to the allergist may improve the overall assessment of patients, particularly when other type-2 conditions are present.

STATEMENT 11

The association of EoE with autoimmune diseases is still uncertain. Patients should undergo specific tests only in case of clinical suspicion.

Agreement: 93.3% [D + (0%); D (0%); D- (0%); A- (6.7%); A (40%); A + (53.3%)]

Level of evidence: Low

Level of recommendation: Not Applicable

4.4. Summary of evidence

A genome-wide association study identified four new loci associated with EoE, two of which (c11orf30 and STAT6) were previously reported to be associated with autoimmune diseases [3,69]. A meta-analysis published in 2017 concluded that the diagnosis of celiac disease in children is not associated with an increased risk of EoE [70]. Recently, the prevalence and clinical features of autoimmune and connective tissue disorders (AI/CTDs) have been investigated in a retrospective cohort study of 1029 adults and children EoE patients. The most common AI/CTDs were psoriasis/psoriatic arthritis (1.7%), Hashimoto's (1.2%), and rheumatoid arthritis (RA) (1%). Older age, female sex, and allergic rhinitis were independently associated with AI/CTDs [71]. An association between autoimmune diseases and EoE has been previously described in children in a population-based cohort study [72] and in a retrospective cross-sectional review of electronic medical records comparing children with and without EoE [73].

STATEMENT 12

Psychiatric comorbidities are not uncommon in patients with EoE. Disease-specific anxiety may account for increased dysphagia

severity and should be evaluated and actioned when managing patients with EoE.

Agreement: 93.3% [D + (0%); D (0%); D- (0%); A- (6.7%); A (36.6%); A + (56.7%)]

Level of evidence: Low

Level of recommendation: Conditional

4.5. Summary of evidence

A retrospective medical record review investigating the prevalence of psychiatric comorbidities based on ICD-9 and ICD-10 codes in 950 adult patients with EoE found that 31% had at least one psychiatric or neuro-psychiatric comorbidity, with depression (12%) and anxiety (9.3%) being the most prevalent [74]. In a multi-centre study conducted on 170 adults with EoE [75], the prevalence of probable or certain anxiety and depression was 31.1% and 9.8%, respectively, based on the Hospital Anxiety and Depression Scale-8 (HADS-8). In another study on 705 EoE patients, depression and anxiety were reported in 15.5% of patients <17 years old. Additionally, the authors found significant increase of depression and anxiety across age groups, with a prevalence of 24% in patients ≥18 years of age compared to 9.3% in children [76]. In a recent study, 1458 EoE patients were followed-up for a median time of 4 years and compared to a matched reference group. In total, 15.96/1000 person-years in the EoE group developed a psychiatric disorder compared with 10.93/1000 person-years of the reference population, corresponding to a hazard ratio of 1.50 (95% CI, 1.20–1.87) [77]. Finally, a recent study demonstrated that symptom-specific anxiety and hypervigilance, as assessed by the Esophageal Hypervigilance and Anxiety Scale (EHAS), were the only predictors of increased dysphagia symptoms when accounting for endoscopic and histologic severity [60]. Accordingly, EoE patients should be offered psychological support when appropriate [61].

STATEMENT 13

EoE is a chronic esophageal inflammation with a possible progression from an inflammatory to a fibrostenotic phenotype and, when untreated, can be associated with persistent symptoms and strictures development. Effective therapy may limit disease progression.

Agreement: 100 % [D + (0%); D (0%); D- (0%); A- (0%); A (26.7%); A + (73.3%)]

Level of evidence: Low

Level of recommendation: Conditional

4.6. Summary of evidence

In an old study on 30 untreated adults that were followed-up for an average of 7.2 years, dysphagia persisted in nearly all patients who also showed subepithelial fibrosis (i.e., remodelling) in 86% of esophageal biopsies [78]. In addition, a multicenter longitudinal study found that up to 70% of untreated patients developed strictures and 9% of subjects were found to have an extremely narrow caliber esophagus [79]. Older age and duration of inflammation are now considered the major risk factors for esophageal strictures, while it is known that fibrostenotic features and impaction are less frequent in the paediatric population [80,81]. The main concern is that a long-standing, untreated eosinophilic inflammation leads to fibrosis with wall thickening, abnormal fragility and strictures, finally provoking a structural and functional damage of the esophagus known as remodelling [82–84], which predisposes to complications including food impaction, reflux disease or retching-induced esophageal rupture [55,82,85]. In another retrospective study on 721 patients that investigated the association between undiagnosed EoE and the occurrence of complications over two decades, diagnostic delay and male gender were the major risk

factors for stricture presence with each additional year of undiagnosed EoE increasing the risk of strictures by 9%, implying that effective therapy may limit disease progression [86].

STATEMENT 14

There is no evidence that EoE is a pre-malignant condition. However, the relationship between a chronic inflammatory condition like EoE with Barrett's esophagus and esophageal cancer remains unclear.

Agreement: 93.4% [D + (3.3%); D (0%); D- (0%); A- (3.3%); A (36.7%); A + (56.7%)]

Level of evidence: Moderate

Level of recommendation: Not applicable

4.7. Summary of evidence

EoE is associated with chronic inflammation and tissue remodelling, which may raise concerns on the malignant potential of the disease [3]. Esophageal eosinophilia is associated with Barrett's esophagus (BE), which is a well-known precursor of esophageal adenocarcinoma [87,88]. However, whether esophageal eosinophilia in patients with EoE increases the risk for subsequent esophageal cancer is unclear. In this regard, some studies have shown an inverse relationship between EoE and BE [89,90], while other studies have concluded that some patients with EoE may develop BE during follow-up [91]. However, follow-up studies with a mean duration of up to 13.6 years have not demonstrated any association between EoE and the development of esophageal cancer [78,91]. Another retrospective study conducted over 5 years demonstrated that EoE, unlike GERD and BE, was not associated with the development of esophageal cancer [92]. There is currently no evidence that EoE is a pre-malignant condition, although the relationship between EoE and BE remains unclear. Longer follow-up studies are needed to clarify this topic.

5. Chapter 3: diagnosis

Figure 1 provides a summary of the diagnostic algorithm of EoE.

STATEMENT 15

- A conclusive diagnosis of EoE requires a combination of symptoms of esophageal dysfunction and histology showing ≥ 15 eosinophils/high-power field in at least one esophageal biopsy while off drugs potentially interfering with esophageal eosinophil counts.
- Proton pump inhibitors should be withdrawn at least 3–4 weeks prior to biopsy collection to achieve an accurate diagnosis of EoE.
- Alternative causes of esophageal eosinophilia should be excluded.

