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REVIEW ARTICLE

Eosinophilic Esophagitis in Children: Clinical Findings and Diagnostic Approach

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Abstract: Eosinophilic esophagitis (EoE) is an emerging chronic immune and antigen-mediated clinicopathologic disease. During the last 2 decades, the incidence of this condition in children has increased significantly, thanks to practitioners for creating the awareness and higher use of diagnostic endoscopy. We have analysed paediatric literature on EoE focusing on the epidemiology, pathophysiology, clinical findings and diagnostic approach.

EoE is pathogenically related to a Th2 inflammation characterized by a mixed IgE and non-IgE-mediated reaction to food and/or environmental agents. This leads to esophageal dysfunction and remodeling accompanied by subepithelial fibrosis. EoE can be presented with several range of gastrointestinal symptoms, including regurgitation, vomiting, feeding difficulties or feeding refusal in infants and toddlers, as well as heartburn, dysphagia and food bolus impaction in older children and adults. The diagnostic suspicion is based on the presence of chronic symptoms of esophgeal dysfunction and esophageal eosinophilia characterised histologically by a significant eosinophilic infiltration of the oesophageal mucosa (>15 eosinophils per high powered field). In this review, we will provide an update on clinical presentation and diagnostic approach to EoE in children. We emphasized on the relevant aspects of the new clinical condition termed *"PPI responsive esophageal eosinophilia"*, as entities distinct from EoE and the role of PPI trial in the diagnostic workup, therefore we proposed a new diagnostic algorithm.

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1. INTRODUCTION

Eosinophilic esophagitis (EoE) is an emerging chronic immune and antigen-mediated clinicopathologic disease, affecting both children and adults. This condition is characterized by severe eosinophil-predominant inflammation into the esophageal epithelium resulting in esophageal disfunction. EoE was first described as a disease entity in 1995 by Kelly et al. [1]. Over the last decade, EoE has become increasingly recognized with an incidence considered to be similar to that of Chron's disease [2]. In 2007, a multidisciplinary group of experts published the first consensus guidelines on the diagnosis and treatment of EoE [3], which was updated in 2011 [4]and recently revised in 2017 [5].

Here, we will revise new insights on clinical presentation and diagnostic approaches to EoE in children. Specifically the increasing incidence, the new clinical conditions (such as PPI responsive esophageal eosinophilia) and the revaluation of the role of PPI in the diagnostic workup, will be addressed.

2. EPIDEMIOLOGY

In recent years, the incidence and prevalence of eosinophilic esophagitis (EoE) in children and adults, have increased significantly [6]. A recent systematic review showed that population-based prevalence of EoE in children is 19.1 cases per 100.000 children/year [7], with a wide geographic variation from 2.3 in Denmark [8] to 50.5 per 100.000 children in the United States [9]. Likewise, the population-based incidence varies among the Westernised countries, with over-all incidence rate estimates of 5.1 per 100.000 children/year [7]. Possible biases of these variations may depend

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on the studied population, study design and diagnostic criteria for EoE. Population-based data on the epidemiology of EoE in developing countries are scarce. There is a predominance of EoE among male patients [7, 9-11] with a male to female ratio of 3:1 in both children and adults [4]. The increasing of incidence and prevalence, during the last few decades, may be explained with improved recognition of EoE, more awareness of practitioners and higher use of diagnostic esophagogastroduodenoscopy (EGDS) with biopsies in children. Data showing that increasing incidence closely matches the increase in endoscopy volume and biopsies rates supported this hypothesis [12, 13]. Further factors may affect the increasing frequency of EoE such as a change in food allergens, increasing aeroallergens and other environmental factors, the decrease of H. pylori and microbiome changes [10].

3. PATHOPHYSIOLOGY

In the last years, there has been a rapid advancement in understanding the mechanisms involved in EoE generally attributed to an interplay between genetic, immunologic and environmental factors [14]. EoE is now considered as a chronic atopic disorder, histologically characterized by a dense epithelial eosinophilic infiltrate. Pathogenically related to a Th2 inflammation characterized by a mixed IgE and non-IgE-mediated reaction to food and/or environmental agents, which is driven [15, 16] by Thymic Stromal Lymphopoietin (TLSP) secreted by esophageal epithelial cells under the influence of genetic predisposition [17].

