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REVIEW

Optimal Assessment, Treatment, and Monitoring of Adults with Eosinophilic Esophagitis: Strategies to Improve Outcomes

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Abstract: Eosinophilic esophagitis (EoE) is a chronic type 2 inflammation-mediated disease characterized by an eosinophil-predominant inflammation of the esophagus and symptoms of esophageal dysfunction. Relevant treatment outcomes in the setting of EoE include the improvement of histology, symptoms, and endoscopy findings, quality of life (QoL), and the psychological burden of the disease. Established validated tools for the assessment of EoE include questionnaires on dysphagia and QoL (ie, DSQ, EEsAI, and EoE-IQ). More recently, esophageal symptom-specific anxiety and hypervigilance, assessed using the esophageal hypervigilance and anxiety scale (EHAS), have emerged as contributors to disease burden, confirming the importance of psychological aspects in EoE patients. The EoE endoscopic reference score (EREFS) is the only validated endoscopy score in EoE and can quantify mucosal disease burden. However, esophageal panometry using the functional lumen imaging probe (FLIP) and high-resolution manometry (HRM) have shown potential to optimize the assessment of fibrostenotic features of EoE, providing novel insights into the pathophysiology of symptoms. There is a growing number of licenced and off-label therapeutic options in EoE, with various randomized controlled trials demonstrating the efficacy of proton pump inhibitors, topical steroids, food elimination diets, biological drugs, and esophageal dilatation. However, standardized optimal management strategies of EoE are currently lacking. In this review, we provide an overview of established and novel assessment tools in EoE including patient reported outcomes, FLIP panometry, HRM, endoscopy, and histology outcome measures to improve the outcomes of EoE patients. In addition, we summarize available therapeutic options for EoE based on the most recent evidence.

Keywords: eosinophilic esophagitis, treatment, monitoring

Introduction

Eosinophilic esophagitis (EoE) is a chronic type 2 inflammation-mediated disease characterized by an eosinophil-predominant inflammation of the esophagus in combination with symptoms of esophageal dysfunction.[1] The disease is diagnosed and considered histologically active when at least one esophageal biopsy, obtained during an esophagogastroduodenoscopy (EGD), shows 15 or more eosinophils per high-power field (eos/HPF), while <15 eos/HPF on multiple esophageal biopsies designates histological remission.[2]

Several therapeutic options are currently available to induce and maintain remission in EoE based on randomized controlled trials (RCTs) demonstrating efficacy of proton pump inhibitors (PPIs), topical steroids, food elimination diets,

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and biological drugs.[3–5] In this regard, it must be noted that EoE is a lifelong disease that rapidly recurs when an effective treatment is withdrawn[6] and that a proportion of patients may lose response during maintenance therapy.[7,8]

Despite growing research on EoE over the past three decades,[9] international expert recommendations on the monitoring of EoE,[10] and the first clinical guidelines addressing the issue of the follow-up of the disease have been published only recently.[11]

In the setting of EoE, treatment endpoints include the improvement of classical markers of disease activity, namely histology, symptoms, and endoscopy findings, as well as quality of life.[12,13] However, an accurate assessment and monitoring of EoE can be complex due to the discrepancies between histological disease activity and reported symptoms,[14,15] especially following dilatations of esophageal strictures.[16] In addition, endoscopy findings correlate modestly with histological disease activity and response to treatment.[17,18] In this regard, recent evidence has suggested a role of esophageal symptom-specific anxiety, hypervigilance, and esophageal dysmotility on symptom severity,[19,20] which may affect an accurate assessment of the global disease activity if neglected.[21,22] In addition, novel insights into esophageal distensibility and compliance, based on esophageal panometry measured using the functional luminal imaging probe (FLIP), are improving the understanding of the mechanisms underlying symptoms in EoE.[23] In this comprehensive review, we summarized updated evidence on the optimal management and clinical assessment of patients with EoE to help clinicians disentangling clinical conundrums and improve the outcomes of EoE patients.