Agreement: 96.7% [D + (0%); D (0%); D- (0%); A- (3.3%); A (16.7%); A + (80%)]

Level of evidence: High

Level of recommendation: Strong

5.1. Summary of evidence

EoE is considered a distinct clinical-pathological entity characterized by a combination of esophageal symptoms (dysphagia, food bolus impaction) and/or other upper gastrointestinal symptoms (heartburn, regurgitation, non-cardiac chest pain, epigastric discomfort) with evidence of ≥ 15 eosinophils/high-power field in at least one esophageal biopsy, in the absence of secondary causes of eosinophilia [2,93]. Both clinical and histopathological criteria

are required to achieve a conclusive diagnosis of EoE. The resolution of esophageal eosinophilia following treatment with PPI does not rule out a diagnosis of EoE, rather it identifies patients with EoE who respond to PPI treatment [94–96]. These criteria are applicable to all age groups and to patients with concomitant GERD. Recently, a validated artificial intelligence algorithm for the diagnosis of EoE based on clinical or clinical and endoscopic characteristics has become available for use as a point-of-care tool [97].

Since PPIs can induce histological remission in a significant proportion of EoE patients, ongoing PPI treatment may mask an histological diagnosis of EoE in patients with suggestive symptoms [98]. In this regard, a small study showed that, following an initial non-diagnostic endoscopy with biopsies performed on PPIs, a repeat EGDS with biopsies performed after 3–4 weeks off PPIs allowed to achieve a histological diagnosis of EoE [99]. Accordingly, we suggest that, in case of clinical suspicion of EoE, PPI should be withdrawn at least 3–4 weeks prior to endoscopy and biopsy collection to achieve an accurate diagnosis, although more data regarding the optimal timing of PPI withdrawal is needed. Finally, several disorders can cause esophageal eosinophilia and resemble EoE for their clinical or endoscopic appearance. Before achieving a conclusive diagnosis of EoE, local and systemic cause of esophageal eosinophilia should be taken into account and ruled out, including lymphocytic esophagitis, infectious esophagitis, achalasia, Crohn's disease (CD), connective tissue disorders, hypereosinophilic syndrome, and vasculitis [12,28,100–104]. In addition, in the presence of non-esophageal gastrointestinal symptoms or endoscopic findings, non-esophageal EGIDs should be ruled out by collecting biopsies also from the stomach and/or duodenum [12,28].

STATEMENT 16

The endoscopic features of EoE reflect its natural history, made of active inflammation (edema, exudates and longitudinal furrows), that leads to a fibrostenotic remodelling of the esophagus (rings, strictures, narrowing, and crêpe-paper mucosa).

Agreement: 96.7% [D + (0%); D (0%); D- (0%); A- (3.3%); A (6.7%); A + (90%)]

Level of evidence: High

Level of recommendation: Not Applicable

5.2. Summary of evidence

To increase the identification and to standardize the nomenclature and the scoring of the endoscopic findings, the EoE endoscopic reference score (EREFS) was developed in 2012 [105]. The score is calculated based on five major findings (Edema, Rings, Exudates, Furrows, and Strictures; EREFS), with crêpe-paper mucosa as adjunctive finding. The system showed good interobserver agreement with consistent scoring among practicing and academic gastroenterologists [106,107]. In contrast, conflicting results have been reported concerning the correlation between EREFS values and histologically defined activity for diagnosis and monitoring [18,106–112]. Edema (pallor due to loss of vascular pattern), exudates (whitish plaques or spots) and longitudinal furrows (vertical lines) are linked to active inflammation, while esophageal rings (trachealization), strictures, narrowings and crêpe-paper esophagus (mucosal fragility on the scope passage), are signs of fibrotic esophageal remodelling [1,105]. The prevalence of these features, that can coexist in the same patient, varies by age, with fibrotic features being more frequent in adults with a longer history of active EoE [113]. Data from a meta-analysis published in 2012, including about 4700 patients with EoE and 2700 controls, showed that their prevalence is heterogeneous among studies, revealing only a modest sensitivity and positive and negative predictive values for endoscopic features to identify EoE [113]. Some findings

