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REVIEW



## The role of endoscopy in eosinophilic esophagitis: from diagnosis to therapy

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### ABSTRACT

**Introduction:** Eosinophilic esophagitis (EoE) has arisen as a common disorder in current clinical and endoscopic gastroenterology practice.

**Areas covered:** A comprehensive review of the literature to summarize and update different aspects related with the use of endoscopy in the diagnostic workout and treatment of pediatric and adult EoE patients is conducted.

**Expert commentary:** Endoscopic features in EoE are frequently subtle, so were inadverted in some initial reports of the disease. Literature has described a wide number of EoE-associated features, systematized in the EREFS classification, which standardized the grade and severity of exudates, rings, edema, furrows, and strictures. The insufficient reliability of these features to predict eosinophilic inflammation still makes biopsies essential in diagnosing or monitoring EoE.

EoE causes half of the food impactions requiring endoscopy; food impaction leads to EoE diagnosis in up to half of cases. Long term consequences of EoE include esophageal remodeling leading to strictures and narrowing, thus impairing symptoms and needs dilation. Recognizing the risks from dilation in EoE required carrying out a safe technique to avoid the high complication rate reported in the early literature. Endoscopic dilation should be considered in patients with esophageal narrowing and dysphagia/food impaction unresponsive to diet or drugs-based anti-inflammatory treatment.

### ARTICLE HISTORY

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### KEYWORDS

Eosinophilic esophagitis; endoscopy; treatment; therapy; dilation; dysphagia; food impaction

## 1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, local immune-mediated, food allergy-associated disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [1]. From its initial description during the early 1990s [2], EoE has emerged in recent years as a rapidly increasing disease, which persists from childhood into adulthood [3], to constitute currently the second leading cause of chronic esophagitis after gastroesophageal reflux disease (GERD) [4] and the most frequent cause of dysphagia in young patients in Westernized countries [5]. The prevalence of EoE in Europe and the USA ranges from 43 to 55 affected patients per 100,000 inhabitants, with an increasing trend developing [6]. Cases of EoE are currently reported throughout the world, including most of Europe [4,7–12], North America [13,14], Brazil [15], Australia [16], Japan [17], China [18], and North of Africa [19,20]. In spite of it, EoE remains underdiagnosed in many settings, because endoscopic findings are usually harder to detect than those observed in other common esophageal conditions. However, a variety of endoscopic features can be identified during endoscopy in EoE patients [21], affecting either the esophageal caliber or the mucosal surface, with a prevalence that substantially varies among available studies [22].

Research efforts aimed at providing efficient therapy for this chronic disease have intensified in the last years. Allergy

to certain components of the diet contributes to the pathogenesis of EoE [23], as demonstrated from the early studies performed on pediatric patients; indeed both symptoms and histology improve after eliminating certain foods from the diet [24–27], as well as after administering anti-inflammatory agents, such as proton pump inhibitors (PPIs) [28,29], and swallowed topic steroids [30,31]. The role played by PPIs in patients with esophageal eosinophilia and symptoms referred to this organ has recently changed: the attempts to distinguish GERD from EoE by response to a trial of PPIs unexpectedly uncovered ‘PPI-responsive esophageal eosinophilia’ (PPI-REE) [32]. Evolving evidence, mostly from adults, shows that patients with EoE and PPI-REE at baseline are clinically, endoscopically, and histologically indistinguishable and have a significant overlap in terms of features of Th2 immune-mediated inflammation and gene expression. PPI therapy also restores esophageal mucosal integrity, reduces Th2 inflammation, and reverses the abnormal gene expression in patients with PPI-REE, similar to the effects of topic steroids in patients with EoE [28]. Therefore, new guidelines on EoE now consider PPI therapy not as a diagnostic test, but as a therapeutic anti-inflammatory agent [1] (Figure 1).

However, because no drugs specifically approved for EoE are currently available, these treatments are usually given off label. The frequent association of EoE with a narrowing of the esophageal lumen has determined the use of mechanical

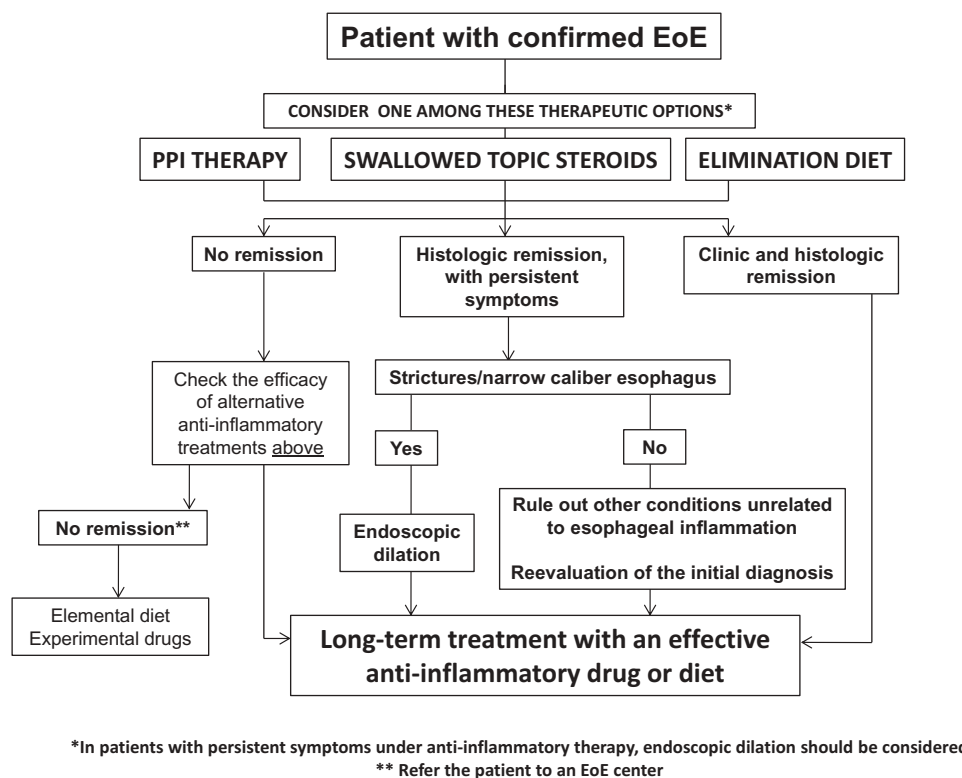


Figure 1. Evidence-based proposed algorithm for short- and long-term management of patients with EoE [1].

dilation as a treatment option for EoE from the earliest documented cases, similarly to its use in other fibrous esophageal strictures. Unfortunately, studies that compare different strategies to manage the disease are lacking [33], and limited information regarding the sustained effect of the different treatment modalities in terms of disease remission, health-related quality of life, and costs for health systems is available.