The role of TSLP as a strong inducer of a Th2 response is well-known and it has been linked to atopic diseases [18, 19]. TLSP is similar to IL-7 and regulates host adaptive immune responses through dendritic cells and T-cell interactions. Rothenberg et al. found an association between a single nuclear polymorphism (SNP) in the gene encoding TSLP and the risk for EoE [17]. In addition, Sherill et al. identified a significant association between an SNP located in the TSLP receptor and male EoE patients [20]. Another identified risk factor linked to EoE is a polymorphism in eotaxin-3 that is a chemokine and a potent eosinophil and mast cell chemoattractant [21]. The most recently described is an SNP located in the proximity of CAPN 14, a gene specifically expressed in esophagus and upregulated by Th2 cytokines [22]. However, a recent study, focusing on the risk of developing EoE in monozygotic and dizygotic twins, suggests a minor genetic contribution in favor of more relevant environment factors [23].

Environmental exposures such as birth by cesarean section, premature delivery, antibiotic exposure during infancy, food allergy, lack of breastfeeding, lack of early exposure to microbes and altered microbiome can create an epigenetic signature that may increase the risk for EoE onset [24-26].

In most patients, food has been identified as a trigger of EoE inflammation with non-IgE-mediated mechanism [27, 28] and his role is supported by the response to dietary elimination of food antigens and relapse with the reintroduction of similar food antigens [29, 30]. However, the role of aeroallergens still remains unclear.

Most studies have shown that EoE inflammation has the typical characteristics of Th2 atopic inflammation. Esophageal biopsies and blood samples of patients with active EoE, have high levels of Th2 prototypical cytokines and chemokines such as interleukin IL-5, IL-4, IL-13, IL-5, TSLP, eotaxin-3 secreted by the typical cells involved in allergic inflammation: mast cells, T cells, basophils, invariant natural killer T cells (iNKTs) [4, 31-33].

Eosinophils are pathognomonic of EoE inflammation in the absence of GERD and although they represent the histologic mark of the disease [4], do not guarantee the EoE pathogenesis being most likely a consequence of the local Th2 inflammation. Recent clinical trials with antibodies against IL-5, which is the most important eosinophils growth factor, have shown a partial reduction of esophageal inflammation, and minimal symptomatic relief in patients with EoE [34, 35].

Finally, the esophageal epithelium plays a major role in EoE by promoting a local Th2 inflammation. As for atopic dermatitis, EoE patients have an altered epithelial barrier function [36], and a down-regulation of proteins associated with barrier function (filaggrin and zonulin-1) [37] and adhesion molecules (desmoglein-1) [4], that favors antigen penetration and sensitization. Altered epithelial permeability can lead to a permissive environment that enhances antigen presentation, which in turn leads to recruitments of eosinophils and pro-inflammatory cytokines [38, 39].

The major long-term consequence of chronic inflammation in EoE is esophageal remodeling followed by the development of irreversible structures. Aceves et al [40] observed basal thickening and increased vascular activation in untreated patients with EoE, associated with high levels of TGF-β 1 that stimulates myofibroblast differentiation and extracellular matrix remodeling [41, 42].

4. CLINICAL FINDINGS

Eosinophilic esophagitis (EoE) can affect individuals at any age and clinical presentation depends on the patient's abilities to report symptoms associated with esophageal dysfunction [43-45]. Symptoms can be present for a long time (mean of 3-5 years) before reaching a diagnosis of EoE, especially if the disease appears progressively [46].

In pediatric population, vomiting, abdominal pain, dysphagia and bolus impaction are the most prevalent symptoms (Table **1**) [43, 44, 47-65].

Clinical features of EoE are also different based on the age of children (Table **2**). In toddlers and infants, the most frequent symptoms are feeding difficulties and failure to thrive (median age 2,8 years); vomiting and sleeping disturbance are also described. In EoE, vomit rarely appears before 6 months of life; it's sporadic and not associated with meals, as in the case of food protein-induced enterocolitis or IgE-mediated food allergy [66]. School-aged children are present with nausea, vomiting, regurgitation and abdominal pain. In a study that included 43 patients with EoE [67], 100% of children under 7 years presented these symptoms. Abdominal pain in this age is mainly epigastric [66].

Table 1. Symptoms and signs of EoE in children.