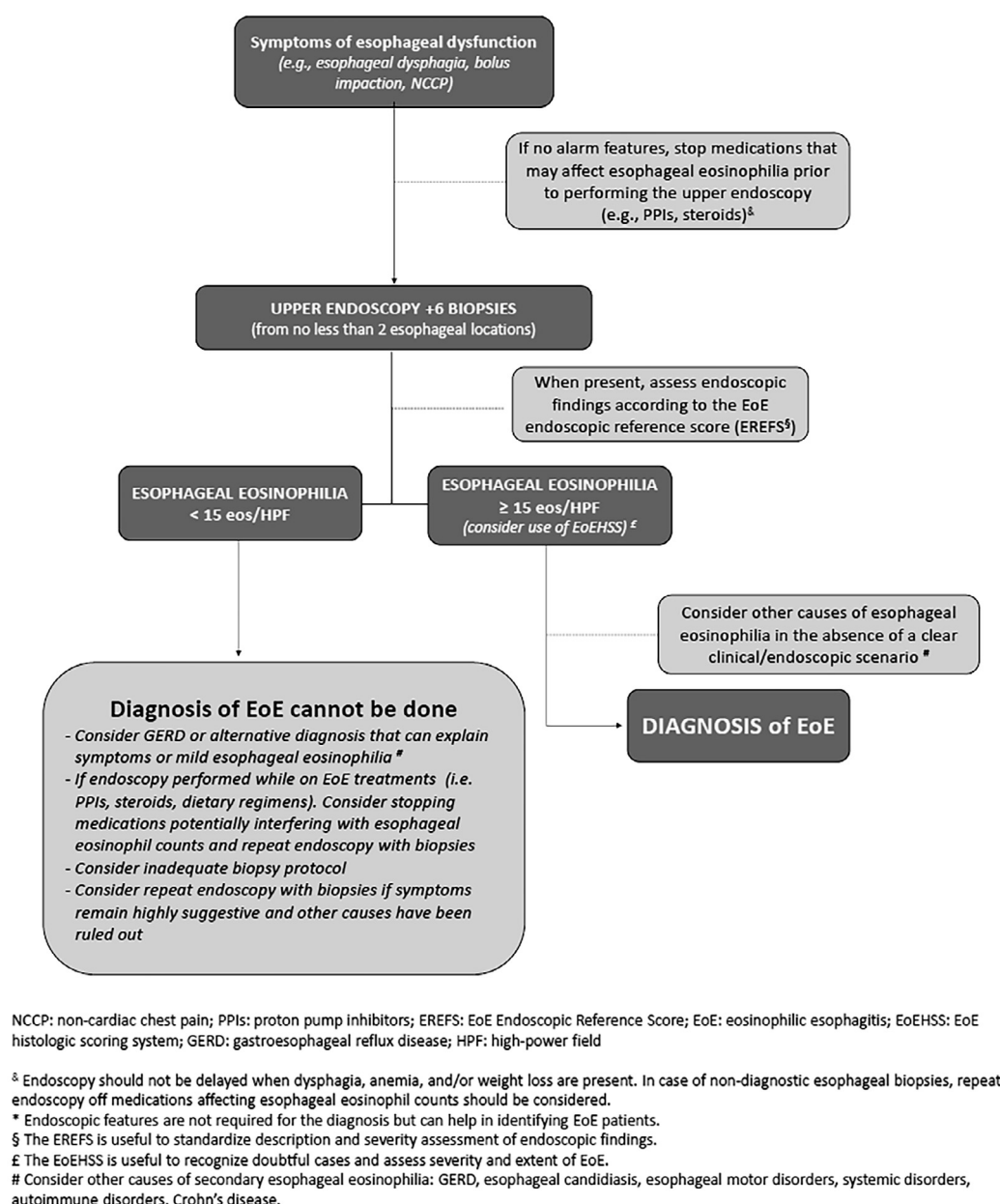


Fig. 1. Diagnostic algorithm of eosinophilic esophagitis.

can be seen in other conditions such as GERD (e.g., edema and furrows), or can be mistaken for something else by an untrained eye (e.g., exudates for esophageal candidiasis) [114]. In a variable proportion of patients (5–32%), the esophageal mucosa may appear normal, especially in non-tertiary centres [113,115]. Age of patients (children>adult), type of the study (retrospective>prospective) and previous treatments (treated>untreated) have been linked to normal endoscopic appearance. However, with increasing awareness, this scenario is becoming less common at index endoscopy [2,105,113,115].

STATEMENT 17

- All patients with dysphagia and/or episodes of food bolus impaction should undergo at least six esophageal biopsies to rule out EoE even when the esophagus appears normal at endoscopy.

- All patients with endoscopic signs of EoE should undergo multiple esophageal biopsies to rule out EoE.
- Esophageal biopsies should be obtained at index endoscopy following an episode of food bolus impaction.

Agreement: 93.3% [D + (0%); D (0%); D- (3.3%); A- (3.3%); A (10%); A + (83.3%)]

Level of evidence: High

Level of recommendation: Strong

5.3. Summary of evidence

Prevalence of EoE in adult patients undergoing endoscopy for dysphagia has been reported up to 23%, with higher incidence in people of white ethnic origin, male and younger than 50 years [38,51]. Although both EoE and GERD may have pathological endoscopic findings, about 65% of patients suffering from GERD and up

to 31% of patient with EoE have normal endoscopy [39,113,116,117]. Dysphagia being the predominant manifestation in adult patients with EoE and taking into consideration the prevalence of macroscopically normal esophagus in both children and adult patients affected by the disease, it is recommended to perform multiple esophageal biopsies in patients with dysphagia and normal endoscopy.

STATEMENT 18

To diagnose EoE, at least six biopsies should be taken from no less than two different esophageal sites, preferably from areas with esophageal abnormalities.

Agreement: 96.6% [D + (0%); D (0%); D – (0%); A– (3.4%); A (23.3%); A + (73.3%)]

Level of evidence: Moderate

Level of recommendation: Strong

5.4. Summary of evidence

Esophageal biopsies to diagnose EoE are always mandatory and should be taken in any case of clinical suspicion of EoE. Since inflammatory changes have a patchy distribution, we recommend taking at least six biopsies, from different esophageal anatomical sites, to increase diagnostic sensitivity [118,119]. In a retrospective study published in 2014, Nielsen and Colleagues, evaluated biopsy samples of 102 EoE patients. The probability of one, four, five, and six biopsies to contain >15 eos/HPF was 0.63, 0.98, 0.99, and >0.99, respectively [119]. Sampling should primarily include targeted areas where endoscopic inflammatory features (e.g., exudates and longitudinal furrows) are evident, as these are associated with higher peak eosinophil counts [119,120]. Although most of available protocols consider taking two to four biopsies both in the distal and in the proximal esophagus [1,28], some recent studies have supposed that adding mid-esophageal biopsies could increase the diagnostic yield [121]. In a cohort of 96 EoE patients, the retrospective evaluation of esophageal biopsies taken with a three-site protocol, revealed that in 17 patients (17.7%) the diagnostic criteria were met only in specimens from mid esophagus [121]. Based on available evidence, other than distal and proximal biopsies, additional biopsies from mid-esophagus may be advisable as they could increase the diagnostic sensitivity, although further studies are needed to clarify this aspect. Besides esophageal biopsies, in the presence of other gastrointestinal symptoms, gastric and duodenal samples should also be collected at index endoscopy, in order to exclude other eosinophilic gastrointestinal disorders [59,122].

STATEMENT 19

The accepted diagnostic threshold for a diagnosis of EoE corresponds to a peak eosinophil count of 15 eosinophils/high-power field (about 60/mm²) in at least one high-power field on esophageal biopsy.

Agreement: 100% [D + (0%); D (0%); D – (0%); A– (0%); A (36.7%); A + (63.3%)]

Level of evidence: Moderate

Level of recommendation: Strong

5.5. Summary of evidence

The diagnosis of EoE relies on the assessment of the eosinophilic infiltration in the esophageal mucosa [12,28]. The main issue for setting an optimal cut-off for this condition is to discriminate EoE from other causes of esophageal eosinophilia, in particular GERD and reflux esophagitis, that may coexist with EoE. The cut-off originally identified for the diagnosis of EoE was 20

eos/HPF [123], but then it was lowered to 15 eos/HPF after an international consensus [10] and subsequent guidelines [1,12,28,124]. It must be noted, however, that there are no RCT designed to explore the optimal eosinophilic cut-off, and comparative studies are lacking. Accordingly, the cut-off of 15 eos/HPF should be considered arbitrary. Only recently, the accuracy of this cut-off has been assessed in a prospective study, finding a sensitivity of 100% and a specificity of 96%, which highlights an excellent accuracy for the cut-off of 15 eos/HPF [125]. The peak eosinophil count of ≥ 15 eos/HPF should be considered diagnostic regardless of the esophageal tract (i.e., proximal, or distal). It must be noted that, as PPI treatment is effective in inducing remission of EoE, these medications should be discontinued prior to esophageal biopsy sampling to establish a diagnosis of EoE [28].

STATEMENT 20

Besides mucosal eosinophilia, additional histologic features of EoE should be assessed for an accurate diagnosis and monitoring of disease activity. These include basal zone hyperplasia, eosinophil micro abscesses, eosinophil surface layering, dilated intercellular spaces, lamina propria fibrosis and papillary elongation.