This article aims to comprehensively review current evidence on the importance and limitations of endoscopic assessment in the diagnostic workout of EoE, the diagnostic accuracy of the several endoscopic finding described in EoE to date, and the central role that endoscopy has in the therapy and follow-up of EoE patients. A literature search was carried out for the period between 2000 and February 2017 in the PubMed, Cochrane, and Scopus libraries using the following individual and combined key words: EoE, endoscopy, therapy, therapeutic interventions, dilation, complications, and risk factors. References cited in the articles obtained were also searched in order to identify other potential sources of information. The results were limited to human studies with no restriction in language.

## 2. Endoscopic features in EoE: from unnoticed to systematically reported

EoE was firstly identified as a distinct esophageal disease only two decades ago [2]. This reflects that endoscopic findings are frequently subtle and unspecific in most of the patients with EoE. In fact, esophageal features were unnoticed in the vast majority of patients reported in several of the seminal papers

that contributed to define the disease [2,24,34], which contrasts with the esophageal appearance of other common esophageal conditions causing dysphagia, which usually show evident endoscopic findings, such as peptic erosions, ulcers, protruding masses, or strictures. Therefore, a successful diagnosis of the disease required (and still does) a high level of suspicion on the part of the clinician and the inexperienced endoscopist, who should perform a careful examination of the esophagus and take esophageal biopsies to achieve a diagnosis of EoE in every patient with unexplained symptoms of esophageal dysfunction, even if the mucosa appears to be normal [1], or whether potential cause of dysphagia other than EoE is identified.

An important diagnostic delay has been described for patients suffering from EoE in multiple settings [35,36]. Many EoE patients underwent previous endoscopies for dysphagia or food impaction and received different diagnoses before achieving the definitive diagnosis [37]. The endoscopic appearance of the esophagus was reported as 'normal' in between one third and one quarter of the patients eventually diagnosed from suffering EoE, as stated by several retrospective studies [38,39]. Despite the endoscopic findings could be subtle enough to be inadvertent in a proportion of cases, remarkable abnormalities can be currently detected in the majority of patients with EoE.

### 2.1. Endoscopic esophageal appearance in EoE patients

A number of esophageal abnormalities have been identified in patients with EoE, with a significantly variable frequency among studies [22]. All of them were reviewed during the

development of a novel classification and grading system and systematized into eight categories [40]: fixed rings (also referred to as trachealization), exudates (described as plaques or white spots on the mucosal surface), furrows (also referred to as vertical lines and longitudinal furrows), edema (also expressed as mucosal pallor), stricture, feline esophagus (also referred to as transient mucosal plications), narrow caliber esophagus (also referred to as small caliber esophagus), and crêpe paper esophagus (also referred to as mucosal fragility). Therefore, all the spectrum of severity and activity of EoE were condensed into five major and one minor features (Table 1; Figure 2). Consequently, the EoE endoscopic reference score EREFS (acronym for exudates, rings, edema, furrows, and strictures) was proposed as a standardized tool to classify and grade the presence and severity of the five major endoscopic features of EoE [40]. This EREFS classification system was validated in adult patients in a prospective multicenter study, with good inter-observer agreement among practicing and academic gastroenterologists [41]. External validation also showed consistency between experts and trainee endoscopists [42], making the EREFS a reliable uniform nomenclature system for the complex endoscopic appearance of EoE that enables the assessment of the evolving changes along a therapy and between different explorers or centers.

Aside from the above, EoE has been associated with an increased frequency of Schatzki rings from its early descriptions, especially in children [43], but also in adults [18,44]. Schatzki rings may not constitute a unique esophageal entity, but the result of a multifactorial etiology [45]. In children, Schatzki ring is a rare diagnosis that can be found in three common situations: hiatus hernia, EoE, and GERD. Because of the relatively high incidence of EoE, it has been proposed that esophageal biopsy should be considered whenever a Schatzki

ring is identified in a child [46]. In addition, endoscopic features associated with EoE and clinical presentation may vary across patients' races and, to a lesser extent, genders. According to a multicenter retrospective study involving 793 patients of all ages with EoE, white people presented dysphagia and food impaction significantly more frequently than African Americans and other races. Esophageal rings and furrows were also more common among white patients. Male patients also had a significantly higher presence of esophageal strictures compared to women [47]. These findings underscore the importance of considering a diagnosis of EoE in African American subjects even in the absence of typical EoE-associated findings.

Finally, it should be noted that each of the endoscopic features described for EoE has been also identified in other esophageal disorders [48], so none can be considered pathognomonic for the disease.