Study (Number of Patients) [ref.]	Food Impaction	Abdominal Pain	Dysphagia	Chest Pain	Heartburn	Vomiting
Mansoor E. *et al.*, 2016 (1250) [48]	48%	-	29,6%	8,8%	4%	16%
Fahey L. *et al.*, 2017 (36) [49]	13,8%	30,5%	16,6%	-	-	30,5%
Assa'ad *et al.,* 2007 (89) [50]	6,7%	24,7%	15,7%	6,7%	21,3%	59,5%
Gill R *et al*., 2007 (44) [51]	-	55%	-	-	39%	43%
Weiler T *et al.*, 2014 (50) [52]	-	40%	22%	-	-	74%
Kubik *et al*., 2017 (251) [53]	-	57%	43%	-	-	49%
Bohm *et al*., 2017 (58) [54]	3%	53%	33%	2%	19%	24%
Vigier *et al*., 2017 (28) [55]	46%	11%	32%	-	21%	42%
Homan *et al*., 2015 (30) [56]	-	19%	33%	-	-	43%
Prasad GA *et al*., 2009 (23) [44]	21,7%	30,4%	60,9%	-	17,4%	43,5%
Gomez Torrijos *et al*., 2017 (35) [58]	20%	31%	51%	8,5%	6%	20%
Alves Marcelino *et al*., 2018 (25) [57]	52%	-	56%	-	40%	32%
Sun MF *et al*., 2017 (22) [59]	-	41%		-	-	45%
La Orden Izquierdo *et al*., 2018 (254) [60]	22%	-	23,6%	-	-	-
Saeed *et al*., 2018 (37) [61]	21,6%	-	56,7%	-	-	48,6%
Rodrigues *et al*., 2013 (43) [62]	28%	58%	-	-	30%	53,5%
Rezende ER *et al*., 2014 (35) [63]	11,4%	51,4%	28,5%	-	-	71,4%
Kapel *et al*., 2008. (42) [43]	-	31%	26,2%	4,8%	-	-
Hoofien A *et al*., 2018 (410) [64]	24,4%	9%	38%	9,2%	9%	14,3%
Romano C *et al*., 2014 (23) [65]	43%	35%	65%	22%		43%

Table 2. Main symptoms of EoE based on age (revisited by Carr et al. 2019).

Infant/Toddlers	Children	Adolescent/Adults
Failure to thrive	Dysphagia	Dysphagia
Food refusal	Food impaction	Food impactions
Vomiting	Choking/gagging with meals	Food avoidance
Choking with meals	Abdominal/chest pain	Intractable heartburn
Sleep disturbance	Throat pain	Regurgitation
-	Vomiting/regurgitation	Retrosternal pain
-	Nausea	Chest pain
-	Sleep disturbance	-
-	Decrease appetite	-

Mainly in infants, toddlers or young children EoE can be present with GERD like symptoms, such as heartburn, regurgitation and vomit. As demonstrated in some studies [68, 69], there are cases of PPI refractory GERD that underwent fundoplication without clinical improvement, some of these patients receive a post-operative diagnosis of EoE. The misdiagnosis of EoE in GERD like symptoms patients can be related to the lack of routine esophageal biopsies as part of the standard preoperative evaluation before anti-reflux surgery.

In adolescents, the most common symptoms are dysphagia, heartburn, food impaction and chest pain. The prevalence of EoE among EGDS performed in children with esophageal food impaction and/or dysphagia is high (63-88%) [70-72], so children with these presenting symptoms should be rapidly tested with EGDS and multiple esophageal biopsies. A study [43] evidenced an increasing prevalence of EoE in patients with dysphagia; moreover, they were more likely to have higher eosinophils peak mucosal counts. Furthermore, the incidence of EoE in patients having these symptoms is probably underestimated, because biopsies are not always performed.Food impaction is a gastrointestinal emergency, requiring endoscopic intervention to remove the impacted food: considering the close link with EoE biopsies during endoscopic disimpaction are recommended.Food impaction is often associated with acute severe retrosternal or chest pain. When symptoms do not respond to medical treatments for GERD, EoE should be strongly considered [69]. Chest pain, which is spasmodic, can be severe enough to lead patients to seek emergency evaluation and lead to cardiac evaluation [66]. Dysphagia in children is not always related to esophageal anatomical damage, but also it can be related to secondary esophageal dysmotility [43].

It is important to realize that children may develop long-term coping strategies to avoid symptoms, including taking small bites, eating slowly with excessive chewing, and drinking fluids after each bite [66]. The patients may also avoid certain kinds of food due to their not easy swallowing.