Agreement: 93.3% [D + (0%); D (0%); D – (3.3%); A– (3.3%); A (33.4%); A + (60%)]

Level of evidence: Moderate

Level of recommendation: Strong

5.6. Summary of evidence

Although the threshold of 15 eosinophils can reliably distinguish EoE patients from GERD patients, this single parameter may not be sufficient to rule out a possible overlap of these two disorders [125].

The inflammatory milieu in EoE is not restricted to the epithelium but might encompass all esophageal wall layers, leading to esophageal remodelling with subepithelial fibrosis. In addition to the eosinophilic count, some ancillary histologic features including basal zone hyperplasia, eosinophil micro-abscesses, eosinophil surface layering, dilated intercellular spaces (spongiosis), lamina propria fibrosis and papillary elongation should be evaluated. These features have been recently described in two validated histological scoring systems namely the Eosinophilic Esophagitis Histology Scoring System (EoEHSS) and the Eosinophilic Histology Remission Score (EoEHRS) in which eight EoE associated histologic abnormalities are scored for severity (grade) and extent (stage) in a four-point scale [126,127]. These scores have been developed in EoE research trials, with still limited use in clinical practice. Nevertheless, their reliability was demonstrated by excellent agreement scores between pathologists after minimal training. Of particular note, the EoEHSS has shown to discriminate treated from untreated patients better than the peak eosinophil count, also showing a correlation with symptoms scores [126,127]. It should be noted that the presence of lamina propria fibrosis was not included in EoEHSS. This feature is rarely reported by pathologists because of the lack of subepithelial tissue in the majority of esophageal biopsies taken with standard forceps [128]. However, when possible, it should be evaluated, since EoE therapies can lead to a resolution of the esophageal remodelling and fibrotic changes [129–131].

STATEMENT 21

Endoscopy has poor sensitivity for the detection of esophageal narrowing and subtle strictures compared to a barium esophagogram. In case of suspicion, a barium study could be performed for a more accurate assessment of strictures in patients with EoE.

Agreement: 86.6% [D + (0%); D (0%); D – (3.4%); A– (10%); A (33.3%); A + (53.3%)]

Level of evidence: Moderate

Level of recommendation: Strong

5.7. Summary of evidence

Endoscopy has suboptimal sensitivity for the assessment of esophageal strictures [132]. A retrospective study showed that the sensitivity of endoscopy for the identification of strictures ≤ 15 mm was as low as 25% compared to a barium esophagogram [114]. Another retrospective study conducted in 22 pediatric EoE patients with esophageal strictures showed that, compared to the barium esophagogram, endoscopy failed to identify esophageal strictures in 55% of patients [133]. However, in another retrospective study on 26 EoE paediatric patients, barium x-ray identified narrow-calibre esophagus in 10 out of 11 patients when compared to EGDS, and was unable to detect concentric rings in 4 out of 14 patients seen on EGDS [134]. Although a barium study could be performed for an accurate assessment of strictures in patients with EoE, it must be noted that the assessment of a barium swallow in patients with EoE is not standardized at the present time because of the heterogeneity of acquisition protocols and the lack of reference values for esophageal diameters.

STATEMENT 22

- High-resolution manometry should be performed to rule out motility disorders in patients with persistent symptoms despite proven histological remission of EoE and no evidence of esophageal stricture
- pH-impedance should be considered in patients with persisting reflux symptoms despite proven histological remission of EoE

Agreement: 90% [D + (0%); D (0%); D - (3.3%); A- (6.7%); A (33.3%); A + (56.7%)]

Level of evidence: Very low

Level of recommendation: Conditional

5.8. Summary of evidence

Eosinophils can cause esophageal dysmotility by means of different mechanisms [135]. When EoE is recognized, esophageal motor function could be investigated by means of high-resolution manometry (HRM) [136,137]. The spectrum of esophageal motility patterns in patients with EoE is inconsistent [102,135,138]. Savarino et al. [139] prospectively assessed HRM findings in 35 consecutive EoE patients. Fifty-seven percent of subjects showed no abnormalities, whereas ineffective or fragmented peristalsis were observed in 20% of patients, absent peristalsis or DES in 6%, EGJOO in 9%, and achalasia in 3%. A more recent large cohort multicentre retrospective study by Ghisa et al. [101] was aimed at assessing the HRM patterns of 109 EoE patients. Overall, abnormal peristalsis was found in 38% of the cohort, displaying a range of hypo- or hypercontractile disorders. Achalasia or other obstructive motor disorders were diagnosed in approximately 15% of cases.

It has been recently demonstrated that pH-impedance monitoring might be helpful in the evaluation of EoE patients. Frazzoni et al. demonstrated that higher efficacy of esophago-salivary reflex and more severe mucosal damage in the distal esophagus, assessed by means of PSPW index and MNBI at distal esophagus, are associated with EoE response to PPIs [49].

Esophageal panometry with functional lumen imaging probe (FLIP) measurements in children and adults demonstrated that patients with a history of food impactions have decreased distensibility compared to those without [140]. Impaired esophagogastric junction distensibility is partially reversible after successful treatment with steroids or diet [141]. In the setting of persisting symptoms despite optimal therapy, serial assessment of distensibility and luminal diameter using FLIP could provide an objective out-

come metric that can indicate the need for endoscopic dilatation [142].

STATEMENT 23

There are currently no validated non-invasive or minimally invasive biomarkers that can be used for the management of EoE in clinical practice.

Level of evidence: Very low

Level of recommendation: Strong

Agreement: 100% [D + (0%); D (0%); D - (0%); A- (0%); A (20%); A + (80%)]

5.9. Summary of evidence

EoE is characterized by a chronic inflammation mediated by innate and adaptive immune cells that produce inflammatory and pro-fibrotic mediators locally in the esophagus, including eosinophil- and mast cells (MC)-derived mediators such as major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil derived neurotoxin (EDN), eosinophil cationic protein (ECP) [143], mast cell tryptase (MCT), periostin (POSTN), and TGF- β [3,144]. These biomarkers have shown to be promising for the non-invasive and minimally-invasive diagnosis and management of EoE [145].

Data sharing statement

No additional data available.

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Declaration of competing interest

Nicola de Bortoli: Advisory board member for: AlfaSigma, Sanofi Genzyme, Dr Falk; Lecture grants from Reckitt-Benckiser, Malesci, Dr. Flak, Sofar, Alfa-Sigma, Pharma-Line.

Pierfrancesco Visaggi: Has served as speaker for Dr Falk, JB Pharmaceuticals, Malesci.

Roberto Penagini: Has served as speaker for Dr Falk, Sanofi.