## 2.2. Reliability of endoscopic findings in diagnosing EoE

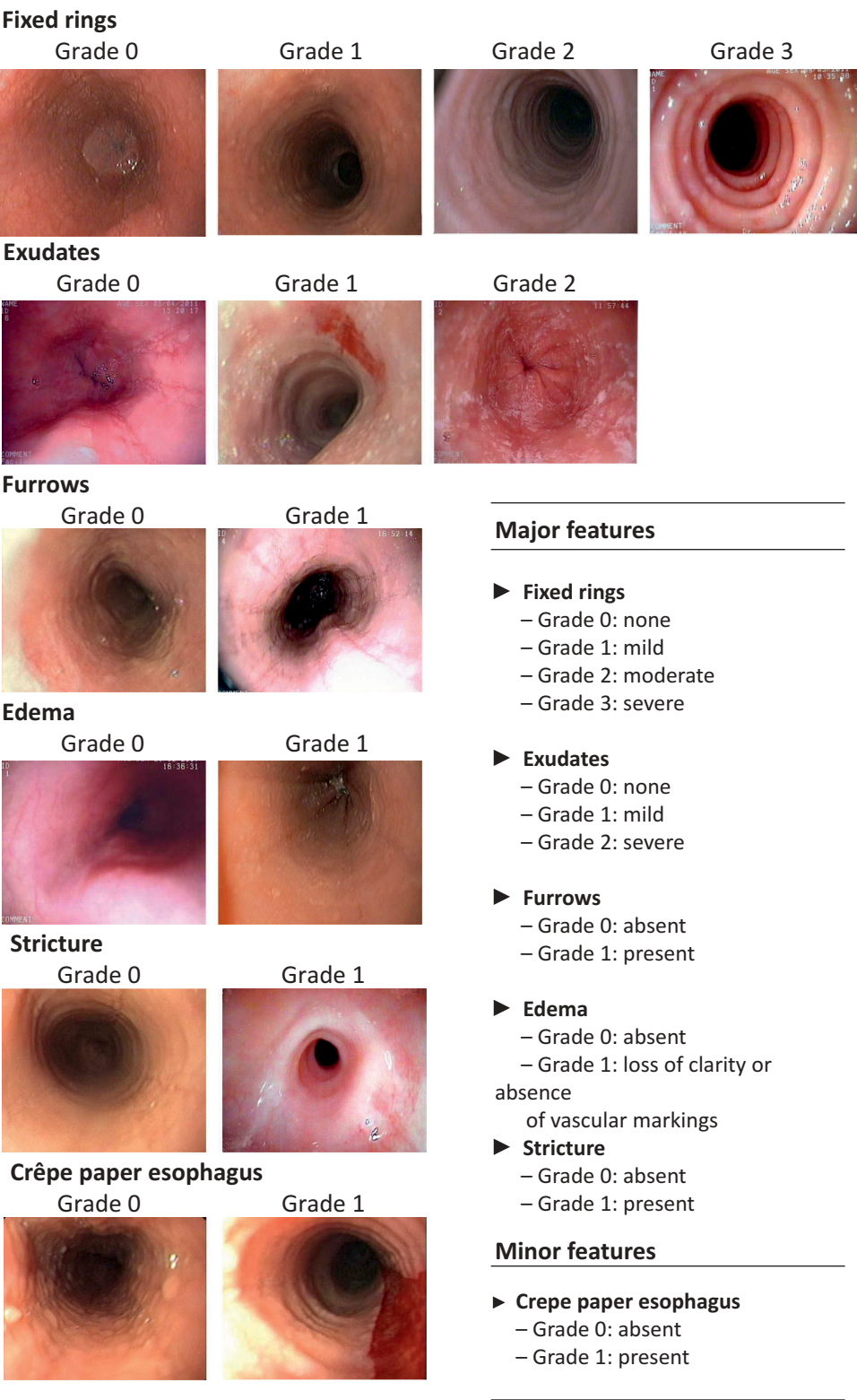
Several prospective studies have tried to evaluate the utility of endoscopic findings for predicting a diagnosis of EoE: in 2007, Prasad and colleagues used endoscopy in conjunction with symptoms of dysphagia in 222 patients who were being attended for non-obstructive dysphagia [49]: of the 21 patients who exhibited endoscopic results characteristic of EoE, the diagnosis was confirmed in only 8 cases (38%). In contrast, 10 of the 102 patients (9.8%) with an apparently normal endoscopic examination also presented histological evidence of EoE. Concordant findings were reported by Mackenzie in 2008 [50]: only 12 of the 35 patients (34%) who showed esophageal rings in their endoscopic exams were confirmed to have EoE after esophageal biopsy.

The overall diagnostic yield of endoscopic features to predict a diagnosis of EoE was summarized in a meta-analysis that included 4678 patients with EoE and 2742 non-EoE controls. According to it, the operating characteristics of endoscopic findings alone were inadequate for diagnosing EoE, with low levels of sensitivity (ranging from 15% to 48%) but greater of specificity (90–95%) [22]. In fact, an apparently normal esophagus was described in 17% of patients with EoE included in this systematic review, which suggests that changes in this organ's appearance are not only complex, but sometimes subtle enough to be overlooked by an endoscopist unaccustomed to attending patients with this disease.

The EREFS system, as a validated reliable method to improve the identification of endoscopic features associated to EoE, was released after the publication of the aforementioned studies. The accuracy of this EREFS system to diagnose and monitor EoE activity in adult patients has provided conflicting results: While an American single-center prospective study on 67 incident EoE cases showed that the score properly identified patients compared to controls and decreased after effective treatment [41], these results were not reproduced in a subsequent Dutch research involving 69 patients [51]: despite the EREFS composite score (but not individual endoscopic signs) correlating weakly with peak eosinophil counts, its predictive value for disease activity was insufficient for

**Table 1.** Proposal of classification and grading system for the endoscopic assessment of the esophageal features of eosinophilic esophagitis: the EREFS system [40].

| Major features   |
|--|
| <ul style="list-style-type: none"> <li>► Fixed rings (also referred to as concentric rings, corrugated esophagus, corrugated rings, ringed esophagus, trachealization) <ul style="list-style-type: none"> <li>– Grade 0: none</li> <li>– Grade 1: mild (subtle circumferential ridges)</li> <li>– Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult endoscope (outer diameter 8–9.5 mm))</li> <li>– Grade 3: severe (distinct rings that do not permit passage of a diagnostic endoscope)</li> </ul> </li> <li>► Exudates (also referred to as white spots, plaques) <ul style="list-style-type: none"> <li>– Grade 0: none</li> <li>– Grade 1: mild (lesions involving &lt;10% of the esophageal surface area)</li> <li>– Grade 2: severe (lesions involving &gt;10% of the esophageal surface area)</li> </ul> </li> <li>► Furrows (also referred to as vertical lines, longitudinal furrows) <ul style="list-style-type: none"> <li>– Grade 0: absent</li> <li>– Grade 1: present</li> </ul> </li> <li>► Edema (also referred to as decreased vascular markings, mucosal pallor) <ul style="list-style-type: none"> <li>– Grade 0: absent (distinct vascularity present)</li> <li>– Grade 1: loss of clarity or absence of vascular markings</li> </ul> </li> <li>► Stricture <ul style="list-style-type: none"> <li>– Grade 0: absent</li> <li>– Grade 1: present</li> </ul> </li> </ul> |
| Minor features   |
| <ul style="list-style-type: none"> <li>► Crepe paper esophagus (mucosal fragility or laceration upon passage of diagnostic endoscope but not after esophageal dilation) <ul style="list-style-type: none"> <li>– Grade 0: absent</li> <li>– Grade 1: present</li> </ul> </li> </ul>  |



**Figure 2.** Reference representative images for the grading system for the endoscopic assessment of the esophageal features of eosinophilic esophagitis.

clinical use. Another recent multicenter Spanish research also failed in predicting dysphagia severity and histological activity by applying the EREFS score to 145 adult patients undergoing 240 consecutive endoscopic exams [52]. As such, larger multicenter studies are required to ascertain the utility of the EREFS system for assessing the activity of the disease, as well as its

predictive capacities in children. In any case, biopsies remain indispensable for the assessment of disease activity at the present.