Children with EoE have a higher rate of atopy compared with normal children. The rates of asthma, allergic rhinitis and atopic dermatitis are approximately three times higher than the general population [73, 74].

Adolescents with EoE may be misdiagnosed as having eating disorders, because of symptoms of food-related anxiety, vomiting and food aversion.

EoE should be considered also in children with chest pain and cough that does not respond to aggressive asthma treatment [66].

Given the variability of the symptom patterns in EoE patients, the measurement of disease activity based on clinical symptoms remains a challenging task. As several clinical trials showed, there is a poor correlation between histological abnormalities and symptoms [75, 76]. A possible explanation for this discrepancy might be that symptoms can be caused not only by esophageal inflammation but also by fibrotic changes in esophageal motility even in the absence of inflammation, or even by psychological factors [77].

5. DIAGNOSIS

EoE diagnosis is difficult because clinical symptoms are variable and sometimes unspecific and the presence of esophageal eosinophilia can be found in several diseases.

The new diagnostic criteria for EoE are the result of the collaboration between paediatrics, gastroenterologists, allergo-immunlogists and pathologists in order to identify clinical and histological characteristics useful for having a clinical suspicion associated with supports elements to confirm the diagnosis.

Guidelines of 2017 and recent updates on EoE showed that diagnostic suspicion is based on the presence of chronic symptoms of esophageal dysfunction and esophageal eosinophilia [5]. The absence of symptoms even in the presence of esophageal eosinophilia does not allow the diagnosis of EoE [78].

Accurate anamnesis can be useful for making the diagnosis of EoE: in addition to clinical symptoms and esophageal eosinophilia recently, independent predictors of EoE have been identified in order to distinguish it from other diseases, first of all, GERD.

The early age of onset of symptoms is more suggestive of EoE [79]. Up to 75% of patients with EoE have a personal or family history of atopic disease (asthma, eczema, allergic rhinitis or food allergies) [80].

Testing for allergic sensitization may be considered: skin prick test, blood testing for allergen-specific IgE or atopy patch testing are useful for making the diagnosis of allergy but they cannot identify EoE trigger and their positive predicted value remains poor [81].

If the clinical evaluation is suggestive for EoE, EGDS with biopsies examination has to be made. At least six biopsies should be taken from different esophageal segments, focusing on areas with endoscopic mucosal abnormalities [5]: a study demonstrated that six biopsies increase diagnostic sensibility to 99% [82]. Hematoxilin-eosin staining is sufficient for histological assessment. The principal diagnostic element for the diagnosis of EoE is the presence of at least 15 eosinophils per high power field. Although GERD can increase eosinophilic infiltration in the distal esophagus, eosinophils associated with GERD generally occur at a lower density. Additional histological features consistently associated with EoE may include eosinophils microabscesses (32-64,8% - defined as aggregates of four or more eosinophils in a cluster), basal zone hyperplasia (35-86,4% - more severe in patients with EoE than in those with GERD), dilated intercellular spaces, eosinophil surface layering and papillary elongation (75,6%) [3, 51, 58, 61, 83].

Endoscopy in EoE can be macroscopically normal, with a range from 4 to 23% [57, 58 61]. There are also some endoscopic characteristics associated with the diagnosis of EoE in order to support the diagnosis of EoE. In adults, their sensibility range from 50% to 90% while in the pediatric population, it is not known. These findings include: fixed rings(6%) (Fig. **1**), exudates(28,5%), furrows(21,6-80%) (Fig. **2**), oedema(26%)and mucosal alterations (Fig. **3**).The presence of strictures in children is rare and less common than in adults. The alterations can be quantified using the EoE Endoscopic Reference Score (EREFS) [84] (Table **3**).

In the case of esophageal eosinophilia, clinical evaluation and endoscopy allow to distinguish EoE from other diseases (Table **4**). The diagnosis of EoE is confirmed if there are no other conditions that justify clinical symptoms and esophageal eosinophilia.