Edda Battaglia: has served as consultant for NZP, GUNA

Gaia Pellegatta has served as speaker for Dr Falk, Sanofi Genzyme, Malesci.

Paola Iovino: Has served as consultant for Dr Falk

Giovanni Marasco: Served as an advisory board member for AlfaSigma, EG Pharma, Monteresearch srl, Recordati, Cineca. Received lecture grants from Agave, AlfaSigma, Bromatech, Clorofilla, Echo-sens, Ferring, Mayoly Spindler, Menarini and Schwabe Pharma.

Salvatore Oliva: Has served as speaker for Sanofi, Medtronic; Has served as consultant for: Sanofi, Medtronic, Bristol; Has received research support from Alfa Sigma, Medtronic.

Francesca Racca: has served as speaker for Sanofi; has served as consultant for Dr Falk, Sanofi, GSK

Erminia Ridolo: has served as consultant for Dr Falk

Edoardo Vincenzo Savarino: has served as speaker for Abbvie, Agave, AGPharma, Alfasigma, Aurora Pharma, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Fresenius Kabi, Galapagos, Janssen, JB Pharmaceuticals, Innovamedica/Adacyte, Malesci, Mayoly Biohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr. Falk, Fenix Pharma, Fresenius Kabi, Janssen, JB Pharmaceuticals, Merck & Co, Nestlè, Reckitt Benckiser, Regeneron, Sanofi, SILA, Sofar, Synformulas GmbH, Tssakeda, Unifarco; he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco, Zeta Farmaceutici.

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Supplementary materials

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References

- [1] de Bortoli N, et al. Eosinophilic esophagitis: update in diagnosis and management. position paper by the Italian society of gastroenterology and gastrointestinal endoscopy (SIGE). *Dig. Liver. Dis.* 2017;49(3):254–60.
- [2] Visaggi P, et al. Eosinophilic esophagitis: clinical, endoscopic, histologic and therapeutic differences and similarities between children and adults. *Therap. Adv. Gastroenterol.* 2021;14:1756284820980860.
- [3] Sciumè GD, et al. Eosinophilic esophagitis: novel concepts regarding pathogenesis and clinical manifestations. *Minerva Gastroenterol.* 2022;68(1):23–39 (Torino).
- [4] Attwood SE, et al. Esophageal eosinophilia with dysphagia. A distinct clinico-pathologic syndrome. *Dig. Dis. Sci.* 1993;38(1):109–16.
- [5] Straumann A, et al. [Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings]. *Schweiz. Med. Wochenschr.* 1994;124(33):1419–29.
- [6] Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. *Gastroenterology* 2018;154(2):319–32 e3.
- [7] Visaggi P, et al. Treatment trends for eosinophilic esophagitis and the other eosinophilic gastrointestinal diseases: systematic review of clinical trials. *Dig. Liver. Dis.* 2022.
- [8] Visaggi P, et al. Comparison of drugs for active eosinophilic oesophagitis: systematic review and network meta-analysis. *Gut* 2023.
- [9] Furuta GT, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133(4):1342–63.
- [10] Liacouras CA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J. Allergy Clin. Immunol.* 2011;128(1):3–20 e6; quiz 21–2.
- [11] Molina-Infante J, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut* 2016;65(3):524–31.
- [12] Lucendo AJ, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United. European. Gastroenterol. J.* 2017;5(3):335–58.
- [13] Dellon ES, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. *Gastroenterology* 2018;155(4):1022–33 e10.
- [14] Simon D, et al. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy* 2016;71(5):611–20.
- [15] Roman S, et al. Eosinophilic oesophagitis: from physiopathology to treatment. *Dig. Liver Dis.* 2013;45(11):871–8.
- [16] Lin SK, Sabharwal G, Ghaffari G. A review of the evidence linking eosinophilic esophagitis and food allergy. *Allergy Asthma Proc.* 2015;36(1):26–33.
- [17] Clayton F, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology* 2014;147(3):602–9.
- [18] Visaggi P, et al. Six-food elimination diet is less effective during pollen season in adults with eosinophilic esophagitis sensitized to pollens. *Am. J. Gastroenterol.* 2023.
- [19] Molina-Infante J, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2–4–6 study. *J. Allergy Clin. Immunol.* 2018;141(4):1365–72.
- [20] Arias A, et al. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology* 2014;146(7):1639–48.
- [21] Alexander ES, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 2014;134(5):1084–92 e1.
- [22] Blanchard C, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J. Clin. Invest.* 2006;116(2):536–47.
- [23] Lampinen M, et al. Cytokine-regulated accumulation of eosinophils in inflammatory disease. *Allergy* 2004;59(8):793–805.
- [24] Blanchard C, et al. Coordinate interaction between IL-13 and epithelial differentiation cluster genes in eosinophilic esophagitis. *J. Immunol.* 2010;184(7):4033–41.
- [25] Sherrill JD, Rothenberg ME. Genetic dissection of eosinophilic esophagitis provides insight into disease pathogenesis and treatment strategies. *J. Allergy Clin. Immunol.* 2011;128(1):23–34.
- [26] Rothenberg ME, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat. Genet.* 2010;42(4):289–91.
- [27] Litosh VA, et al. Calpain-14 and its association with eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 2017;139(6):1762–71 e7.
- [28] Dhar A, et al. British society of gastroenterology (BSG) and british society of paediatric gastroenterology, hepatology and nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults. *Gut* 2022;71(8):1459–87.
- [29] Pasha SF, et al. The role of endoscopy in the evaluation and management of dysphagia. *Gastrointest. Endosc.* 2014;79(2):191–201.
- [30] Dellon ES, et al. The increasing incidence and prevalence of eosinophilic oesophagitis outpaces changes in endoscopic and biopsy practice: national population-based estimates from Denmark. *Aliment. Pharmacol. Ther.* 2015;41(7):662–70.
- [31] Girien B, et al. Escalating incidence of eosinophilic esophagitis in Canton of Vaud, Switzerland, 1993–2013: a population-based study. *Allergy* 2015;70(12):1633–9.
- [32] Prasad GA, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted county, Minnesota. *Clin. Gastroenterol. Hepatol.* 2009;7(10):1055–61.
- [33] Arias A, Lucendo AJ. Epidemiology and risk factors for eosinophilic esophagitis: lessons for clinicians. *Expert. Rev. Gastroenterol. Hepatol.* 2020;14(11):1069–82.