Pathogenesis, Development and Progression of EoE

EoE has been documented across all age groups, from infancy to nearly 100 years old. A retrospective analysis of a large US database, which included both children and adults, revealed that EoE prevalence rises with age, peaking in both males and females between 35 and 39 years, before declining after 45 years of age.[24,25] Moreover, patients with EoE are more commonly males, with a 3:1 male to female ratio at all age groups.[26] Of note, EoE patients frequently have allergic comorbidities, with most patients showing at least one concomitant allergic disorder.[27] The most prevalent disorders among EoE patients are allergic rhinitis, bronchial asthma, and atopic dermatitis.[28]

The development of EoE involves the interplay between genetic factors and environmental triggers, leading to an immune reaction against food and inhaled allergens that penetrate through a defective esophageal mucosal barrier.[17,29] In individuals susceptible to EoE, environmental allergens provoke a chronic inflammatory response in the esophagus. This response is mediated by both the innate and adaptive immune systems and involves eosinophils, mast cells, dendritic cells, basophils, T and B lymphocytes, immunoglobulins (Ig), and cytokines such as interleukin (IL)-4, IL-5, and IL-13, collectively resulting in progressive organ dysfunction. Accordingly, it is believed that EoE progresses over time from a predominantly inflammatory phenotype to a fibro-stenotic disease.[30–32]

Genetic factors are estimated to contribute around 14.5% to the pathogenesis of EoE, with high concordance rates among probands—58% in monozygotic twins and 36% in dizygotic twins.[33] Key genes implicated in EoE pathogenesis impact Th2 lymphocyte responses or epithelial barrier integrity, with significant genes including thymic stromal lymphopoietin (encoded on locus 5q22), CAPN14 (encoded on locus 2p23), and the epidermal differentiation complex (encoded on locus 1q21).[29]

Role of Symptom Questionnaires in the Assessment of EoE

The hallmark symptom of EoE is dysphagia,[25] and this should be investigated querying patients about "troubles swallowing" or "sensation of a slow or delayed passage of food". Currently recommended patient-reported outcome (PRO) measures for the assessment of EoE symptoms in the setting of RCTs include the dysphagia symptoms questionnaire (DSQ) and the EoE activity index (EEsAI), which investigate dysphagia and dysphagia-related behavioural modifications.[13] The latest version of the DSQ (DSQ v4.0) uses a 14-day daily recall period and comprises three questions on the presence and severity of EoE dysphagia. The questionnaire also includes a fourth standalone item on the presence of pain during swallowing, whose score was not part of the psychometric validation of the questionnaire and should therefore not be included in the calculation of the DSQ.[34] Higher DSQ scores correspond to increased severity of dysphagia and change in DSQ scores correlate with disease-level changes, with higher DSQ scores corresponding to increased esophageal eosinophilic burden. The EEsAI is a PRO questionnaire based on items investigating dysphagia

severity and behavioural adaptation over a 7-day recall period.[35] The questionnaire investigates dysphagia caused by eating foods of different consistencies and takes into account behavioural adaptations including avoidance, modification, and slow eating of food. In addition, the EEsAI includes a domain addressing chest pain, heartburn, and acid regurgitation independent of eating or drinking. In the validation study, an increase in the EEsAI score demonstrated association with highly active EoE based on endoscopic and histologic findings.[35]

With regards to daily practice, although there are no consensus-recommended questionnaires,[13] the use of EoE ad-hoc questionnaires has potential to improve the quantification of symptoms burden, increasing the likelihood of obtaining a correct diagnosis and optimizing management. In particular, the DSQ and EEsAI can be administered within a reasonable amount of time and using a short recall period,[35,36] and should be thus implemented in routine clinical practice to investigate and monitor EoE patients. In addition, a recent study developed a point-of-care artificial intelligence tool to predict a diagnosis of EoE in patients with dysphagia based on reported symptoms and clinical data, prior to biopsy collection.[37] Although integrating the use of questionnaires into clinical practice may be challenging, the spread of telemedicine in the post-COVID era and the increasing use of informatic applications in daily clinical settings could be of help. Free applications (eg, Google Forms, Microsoft Forms), allow for the rapid creation of online questionnaires that patients can easily access through their smartphones. This approach enables the collection of questionnaire data during follow-up periods without the need for direct phone call to patients or prolonged time during outpatient clinics.