Therefore, and taking into account that EoE seems to be a very common cause of esophageal symptoms, with a prevalence of up to 22% in patients with non-obstructive dysphagia,



screening for EoE by performing endoscopic biopsies, despite the endoscopic appearance of the esophagus, is of extreme importance [32].

### 3. Bioptic evaluation in EoE: currently the only reliable assessment criteria

EoE was consensually defined as a clinico-pathological disorder characterized by symptoms related to esophageal dysfunction, together with a dense eosinophils-predominant infiltration of the esophageal surface. Both features are required to provide a diagnosis, and none should be considered in isolation [53]. Despite this fact, a recent study conducted in adult EoE patients highlighted that gastroenterologists still rate EoE activity mainly on the basis of endoscopic findings and symptoms and, to a lesser extent, on histologic assessment [54]. Less invasive alternative procedures for diagnosing and monitoring EoE has been largely pursued because of the invasiveness of taking biopsies.

The ability of symptoms (or their absence) to mirror inflammatory activity was assessed in a recent prospective multicenter study that used the validated Eosinophilic Esophagitis Activity Index (EEsAI) patient-reported outcome instrument [55], an index that quantifies the difficulties foreseen by patients with different food consistencies, as well as dietary or behavioral modifications for the same food consistencies. After assessing several cutoff values, the EEsAI index was not sufficient enough to predict either histologic or endoscopic remission of EoE [56]. Therefore, clinicians should not make assumptions about the biological activity of EoE exclusively upon symptoms.

On the other hand, endoscopic features of EoE are not pathognomonic and some of them can be found in other esophageal conditions, including GERD, a disease that symptomatically overlaps with EoE in a proportion of patients. Several studies have shown that endoscopic features suggesting EoE does not always represent esophageal eosinophilia and are non-specific for EoE. Among them, a retrospective analysis of a large American series of EoE and GERD patients showed similar proportions of erythema, erosions, decreased vascularity, and ulceration between both conditions; a normal appearance esophagus was similarly found in patients with EoE and GERD [57,58]. A prospective research in Japan identified linear furrows, corrugated rings, and white exudates, respectively, in 24, 15, and 45 patients out of 2545 consecutively recruited patients. These features represented eosinophilia only in 14%, 23%, and 5%, respectively [59]. A recent single-center prospective research suggests that combining esophageal symptoms and endoscopic features with a set of clinical and demographic variables might improve the ability to differentiate EoE from GERD [60], but at the present, endoscopy with esophageal biopsies remains the only reliable diagnostic test to achieve a diagnosis of EoE in a patient with suggestive symptoms, or to monitor the effect of therapy in already diagnosed patients.

#### 3.1. The number of biopsies determines diagnostic accuracy

Inflammatory changes in the esophagi of patients with EoE are not uniform and frequently patchy [60,61]. Therefore, the characteristic changes that define the disease may not be

present in all biopsy specimens. This significant histologic variability that exists among biopsy specimens from adult [62] and pediatric [63] patients with EoE implies that multiple biopsies are required to increase diagnostic accuracy: the diagnostic sensitivity of a single biopsy was, respectively, 55% and 73% for adults and children, and increased to 100% and >97% after five biopsies, when a diagnostic threshold of  $\geq 15$  eosinophils per high-power field was considered. Furthermore, esophageal biopsies should be targeted to mucosal areas of endoscopic abnormality, mainly white exudates and longitudinal furrows, which are associated with higher peak eosinophil counts [63–65]. Therefore, and in order to achieve the highest diagnostic yield, recent evidence-based guidelines have recommended that at least six biopsies should be taken from different locations, focusing on areas with endoscopic mucosal abnormalities [1]. For optimal pathological evaluation, biopsies from the proximal and distal esophagus should be also obtained, despite no significant difference in eosinophilia being demonstrated between the proximal and distal sites [37,62,66]. The normal appearance of the esophageal mucosa should not preclude taking biopsies if EoE is suspected, because normal esophageal appearances have been reported in up to 10%–32% of adult and pediatric patients, respectively [22,67].

Biopsy samples should be evaluated for a variety of pathological features, the landmark being an eosinophil-predominant inflammation over the currently established diagnostic threshold of  $\geq 15$  eosinophils per high-power field. This cutoff point that was arbitrarily proposed in the consensus guidelines for EoE in 2007 [68] has recently demonstrated a sensitivity of 100% and a specificity of 96% for the diagnosis of EoE [69]. However, a high-power field is not a standardized measure and varies from one microscope manufacture to the other, with different microscopes having different high-power field areas [70]. Therefore, reporting eosinophil density (eos/mm<sup>2</sup>) together with the eosinophil count (eos/hpf) is currently recommended to enable comparisons between patients and centers [1].

In addition to eosinophils, other accompanying findings reinforce the diagnosis and should also be noted by the pathologist (Table 2), despite being rarely reported in clinical practice [36]. They include eosinophil microabscesses, basal zone hyperplasia, dilated intercellular spaces, eosinophil surface layering, papillary elongation, and lamina propria fibrosis.

**Table 2.** Histologic features found in the evaluation of esophageal biopsies of patients with eosinophilic esophagitis.

|   |
|---|
| Eosinophilic inflammation*                |
| Hyperplasia or the epithelial basal zone* |
| Eosinophil microabscess formation*        |
| Eosinophil surface layering*              |
| Dilated intercellular spaces*             |
| Surface epithelial alteration*            |
| Dyskeratotic epithelial cells*            |
| Lamina propria fibrosis*                  |
| Extracellular eosinophil granules         |
| Epithelial desquamation                   |
| Mastocytosis and mast cell degranulation  |
| CD8 lymphocytes and B cells infiltration  |

The biopsy features marked with \* integrates the EoE-specific histologic scoring system [71].

An EoE-specific histologic scoring system has been recently developed, and in-site validated, to provide a standardized method to evaluate esophageal biopsies for features in addition to peak eosinophil count [71].

The effects of inflammation in EoE are isolated to the esophagus; therefore, eosinophilic inflammation should be absent from both gastric and duodenal biopsy samples. In this sense, available guidelines also recommend that gastric antrum and duodenal biopsies be obtained at least once to rule out eosinophilic gastroenteritis [1] both in children and in adults. In contrast, repeating gastric and duodenal biopsies during follow-up endoscopies in patients previously diagnosed with EoE is not required: they will increase costs and may add potential risk of adverse events, while pathology will be found only in a minority of patients [72].