- [34] Kinoshita Y, et al. Systematic review: eosinophilic esophagitis in Asian countries. *World J. Gastroenterol.* 2015;21(27):8433–40.
- [35] Torres J, et al. Crohn's disease. *Lancet* 2017;389(10080):1741–55.
- [36] Ungaro R, et al. Ulcerative colitis. *Lancet* 2017;389(10080):1756–70.
- [37] Arias A, et al. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. *Aliment. Pharmacol. Ther.* 2016;43(1):3–15.
- [38] Kapel RC, et al. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. *Gastroenterology* 2008;134(5):1316–21.
- [39] Savarino E, et al. Clinical, endoscopic, histological and radiological characteristics of Italian patients with eosinophilic oesophagitis. *Dig. Liver Dis.* 2015;47(12):1033–8.
- [40] Dellon ES, et al. Prevalence of eosinophilic esophagitis in the United States. *Clin. Gastroenterol. Hepatol.* 2014;12(4):589–96 e1.
- [41] Molina-Infante J, et al. *Helicobacter pylori* infection does not protect against eosinophilic esophagitis: results from a large multicenter case-control study. *Off. J. Am. Coll. Gastroenterol. ACG* 2018;113(7).
- [42] Hruz P, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. *J. Allergy Clin. Immunol.* 2011;128(6):1349–50 e5.
- [43] Sherrill JD, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. *J. Allergy Clin. Immunol.* 2010;126(1):160–5 e3.
- [44] Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am. J. Gastroenterol.* 2007;102(6):1301–6.
- [45] Siboni S, et al. Improving the diagnostic yield of high-resolution esophageal manometry for GERD: the "straight leg-raise" international study. *Clin. Gastroenterol. Hepatol.* 2022.
- [46] de Bortoli N, et al. Bile reflux in patients with NERD is associated with more severe heartburn and lower values of mean nocturnal baseline impedance and chemical clearance. *Neurogastroenterol. Motil.* 2020;32(12):e13919.
- [47] van Rhijn BD, et al. Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* 2014;12(11):1815–23 e2.
- [48] Frazzoni M, et al. Role of reflux in the pathogenesis of eosinophilic esophagitis: comprehensive appraisal with off- and on PPI impedance-pH monitoring. *Am. J. Gastroenterol.* 2019;114(10).
- [49] Frazzoni M, et al. Response of eosinophilic oesophagitis to proton pump inhibitors is associated with impedance-pH parameters implying anti-reflux mechanism of action. *Aliment. Pharmacol. Ther.* 2021;53(11):1183–9.
- [50] Müller S, et al. Analysis of symptoms and endoscopic findings in 117 patients with histological diagnoses of eosinophilic esophagitis. *Endoscopy* 2007;39(4):339–44.
- [51] Ricker J, et al. Routine screening for eosinophilic esophagitis in patients presenting with dysphagia. *Therap. Adv. Gastroenterol.* 2011;4(1):27–35.
- [52] Hiremath GS, et al. Esophageal food impaction and eosinophilic esophagitis: a retrospective study, systematic review, and meta-analysis. *Dig. Dis. Sci.* 2015;60(11):3181–93.
- [53] Sperry SL, et al. Esophageal foreign-body impactions: epidemiology, time trends, and the impact of the increasing prevalence of eosinophilic esophagitis. *Gastrointest. Endosc.* 2011;74(5):985–91.
- [54] Desai TK, et al. Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest. Endosc.* 2005;61(7):795–801.
- [55] Jackson WE, et al. Boerhaave's syndrome as an initial presentation of eosinophilic esophagitis: a case series. *Ann. Gastroenterol.* 2013;26(2):166–9.
- [56] Salem SB, et al. The potential impact of contemporary developments in the management of patients with gastroesophageal reflux disease undergoing an initial gastroscopy. *Can. J. Gastroenterol.* 2009;23(2):99–104.
- [57] Achem SR, et al. Oesophageal eosinophilic infiltration in patients with non-cardiac chest pain. *Aliment. Pharmacol. Ther.* 2011;33(11):1194–201.
- [58] Marasco G, et al. Current and novel therapies for eosinophilic gastrointestinal diseases. *Int. J. Mol. Sci.* 2023;24(20).
- [59] de Rooij WE, et al. Utility of gastric and duodenal biopsy sampling in adult eosinophilic esophagitis patients to rule out other gastrointestinal disorders. *Scand. J. Gastroenterol.* 2021;56(5):613–20.
- [60] Taft TH, et al. Esophageal hypervigilance and symptom-specific anxiety in patients with eosinophilic esophagitis. *Gastroenterology* 2021;161(4):1133–44.
- [61] Taft TH, Guadagnoli L, Edlynn E. Anxiety and depression in eosinophilic esophagitis: a scoping review and recommendations for future research. *J. Asthma Allergy* 2019;12:389–99.
- [62] Hewett R, et al. Effects of eosinophilic oesophagitis on quality of life in an adult UK population: a case control study. *Dis. Esophagus.* 2017;30(1):1–7.
- [63] Klinnert MD, et al. Symptom burden and quality of life over time in pediatric eosinophilic esophagitis. *J. Pediatr. Gastroenterol. Nutr.* 2019;69(6):682–9.
- [64] Capucilli P, Hill DA. Allergic comorbidity in eosinophilic esophagitis: mechanistic relevance and clinical implications. *Clin. Rev. Allergy Immunol.* 2019;57(1):111–27.
- [65] Mohammad AA, et al. Prevalence of atopic comorbidities in eosinophilic esophagitis: a case-control study of 449 patients. *J. Am. Acad. Dermatol.* 2017;76(3):559–60.
- [66] González-Cervera J, et al. Association between atopic manifestations and eosinophilic esophagitis: a systematic review and meta-analysis. *Ann. Allergy Asthma Immunol.* 2017;118(5):582–90 e2.