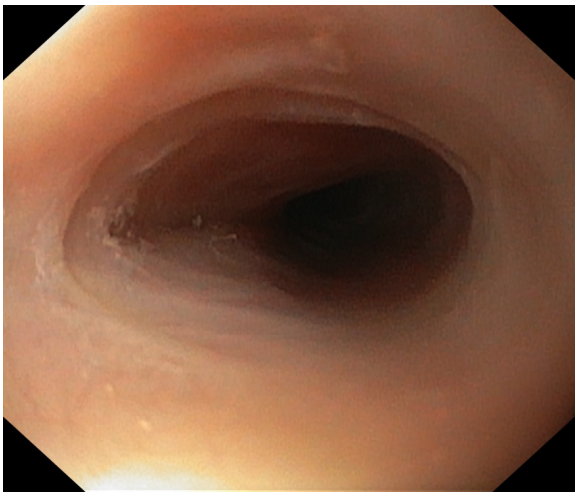

Fig. (1). Fixed rings. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

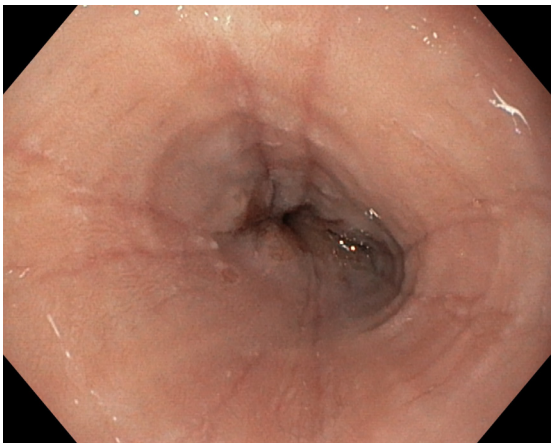

Fig. (2). Furrows. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

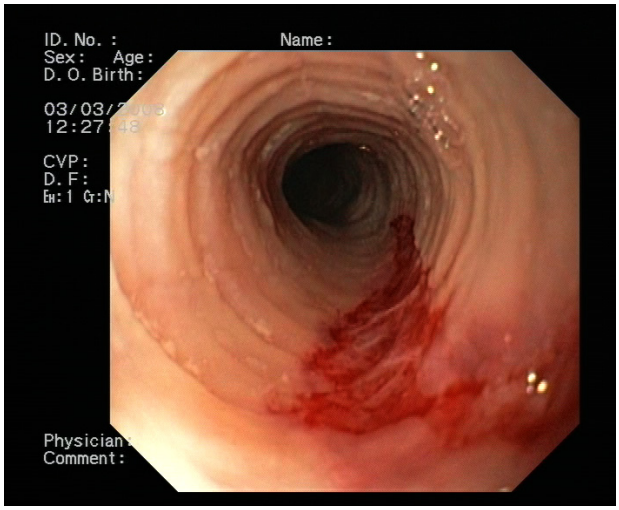

Fig. (3). Mucosal alteration associated with rings. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

GERD is the main disease to consider differential diagnosis with EoE. They often have similar symptoms, and both clinic and endoscopic findings have the low sensibility and specificity [78]: they were felt to be mutually exclusive disorders where a response to PPI/pathologic pH exposure was consistent with GERD and non-reponse/normal pH confirmed EoE [84]. Nowadays, without a definitive method for defining GERD, no single test (including PPI trial) can exclude the presence of GERD.

CONCLUSION

Multiple prospective and retrospective studies found that esophageal eosinophilia (≥ 15 eos/HPF) in patients with symptoms and endoscopic sign suggestive of EoE responded to PPI therapy both in adults and children at a rate of 28-82% [78]. From 2011, diagnostic guidelines defined a new

Table 3. Classification and grading system of endoscopic features of EoE (revisited by Hirano I, 2012).

Findings	Grade 0	Grade 1	Grade 2	Grade 3
Major findings				
Fixed rings (concentric rings, trachealisation)	None	Mild (subtle circumferential ridges)	Moderate (distinct rings that not impair passage of standard diagnostic endoscope)	Severe (distinct rings that do not permit passage of a diagnostic endoscope)
Exudates (plaques)	None	Mild (lesion involving <10% of the esophageal surface area)	Severe (lesion involving >10% of the esophageal surface area)	-
Furrows (vertical lines)	Absent	Present	-	-
Oedema (mucosal pallor)	Absent	Present	-	-
Stricture	Abset	Present	-	-
Minor findings				
Crepe paper esophagus (mucosal fragility or laceration upon passage of diagnostic endoscope)	Absent	Present	-	-

Table 4. Condition associated with esophageal eosinophilia (revisited by Dellon 2018).