#### 4. Other techniques in improving EoE recognition

Few studies deal with finding techniques to improve the diagnostic yield of endoscopy alone in EoE patients. The addition of chromoendoscopy in EoE [73] showed improved inter-observer agreement for all endoscopic findings of EoE. Regarding narrow banding imaging endoscopy, only two published studies and a case report have examined to date its ability to improve reliability [74–76]: while this technique proved helpful in detecting mucosal details that went unnoticed in a routine white-light examination, it only managed to identify rings and furrows with fair to good reliability; no other findings were noticed. Moreover, there was also great interobserver variability. The researchers thus concluded that endoscopic findings alone were not sufficiently reliable for supporting a diagnosis of EoE or for making treatment decisions.

#### 5. Defining the role of endoscopy in the treatment of patients with EoE

In general, primary endoscopic interventions to alleviate EoE-associated symptoms should be considered in both emergency procedures on patients presenting with acute food bolus impaction, and in scheduled endoscopic dilatation on patients who may present esophageal strictures or a narrowed esophageal caliber. Prior to define the real role of endoscopic treatment in patients with EoE, and specifically the aspects related to endoscopic dilatation, several issues should be considered:

- (a) We lack universally accepted therapeutic goals for EoE to date. Currently, treatment objectives in literature range from merely controlling the symptoms to resolving the epithelial inflammatory infiltrate and restoring the esophageal histology [77]. Functional recovery of the organ also appears as a potential target on the horizon. Therefore, the ideal treatment end point must be still defined, and it could include symptoms improvement (as well as providing a definition for such improvement), reversion of esophageal inflammation and/or remodeling, or even reversion of changes in gene expression associated to EoE. Consensus guidelines recommended treating active inflammation even in asymptomatic patients to avoid the potential consequences of fibrous remodeling of the organ [32,68]. Treatment options are

also determined by the experience and availability at each center. In all events, it must be considered that if left untreated, EoE is a chronic disease involving persistent histological inflammation over time [78], and a progressive narrowing disease, in which the prevalence of esophageal strictures increases with patients' age [79,80] and diagnostic delay [35], contributing to persistent and progressive symptoms and impairing patients' health-related quality of life [81,82].

- (b) With regard to what is the best therapeutic option for EoE patients, no studies comparing different therapeutic modalities have been carried out. Expert opinion and best practice support the use of PPIs, diet, or swallowed topical steroids as first-line anti-inflammatory therapy [1], because each of them have demonstrated ability to induce and maintain histological features under remission (Figure 1). The choice of therapy should be individually discussed with the patient and might be potentially interchangeable over time [83,84]. The efficacy of any therapy should be checked by a follow-up endoscopy after a 6- to 12-week initial course. On the other hand, fibrostenotic features can be solved by means of endoscopic dilation, which should be also considered in patients with dysphagia/food impaction unresponsive to anti-inflammatory treatment. Several published case studies combine dilation with concomitant drug therapy (either with steroids, PPIs, or montelukast) [85,86], which makes it difficult to clearly establish the effect of the individual treatment modalities.
- (c) Additionally, esophageal symptoms in EoE are frequently intermittent, and patients may present prolonged asymptomatic periods despite the persistence of eosinophilic inflammation. As a consequence, doubts arise regarding the convenience of restricting therapy to symptomatic periods only or whether to prescribe a maintenance treatment.
- (d) Narrowing of the esophageal caliber in EoE has been recognized to have a double origin [87]: muscle contractions due to motor disturbances secondary to eosinophilic infiltration of *muscularis propria* among other deep esophageal wall structures (which reverse after a short anti-inflammatory treatment), and fibrous remodeling with collagen deposition in the subepithelial strata (which will require enlarging the narrow organ lumen). A combination of both mechanisms is also possible [88]. In addition, making routine distinctions between patients who have a definite stricture and those in whom it can be reversed through drug or diet therapy is frequently difficult.
- (e) The lack of validated end points adds further difficulties to the assessment of the efficacy of individual therapeutic modalities in EoE. Topical corticosteroids are effective in inducing histological remission in children and adults with EoE, but provided heterogeneous results when symptoms

improvement was considered as treatment outcome. Several randomized clinical trials have not been able to demonstrate a statistically significant superiority of swallowed topical corticosteroids over placebo [11,89–92], or even performed worse than PPI therapy [93]. No commonly accepted or validated symptom scores were used in such clinical trials, which makes it difficult not only to extrapolate results from one study to another, but also to objectively evaluate the effect of treatment on symptoms. In this scenario, and with regard to endoscopic treatment, the need for repeated dilations appears as the most valuable criterion for assessing clinical response. In this context, endoscopic dilation can be restricted to two well-established subgroups of EoE patients: those unresponsive to medical therapy [94] and those with a persistent or definitive stricture [95]. The identification of such patients should be made prior to endoscopic therapy, which in clinical practice implies not using endoscopic dilation as an initial treatment, but medical or dietary alternatives able to achieve histologic remission.

## 6. Emergency endoscopy and food disimpaction

Food impaction constitutes a complication of EoE that must be urgently remedied, and has been recognized as the clinical manifestation which most frequently leads to diagnosing EoE in adults: in fact, 43.3% of adult patients studied in a Spanish series underwent endoscopy as an emergency treatment to resolve food impaction before being diagnosed with EoE [37]. Repeated studies show that approximately half of all food bolus impactions requiring endoscopy are likely to be secondary to EoE [96,97], and conversely, EoE was the strongest predictor of multiple food bolus impaction, representing the 46% of diagnosis among patients who underwent biopsy following food bolus removal [97]. Food impaction is also recognized as a predictor for esophageal perforation, a rare but serious complication of EoE [98]. In a large retrospective series of adult Swiss EoE patients, 34.7% of them required extraction of an impacted bolus with the aid of either flexible or rigid esophagoscopy [78,99]; the latter caused a 20% rate of transmural perforations [99]. Bolus removal by means of rigid endoscopy thus may constitute a high-risk procedure and should be avoided in EoE patients.

Until recently, food impaction seemed to be uncommon in pediatric EoE; however, a retrospective chart review for all children who underwent emergency endoscopy due to foreign body/food bolus impaction in two North American centers determined that 8%–10% of children needing endoscopic removal had EoE [100,101]. Additionally, EoE was identified as the major underlying cause leading food bolus impaction in 53% of pediatric patients who underwent to an esophagram or upper gastrointestinal examination [97], similarly to what happens in adults [96]. Meat is involved in the vast majority of food impactions [101,102], and because patient history may be unreliable in the case of children, it has been recommended to perform chest radiography before endoscopy to rule out other radiopaque foreign bodies and concomitant complications of ingestion, such as pneumomediastinum and pneumothorax [102].