- [67] Hill DA, et al. Eosinophilic esophagitis is a late manifestation of the allergic march. *J. Allergy Clin. Immunol. Pract.* 2018;6(5):1528–33.
- [68] Reed CC, et al. Seasonal exacerbation of eosinophilic esophagitis histologic activity in adults and children implicates role of aeroallergens. *Ann. Allergy Asthma Immunol.* 2019;122(3):296–301.
- [69] Sleiman PM, et al. GWAS identifies four novel eosinophilic esophagitis loci. *Nat. Commun.* 2014;5:5593.
- [70] Hommeida S, et al. The association between celiac disease and eosinophilic esophagitis: mayo experience and meta-analysis of the literature. *J. Pediatr. Gastroenterol. Nutr.* 2017;65(1):58–63.
- [71] Xue Z, et al. Association of eosinophilic esophagitis with autoimmune and connective tissue disorders, and the impact on treatment response. *Dis. Esophagus.* 2022;36(1).
- [72] Peterson K, et al. Risk of autoimmunity in EoE and families: a population-based cohort study. *Am. J. Gastroenterol.* 2016;111(7):926–32.
- [73] Capucilli P, et al. Comparison of comorbid diagnoses in children with and without eosinophilic esophagitis in a large population. *Ann. Allergy Asthma Immunol.* 2018;121(6):711–16.
- [74] Leigh LY, Spergel JM. An in-depth characterization of a large cohort of adult patients with eosinophilic esophagitis. *Ann. Allergy Asthma Immunol.* 2019;122(1):65–72 e1.
- [75] Lucendo AJ, et al. Transcultural adaptation and validation of the "adult eosinophilic esophagitis quality of life questionnaire" into Spanish. *Rev. Esp. Enferm. Dig.* 2014;106(6):386–94.
- [76] Chehade M, et al. Phenotypic characterization of eosinophilic esophagitis in a large multicenter patient population from the consortium for food allergy research. *J. Allergy Clin. Immunol. Pract.* 2018;6(5):1534–44 e5.
- [77] Röjler L, et al. Individuals with eosinophilic esophagitis are at greater risk of later psychiatric disorder. *Am. J. Gastroenterol.* 2022;117(7):1046–55.
- [78] Straumann A, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003;125(6):1660–9.
- [79] Singla MB, et al. Early Comparison of inflammatory vs. fibrostenotic phenotype in eosinophilic esophagitis in a multicenter longitudinal study. *Clin. Transl. Gastroenterol.* 2015;6(12):e132.
- [80] Dellon ES, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest. Endosc.* 2014;79(4):577–85 e4.
- [81] Laserna-Mendieta EJ, et al. Differences between childhood- and adulthood-onset eosinophilic esophagitis: an analysis from the EoE connect registry. *Dig. Liver Dis.* 2023;55(3):350–9.
- [82] Schoepfer AM, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 2013;145(6):1230–6 e1–2.
- [83] Lenti MV, et al. Diagnostic delay and misdiagnosis in eosinophilic oesophagitis. *Dig. Liver Dis.* 2021.
- [84] Navarro P, et al. Accurate and timely diagnosis of Eosinophilic Esophagitis improves over time in Europe. An analysis of the EoE connect registry. *United. European. Gastroenterol. J.* 2022;10(5):507–17.
- [85] Lucendo A, Frigal-Ruiz A, Rodriguez B. Boerhaave's syndrome as the primary manifestation of adult eosinophilic esophagitis. Two case reports and a review of the literature. *Dis. Esophagus* 2011;24:E11–15 official journal of the International Society for Diseases of the Esophagus /I.S.D.E.
- [86] Warners MJ, et al. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. *Am. J. Gastroenterol.* 2018;113(6):836–44.
- [87] Visaggi P, et al. Modern diagnosis of early esophageal cancer: from blood biomarkers to advanced endoscopy and artificial intelligence. *Cancers* 2021;13(13) (Basel).
- [88] Visaggi P, et al. Systematic review with meta-analysis: artificial intelligence in the diagnosis of oesophageal diseases. *Aliment. Pharmacol. Ther.* 2022;55(5):528–40.
- [89] Saboorian MH, et al. Inverse association of esophageal eosinophilia and Barrett esophagus. *J. Clin. Gastroenterol.* 2012;46(9):752–7.
- [90] Takashima S, et al. Barrett's esophagus is negatively associated with eosinophilic esophagitis in Japanese subjects. *Esophagus.* 2019;16(2):168–73.
- [91] Lipka S, et al. The natural history of steroid-naïve eosinophilic esophagitis in adults treated with endoscopic dilation and proton pump inhibitor therapy over a mean duration of nearly 14 years. *Gastrointest. Endosc.* 2014;80(4):592–8.
- [92] Syed A, Maradey-Romero C, Fass R. The relationship between eosinophilic esophagitis and esophageal cancer. *Dis. Esophagus.* 2017;30(7):1–5.
- [93] Furuta GT, Katzka DA. Eosinophilic Esophagitis. *N. Engl. J. Med.* 2015;373(17):1640–8.
- [94] Dellon ES, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. *Am. J. Gastroenterol.* 2013;108(12):1854–60.
- [95] Moawad FJ, et al. Eosinophilic esophagitis and proton pump inhibitor-responsive oesophageal eosinophilia have similar clinical, endoscopic and histological findings. *Aliment. Pharmacol. Ther.* 2014;39(6):603–8.
- [96] Visaggi P, et al. Efficacy of Second PPI Course Following Steroid-Induced Remission in Eosinophilic Esophagitis Refractory to Initial PPI Therapy. *Am. J. Gastroenterol.* 2022.
- [97] Visaggi P, et al. Artificial intelligence tools for the diagnosis of eosinophilic esophagitis in adults reporting dysphagia: development, external validation,