• Eosinophilic esophagitis
• Eosinophilic gastritis, gastroenteritis or colitis with esophageal involvement
• GERD
• Achalasia and other disorder ofesophageal dysmotility
• Hyperosinophilic syndrome
• Crohn's disease
• Infections (fungal, viral)
• Connective tissue disorders
• Hypermobility syndromes
• Autoimmune disorders
• Dermatologic condition with esophageal involvement
• Drug hypersensivity reactions
• Pill esophagitis
• GVHD
• Mendelian disorders

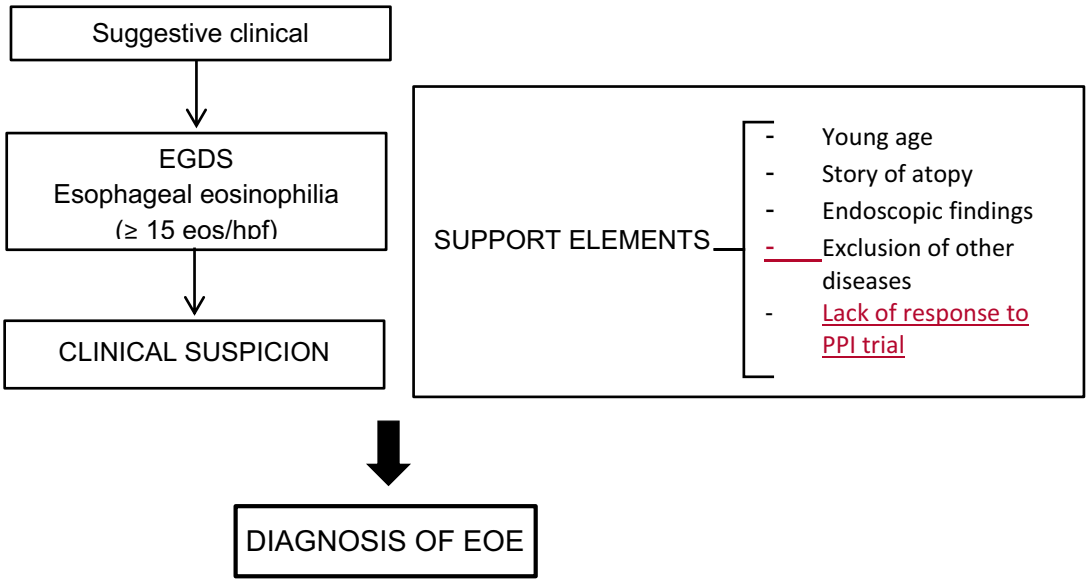

Fig. (4). Diagnostic algorithm for diagnosis of EoE. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

condition termed PPI-responsive esophageal eosinophilia (PPI-REE) [4]. It is a debate if PPI-REE represents a subtype of EoE or GERD, but the latest updates tend to consider it a pattern of EoE. At baseline (prior to a PPI trial) patients with EoE and PPI-REE have similar clinical, endoscopic and histologic features [85, 86], in addition, RNA expression profiles were largely similar between EoE and PPI-REE but distinct from GERD [84]. Finally, patients with PPI-REE can also have a response to dietary elimination or topical steroid therapy.

The complex relationship between GERD and EoE and the identification of PPI-REE questioning the role of PPI trial for diagnosis of EoE, even if PPI trial potentially reduces the number of endoscopies required, helps concomitant GERD and provides a stepwise approach for EoE diagnosis [78]. Most recently, the response of esophageal eosinophilia to PPI has been defined as a treatment option for EoE rather than an exclusion criterion: therefore, we proposed a new diagnostic algorithm (Fig. **4**).

LIST OF ABBREVIATIONS

CAPN14 = Calcium-Activated Neutral Proteinase 14

EGDS = Esophagogastroduodenoscopy

EoE	=	Eosinophilic Esophagitis
EREFS	=	Endoscopic Reference Score
GERD	=	Gastro-Esophageal Reflux Disease
HPF	=	High-Power Field
H. pylori	=	Helicobacter pylori
iNKTs	=	invariant Natural Killer T Cells
PPI	=	Proton Pump Inhibitor
PPI-REE	=	PPI-Responsive Esophageal Eosinophilia
SNP	=	Single Nuclear Polymorphism
TGFβ-1	=	Transforming Growth Factor-β 1
Th2	=	T helper 2
TSLP	=	Thimic Stromal Lymphopoietin

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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