Taking into account that up to half of adults and children with esophageal foreign body/food bolus impaction may have EoE, routine sampling of esophageal mucosa at different levels during esophageal foreign body extraction must always be considered. The recent recognition of PPI-responsive esophageal eosinophilia as a part of the spectrum of EoE, instead of a different condition [1,28], has overcome previous controversy among gastroenterologists regarding postponing the procurement of biopsies after a PPI therapy had been instituted to avoid confounding EoE with PPI-REE [103]. PPIs are considered today a first-line therapy for patients with EoE with intrinsic anti-inflammatory properties and no longer a diagnostic tool to exclude acid reflux in patients with dense esophageal eosinophilia and esophageal symptoms.

Finally, the effectiveness of administering glucagon in relieving esophageal food-bolus impaction in the setting of EoE has been assessed: authors retrospectively reviewed 213 episodes of food bolus impaction during a 6-year period: none of the 17 episodes in EoE patients relieved symptoms following glucagon administration, compared with 28% response rate among patients without EoE [104], so since EoE patients appear less likely to respond to glucagon, primary endoscopic removal is preferred.

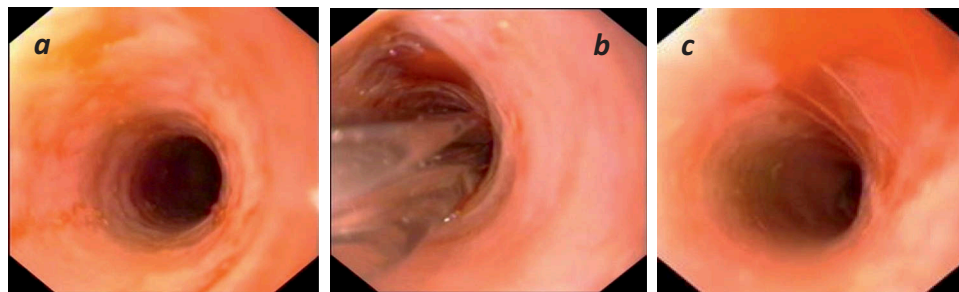
## 7. Dilation treatment for EoE: immediate and sustained efficacy

Esophageal strictures constitute one of the most severe complications of EoE that develop as a result of a long-standing untreated eosinophilic inflammation. Despite patient age and delayed diagnosis being recognized as determining factors for a fibrotic esophageal strictures [35,80,105], not every patient with prolonged EoE evolution develops such strictures. Esophageal strictures are less commonly found in pediatric cases of EoE, likely due to the limited progression of the disease.

From the earliest documented cases, mechanical dilation with through-the-scope hydropneumatic balloons (Figure 3) and Maloney or Savary bougies has been employed as a treatment option for EoE patients. Similarly, it is used in other cases of rigid or fibrous esophageal strictures resulting from a prolonged esophageal inflammatory process such as GERD or after the ingestion of caustic substances. The chronic inflammatory phenomena that characterize EoE cause subepithelial collagen deposition and fibrous remodeling, as shown in both pediatric [106,107] and adult [79,108] patients, and reproduced in animal models [109].

The effectiveness of esophageal dilation in patients with EoE has been mostly reported in retrospective and single-center studies, the results of the nine published up to March 2013 were summarized in a first meta-analysis that overall included 525 adult patients who underwent 992 dilation procedures [110]. According to it, any symptomatic improvement was documented in 75% (95% CI 58–93%) of patients. Notably, high between-study heterogeneity was found, reflected by an  $I^2$  statistic value of 86%. An updated meta-analysis to also retrieve subsequent publications up to 2016 has been recently released [111]: overall, it includes 27 studies assessing 845





**Figure 3.** Endoscopic dilation for treatment of EoE. In a patient with EoE and narrow caliber esophagus (a) a 12-to-15 mm diameter through-the-scope balloon dilator has been inflated (b). When the balloon is deflated, a longitudinal rent is noted, indicating effective dilation effect (c).

individual patients undergoing 1820 dilation procedures; dysphagia improved in 95% of patients following dilation (95% CI 90–98%); heterogeneity ( $I^2$ ) reduced to 10%.

It should be noted that because endoscopic dilation is a mechanical procedure with no effect on the underlying inflammatory process [112], its efficacy is limited over time. In the case studies published to date, the duration of the effect cannot be appropriately estimated owing to the short monitoring period, although it ranged from 1 to 36 months in the most updated systematic review [111]. Still, it is common for patients to undergo repeated dilations, with an average of 2 but in one case up to 23 times, in order maintain dysphagia symptoms under control. Only few studies assessed the increase in the esophageal caliber after dilation, reporting an average pre-dilation caliber of 9.9 mm that increased to 16.1 after the procedure. A proportion of patients undergoing dilation also received concomitant drug therapy, thus masking the clinical effect of the endoscopic therapy [113,114].

According to evidence-based recommendations [1], endoscopic dilation should be considered as a treatment option for patients with EoE and esophageal strictures after other measures (especially swallowed topical steroid treatment) have failed. It is also advisable that the procedure be used together with other therapy modalities in order to avoid complications derived from active eosinophilic inflammation of the organ.

### 7.1. Is there a patient profile that benefits the most from esophageal dilation?

There has been a growing interest in the potential role played by several technologies to explore the functional behavior of the esophagus (including the location of the esophageal narrowing and localized strictures) in defining the profile of patients who could benefit the most from esophageal dilation.

An intrabolar pressure of >16 mmHg as determined by high-resolution manometry showed a moderate capacity to distinguish fibrostenotic from inflammatory phenotypes of EoE [115]. However, the classification on patients in this research according to their esophageal caliber was done with endoscopy, so the predictive capacity of high-resolution manometry could not been assessed. On the other hand, endoscopy has been demonstrated to underestimate the reductions in the esophageal caliber when compared to barium esophagography [116], hindering the ability of

endoscopic assessment to identify a narrow caliber esophagus. The recent release of the Endoluminal Functional Lumen Imaging Probe (EndoFLIP; Crospon, Inc, Carlsbad, CA), a device that has demonstrated a significant reduction in esophageal distensibility in patients with EoE [117] may change this scenario in the future. A lack of correlation between eosinophil counts and esophageal distensibility has been shown with EndoFLIP, partially explaining the dissociation between inflammatory activity and symptoms in EoE [118]. Reduced esophageal distensibility predicted the risk for food impaction and correlated with endoscopically identified ring severity [119]. Whether the addition of the EndoFLIP system to other patient-reported outcomes measures can enhance the accuracy in predicting the real biological activity of EoE warrants further investigation.