- and software creation for point-of-care use. *J. Allergy Clin. Immunol. Pract.* 2023.
- [98] Laserna-Mendieta EJ, et al. Efficacy of proton pump inhibitor therapy for eosinophilic oesophagitis in 630 patients: results from the EoE connect registry. *Aliment. Pharmacol. Ther.* 2020;52(5):798–807.
- [99] Odias E, et al. New eosinophilic esophagitis concepts call for change in proton pump inhibitor management before diagnostic endoscopy. *Gastroenterology* 2018;154(5):1217–21 e3.
- [100] Pimentel AM, Rocha R, Santana GO. Crohn's disease of esophagus, stomach and duodenum. *World J. Gastrointest. Pharmacol. Ther.* 2019;10(2):35–49.
- [101] Ghisa M, et al. Achalasia and obstructive motor disorders are not uncommon in patients with eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* 2020.
- [102] Visaggi P, et al. Systematic Review: esophageal motility patterns in patients with eosinophilic esophagitis. *Dig. Liver Dis.* 2022.
- [103] Mastracci L, et al. Non gastro-esophageal reflux disease related esophagitis: an overview with a histologic diagnostic approach. *Pathologica* 2020;112(3):128–37.
- [104] Abonia JP, et al. High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. *J. Allergy Clin. Immunol.* 2013;132(2):378–86.
- [105] Hirano I, et al. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut* 2013;62(4):489–95.
- [106] Dellon ES, et al. Accuracy of the eosinophilic esophagitis endoscopic reference score in diagnosis and determining response to treatment. *Clin. Gastroenterol. Hepatol.* 2016;14(1):31–9 the official clinical practice journal of the American Gastroenterological Association.
- [107] van Rhijn BD, et al. Evaluating the endoscopic reference score for eosinophilic esophagitis: moderate to substantial intra- and interobserver reliability. *Endoscopy* 2014;46(12):1049–55.
- [108] Navarro P, et al. Proton pump inhibitor therapy reverses endoscopic features of fibrosis in eosinophilic esophagitis. *Dig. Liver Dis.* 2021.
- [109] Cotton CC, et al. Determination of a treatment response threshold for the eosinophilic esophagitis endoscopic reference score. *Endoscopy* 2022;54(7):635–43.
- [110] Wechsler JB, et al. Eosinophilic esophagitis reference score accurately identifies disease activity and treatment effects in children. *Clin. Gastroenterol. Hepatol.* 2018;16(7):1056–63.
- [111] van Rhijn BD, et al. The Endoscopic Reference Score shows modest accuracy to predict histologic remission in adult patients with eosinophilic esophagitis. *Neurogastroenterol. Motil.* 2016;28(11):1714–22 the official journal of the European Gastrointestinal Motility Society.
- [112] Ma C, et al. Reliability and responsiveness of endoscopic disease activity assessment in eosinophilic esophagitis. *Gastrointest. Endosc.* 2022;95(6):1126–37 e2.
- [113] Kim H, et al. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. *Clin. Gastroenterol. Hepatol.* 2012;10:988–96 the official clinical practice journal of the American Gastroenterological Association.
- [114] Gentile N, et al. Oesophageal narrowing is common and frequently under-appreciated at endoscopy in patients with oesophageal eosinophilia. *Aliment. Pharmacol. Ther.* 2014;40(11–12):1333–40.
- [115] Liacouras CA, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin. Gastroenterol. Hepatol.* 2005;3(12):1198–206.
- [116] Savarino E, Zentilin P, Savarino V. NERD: an umbrella term including heterogeneous subpopulations. *Nat. Rev. Gastroenterol. Hepatol.* 2013;10(6):371–80.
- [117] Pouw RE, et al. Endoscopic tissue sampling - Part 1: upper gastrointestinal and hepatopancreatobiliary tracts. European society of gastrointestinal endoscopy (ESGE) guideline. *Endoscopy* 2021;53(11):1174–88.
- [118] Gonsalves N, et al. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest. Endosc.* 2006;64(3):313–19.
- [119] Nielsen JA, et al. The optimal number of biopsy fragments to establish a morphologic diagnosis of eosinophilic esophagitis. *Am. J. Gastroenterol.* 2014;109(4):515–20.
- [120] Salek J, et al. Endoscopic appearance and location dictate diagnostic yield of biopsies in eosinophilic oesophagitis. *Aliment. Pharmacol. Ther.* 2015;41(12):1288–95.
- [121] Radicic K, Stokes RF. Analysis of midesophageal biopsies increases sensitivity of detection of eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* 2019;17(7):1408–9.
- [122] Kaur S, et al. Utility of gastric and duodenal biopsies during follow-up endoscopy in children with eosinophilic esophagitis. *J. Pediatr. Gastroenterol. Nutr.* 2017;65(4):399–403.
- [123] Villalta D, Baragiotta AM. Eosinophilic esophagitis: from the case report to the evidence. *Eur. Ann. Allergy Clin. Immunol.* 2008;40(2):53–60.
- [124] Dellon ES, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am. J. Gastroenterol.* 2013;108(5):679–92 quiz 693.
- [125] Dellon ES, et al. Distribution and variability of esophageal eosinophilia in patients undergoing upper endoscopy. *Modern Pathol.* 2015;28(3):383–90.
- [126] Collins MH, et al. Eosinophilic esophagitis histology remission score: significant relations to measures of disease activity and symptoms. *J. Pediatr. Gastroenterol. Nutr.* 2020;70(5):598–603.
- [127] Collins MH, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. *Dis. Esophagus* 2016;30(3):1–8.
- [128] Bussmann C, et al. Comparison of different biopsy forceps models for tissue sampling in eosinophilic esophagitis. *Endoscopy* 2016;48(12):1069–75.
- [129] Kagalwalla AF, et al. Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodeling and reverses with treatment. *J. Allergy Clin. Immunol.* 2012;129(5):1387–96 e7.
- [130] Aceves SS, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy* 2010;65(1):109–16.
- [131] Lieberman JA, et al. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. *Allergy* 2012;67(10):1299–307.
- [132] Aceves SS, et al. Endoscopic approach to eosinophilic esophagitis: American society for gastrointestinal endoscopy consensus conference. *Gastrointest. Endosc.* 2022;96(4):576–92 e1.
- [133] Menard-Katcher C, et al. Contribution of esophagram to the evaluation of complicated pediatric eosinophilic esophagitis. *J. Pediatr. Gastroenterol. Nutr.* 2015;61(5):541–6.
- [134] Al-Hussaini A, AboZeid A, Hai A. How does esophagus look on barium esophagram in pediatric eosinophilic esophagitis? *Abdom. Radiol.* 2016;41(8):1466–73 (NY).
- [135] Visaggi P, et al. Esophageal dysmotility in patients with eosinophilic esophagitis: pathogenesis, assessment tools, manometric characteristics, and clinical implications. *Esophagus* 2022.
- [136] Yadlapati R, et al. Esophageal motility disorders on high-resolution manometry: chicago classification version 4.0©. *Neurogastroenterol. Motil.* 2021;33(1):e14058.
- [137] Visaggi P, et al. Chicago classification v4.0 protocol improves specificity and accuracy of diagnosis of oesophagogastric junction outflow obstruction. *Aliment. Pharmacol. Ther.* 2022.
- [138] Savarino E, et al. Achalasia with dense eosinophilic infiltrate responds to steroid therapy. *Clin. Gastroenterol. Hepatol.* 2011;9(12):1104–6.
- [139] Savarino EV, et al. The GerdQ questionnaire and high resolution manometry support the hypothesis that proton pump inhibitor-responsive oesophageal eosinophilia is a GERD-related phenomenon. *Aliment. Pharmacol. Ther.* 2016;44(5):522–30.
- [140] Nicodème F, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* 2013;11(9):1101–7 e1.
- [141] Carlson DA, et al. Improvement in esophageal distensibility in response to medical and diet therapy in eosinophilic esophagitis. *Clin. Transl. Gastroenterol.* 2017;8(10):e119–e119.
- [142] Savarino E, et al. Use of the functional lumen imaging probe in clinical esophagology. *Off. j. Am. Coll. Gastroenterol.* 2020;115(11) ACG.
- [143] Davis BP, Rothenberg ME. Mechanisms of disease of eosinophilic esophagitis. *Annu. Rev. Pathol. Mech. Dis.* 2016;11(1):365–93.
- [144] Vicario M, et al. Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. *Gut* 2010;59(01):12.
- [145] Visaggi P, et al. Non-invasive and minimally invasive biomarkers for the management of eosinophilic esophagitis beyond peak eosinophil counts: filling the gap in clinical practice. *Diagnostics* 2023;13(17) (Basel).