### 8. Perforation risk during EoE endoscopy

From the early descriptions of the disease, endoscopic dilation has been extensively proved as an efficient treatment for EoE, providing immediate relief of symptoms [120,121], which is why some authors regarded it as a front-line treatment [78,122]. However, these initial reports on the use of esophageal dilation in EoE patients also found a high rate of complications, ranging from chest pain to esophageal perforation, which appeared in 7% and 5% of all reported cases, respectively [68,123], and which were substantially higher than those for esophageal dilation for other benign strictures. Most of the perforations reported (spontaneously or after endoscopic procedures) only led to pneumomediastinum [124,125] that was conservatively resolved [126]. However, in some exceptional cases, an emergency esophagectomy via thoracotomy or esophagogastroplasty was required [126–129]. Although no patient fatalities have been reported to date, the seriousness of these complications in the early EoE literature, along with the efficacy and proved safety of dietary modifications and swallowed topical steroids for this disease, led some researchers to recommend not to dilate until an active eosinophilic inflammation was ruled out or reduced [130,131]. The need of anesthesia in some patients undergoing to esophageal dilation, especially in the case of children, may represent additional risks and increased costs.

The increased fragility described for the esophageal mucosa in EoE has been directly related to the cytotoxic proteins contained in the cytoplasmic granules of

eosinophils in the inflammatory infiltrate, which are capable of damaging tissues [132], the risk of which is likely higher in the case of a high eosinophil density and long-term symptoms [78]. Repeated evidence derived from patients [129,133,134] and from animal models of EoE [109] have shown that eosinophils penetrate deeply into the esophageal wall, including the lamina propria and submucosa and reach up to the muscle layers. Indeed, esophageal fibrous remodeling reduces the elastic properties of this organ, as also described in EoE patients [79,106–108]. As a result, the mechanical properties of the esophageal wall are significantly impaired in adult EoE patients in comparison to controls [117]. This reduced esophageal resistance and compliance leads to an increased fragility during endoscopic dilation procedures [131] (Figure 4) and in traction movements around the gastroesophageal junction in cases of nausea and vomiting. Thus, a simple brush of the endoscope may give rise to mucosal rents, and spontaneous esophageal perforation [135] and Boerhaave's syndrome [126,134] have been reported in EoE patients after the mere passage of the scope [136] or following biopsy sampling [137].

Perforation rates in EoE reported in the most recent studies contrast with those reported in earlier case series: Dellon and colleagues documented a 7% complication rate, with 2 deep mucosal rents and 3 episodes of chest pain [113], as well as a perforation rate of 2% [98]. In a second case series, Jung's group found that 9.2% of patients suffered deep mucosal tears while major bleeding and immediate perforation occurred in 0.3% and 1% of the patients, respectively [138]. The first systematic review of the literature reported a total of three esophageal perforations (0.3%) and one hemorrhage (0.1%), all from the same institution [138], and no death was reported, providing the knowledge that the rate of major complications in EoE is consistent with that reported for endoscopic dilation in other esophageal diseases. The updated systematic review retrieved only 7 cases of perforation, 1 hemorrhage, 10 hospitalizations, and no deaths in the overall 1820 endoscopic dilation procedures. However, post-procedural chest pain occurred in 9.4% of cases [111].

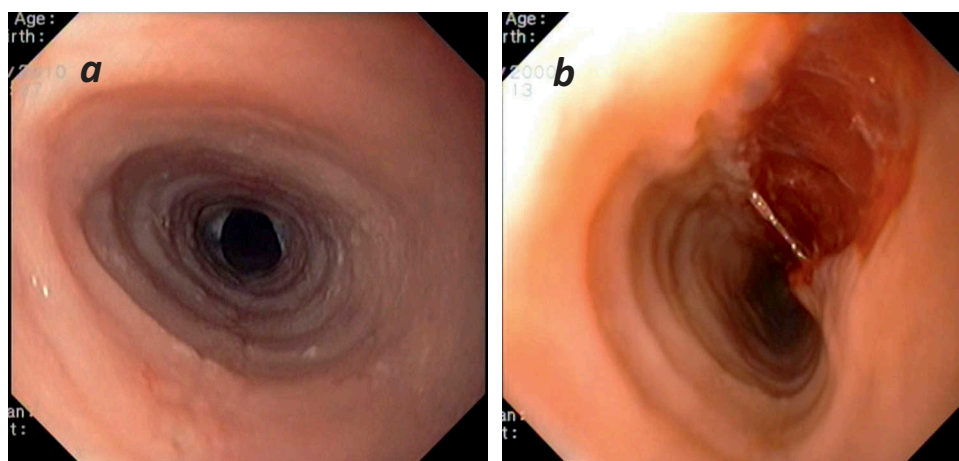
Several predictive factors for complications during dilation were identified in the early studies with larger patient numbers and included a long evolution of dysphagia, the existence of

fixed esophageal strictures, and a high density of eosinophils [139]. Complications were also significantly associated with younger age and repeated procedures [113], along with luminal narrowing in the upper and middle esophageal thirds, a luminal stricture incapable of being traversed with a standard upper endoscope, and the use of Savary bougies [138]. However, this last aspect was not identified by other authors, and no differences in perforation risks related to the dilation device used were found in the most recent systematic review [111].

Despite the use of esophageal dilation in children having been occasionally described [140,141], its efficacy in children has only recently been evaluated in a large single-center series [142]: After retrospectively reviewing 68 dilations performed during a five-year period, no significant differences were found in terms of adverse event rates between EoE and non-EoE children. The EoE group included 40 children, 43% of them underwent repeated dilation. Any grade of chest pain was reported in 14.7% of EoE dilations and were independent from the dilation method, final dilator size, medical therapy, or esophageal eosinophil density. No perforations or significant hemorrhages were reported.

### 8.1. How endoscopic dilation should be done in EoE patients

From all the exposed above, endoscopic dilation constitutes an effective and safe treatment for EoE that should therefore be considered in every patient with EoE who exhibit a reduced esophageal caliber and persisting esophageal symptoms despite an effective medical (i.e. topical steroid or PPI treatment) and/or dietary therapy. Whenever possible, dilation should preferably be done when the active inflammatory infiltrate has been banned or significantly reduced [130]. Endoscopic dilation should also be carried out by experienced endoscopists and under sedation to avoid provoking Boerhaave's syndrome if the technique is not well tolerated [143]. In order to minimize complications, the procedure should be carried out gently with medium-sized balloons or bougies, gradually increasing the caliber and never dilating fully to the larger calibers used in the treatment of other



**Figure 4.** Increased esophageal fragility in EoE. Trough-the-scope balloon dilation procedure in a narrow caliber ringed esophagus (a) causing a deep mucosal tear along the organ (b).

strictures. No definitive data exists with regard to which dilation technique(s) should be used, and no differences have been documented between through-the-scope balloons and bougies.

Multiple strictures are also possible in patients with EoE; a common strategy in such cases has likewise yet to be established. Inflating a balloon segmentally in multiple areas can dilate the entire esophagus quickly if necessary while maintaining direct visualization at all times [113], but the final method employed should preferably depend on the endoscopist's experience, since the use of Savary bougies has also been reported to be a safe method [144].

## 9. Role of endoscopy in EoE monitoring

Aside from its therapeutic role, endoscopy is also essential in the diagnostic workout of EoE by allowing biopsy sampling, which cannot be avoided to achieve a diagnosis of EoE. The role of endoscopy in monitoring the effectiveness of different dietary or pharmacological therapeutic options in EoE is also essential. Despite having no commonly accepted therapeutic end points when treating EoE patients currently, vanishing the esophageal eosinophilic infiltration is recognized as the most desirable therapeutic end point [1], also avoiding the development of symptoms and fibrous remodeling. Histopathologic normalization also constitutes a necessary biomarker for clinical trials in EoE and provides an objective measure on the efficacy of a treatment. Endoscopy allowing bioptic monitoring has been used to identify specific food triggers causing EoE in both children [145] and adults [27,146]. Noninvasive or minimally invasive methods assessing disease activity are lacking at present, and no peripheral markers currently predict the presence of inflammation in the esophageal tissue [147], so endoscopy remains essential for this monitoring.

Generally speaking, repeated upper endoscopies can be considered in several circumstances: (a) after settling on a treatment regimen that has controlled symptoms and ideally resolved esophageal eosinophilia; (b) following institution of additional treatment; and (c) based on change in symptoms or compliance with therapy [68]. If repeating endoscopy with biopsy is planned, it should be performed no sooner than 6 weeks after the last therapeutic intervention, in order to guarantee a significant histological change.

## 10. Expert commentary

EoE has arisen as a common disorder in current clinical and endoscopic gastroenterology practice. Endoscopy remains as an essential technique in the integral management of EoE patients, allowing obtaining biopsies for EoE diagnosis and monitoring, to constitute a front-line therapy that provides relief of symptoms in patients with esophageal narrowing. Hitherto, the findings of EoE-associated endoscopic features in a patient with esophageal symptoms have proved insufficient to accurately diagnose EoE, as compared with the gold standard represented by esophageal biopsies. However, whether this accuracy could improve by applying the EREFS scoring system requires evaluation. EREFS scores show inter-observer reliability and might increase the sensitivity in identifying esophageal features associated to EoE. Whether an

increase in the accuracy to predict histologic inflammation could improve when combined with symptoms (as assessed with validated instruments such as the EEsAI scoring system) requires further investigation.

The complex management that patients with EoE often require has benefitted in last few years from well-designed clinical research, including multicenter randomized controlled trials and quasi-experimental prospective studies, summarized in systematic reviews and meta-analyses, assessing the efficacy of the several therapeutic options available for achieving and maintaining disease remission. In contrast, most of the evidence on the use of dilation in EoE comes from retrospective single-center case series, which include a certain risk of bias. Systematic registries of large prospective series of patients are thus required in order to provide clinicians with better quality data for making decisions concerning the endoscopic management of EoE.

## 11. Five-year view

EoE constitutes one of the areas in Gastroenterology with a more intense development in the last few years. The increase in the number of new diagnosed cases has only been surpassed by the interest of clinicians in this disease, which has been reflected in an exponentially growing body of literature. A wide variability in current clinical practice of EoE has been documented from the description of the disease [36,70], which should be now replaced by evidence-based management. A standardized care of patients will also allow systematizing case studies to answer many of the questions that still persist when facing this disease.

At present, the choice of therapy is recommended to be individually discussed with the patient and might be potentially interchangeable over time [1,83,84]. Further research through comparative clinical trials and long-term studies should clearly identify the most suitable scenario for the endoscopic management of EoE patients, as well as determining which patients are the best candidates for each kind of treatment, including endoscopic dilation, due to their better clinical results and/or lower complication rates. This will require the definition of different patient subgroups or phenotypes according to several variables which are yet unidentified.

The development of minimally invasive methods for disease diagnosing and monitoring has been largely pursued in EoE, thus avoiding the use of repeated endoscopies with biopsies. All the attempts to find a novel biomarker from blood have proved unsuccessful, while for minimally invasive devices, both the String Test (a capsule filled with approximately 90 cm of string) and the Cytosponge (an ingestible gelatin capsule comprising of compressed mesh attached to a string) have shown preliminary good correlations with esophageal eosinophilia degree and eosinophil-derived proteins [148,149]. The further comparison of devices with conventional endoscopy is warranted.

## Key issues

- A wide range of endoscopic features have been described in patients with EoE, which were summarized and systematized in the EREFS classification systems, and acronym for exudates, rings, edema, furrows, and strictures. At present,

the accuracy of endoscopic features is insufficient to predict eosinophilic inflammation, so endoscopic biopsies cannot be avoided in the diagnosis or monitoring of EoE.

- Due to the patchy distribution of eosinophilic inflammation in EoE, multiple biopsies must be obtained; in order to achieve the highest diagnostic yield, at least six biopsies should be taken from different locations, focusing on areas with endoscopic mucosal abnormalities. The normal appearance of the esophageal mucosa should not preclude taking biopsies if EoE is suspected.
- Endoscopy to solve food bolus impaction is so common among EoE patients that esophageal biopsies should be always taken to achieve a proper diagnosis, independently of the endoscopic appearance.
- Dilation is required in every symptomatic EoE patient with esophageal strictures or narrow caliber esophagus despite an effective anti-inflammatory drug or dietary treatment. Current evidence shows that, when made carefully to progressively enlarge the esophageal lumen, esophageal dilation is a highly effective and safe procedure that provides immediate relief of dysphagia.
- Since the effectiveness of esophageal dilation tends to reduce along the time if the eosinophilic inflammation remains, every patient should receive an effective treatment with drugs or diets to maintain disease into histological remission.

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