Importantly, the correlation between dysphagia and histological disease activity is weak in EoE.[15,16,34,35] In this regard, recent studies have shown that esophageal symptom-specific anxiety assessed using the validated esophageal hypervigilance and anxiety scale (EHAS),[38] esophageal dysmotility, and adaptive behaviours may have an impact on perceived dysphagia severity,[19,21,39] and these should therefore be considered as possible confounders when clinical and histological disease activities are discordant. Moreover, other upper gastrointestinal symptoms, especially gastroesophageal reflux disease (GERD)-like symptoms, are not infrequent in EoE patients due to the overlap with GERD or esophageal motility disorders.[29,40–43] Although there are no validated questionnaires that uniquely address non-dysphagia symptoms in EoE, such symptoms should be queried, recorded, and actioned when present.

Role of Esophageal Panometry in the Assessment of EoE

The FLIP is a novel esophageal function test consisting of a catheter equipped with a compliant cylindrical bag that has 16 1-cm spaced paired impedance planimetry electrodes, as well as a single pressure sensor placed distally. The test provides dynamic information on the cross-sectional area (CSA) of the esophageal lumen and esophageal distensibility during controlled volumetric distension. The current FLIP study protocol involves the positioning the catheter during a sedated endoscopy with 1–2 distal sensors placed inside the stomach. Subsequently, stepwise 10-mL distensions with saline of the cylindrical bag are performed, beginning with 40 mL, and proceeding to the target volume of 70 mL.[23,44] The protocol allows to acquire dynamic impedance planimetry topographic plots and quantify esophageal distensibility and contractile responses secondary to distension (ie, secondary peristalsis).[45] In the setting of EoE, although FLIP cannot be considered a diagnostic tool and should not be considered prior to performing an EGD, it could be clinically useful by providing a real-time estimate of esophageal diameters, identifying strictures, and assessing the fibrostenotic burden. In addition, FLIP can be leveraged to investigate esophageal biomechanics in response to distension, and identify motility disorders.[23]

Nicodeme et al investigated the correlation between esophageal distensibility assessed with FLIP and clinically relevant outcomes in EoE.[46] In particular, the authors proposed a surrogate measure of esophageal "stiffness" named distensibility plateau (DP), defined as the narrowest, fixed diameter that is observed in response to increasing FLIP volumes and pressures. The study found that a DP <225 mm² (equivalent to a diameter of <17 mm at 70 mL FLIP distension) was associated with an increased risk of food impaction and the need for esophageal dilation over a 4- to 12-month follow-up period. Subsequently, Moosavi et al confirmed that EoE patients have lower values of DP and esophageal compliance compared to asymptomatic controls.[47] In addition, the study found that patients with reduced values of both DP and compliance had the highest proportion of severe rings (61%) and strictures (100%) at endoscopy compared to patients with any of the two metrics within normal values. Complementarily, in another study, the severity

of esophageal rings identified at endoscopy was associated with lower values of DP, corroborating the reliability of FLIP in the quantification of EoE-related fibrotic features.[48]

With regards to contractile response patterns of the esophageal body in response to FLIP distension, Carlson et al demonstrated a significant correlation between abnormal contractile response and features of fibrostenotic remodeling in EoE patients.[20] Similarly, in another study, reduced esophageal distensibility and endoscopic rings were associated with abnormal contractile responses. In addition, symptom duration and diagnostic delay were negatively correlated with DP, indicating that fibrotic features in EoE are progressive and contribute both to mechanical obstruction and abnormal esophageal motility.[30]

Carlson et al recently proposed a physio-mechanical classification of esophageal function in EoE based on a combined assessment of esophageal distensibility and motility from FLIP findings.[49] The physiomechanical classification is hierarchical: first, the presence of normal (compliance>450mm^3/mm and DP>17mm) or reduced (compliance ≤450 mm^3/mm or DP ≤17 mm) distensibility should be established. Subsequently, based on contractile response and esophago-gastric junction (EGJ) opening, patients with normal distensibility are sub-classified as normal, weak, or isolated EGJ outflow obstruction, while patients with reduced distensibility are sub-classified as fibrostenosis with normal reactivity, spastic-reactive fibrostenosis, and non-reactive fibrostenosis. Overall, fibrostenotic phenotypes had greater symptom duration, greater diagnostic delay, and higher EoE endoscopic reference (EREFS) scores compared to non-fibrostenotic phenotypes. However, normal and fibrostenotic phenotypes did not differ significantly in terms of dysphagia scores and history previous bolus impaction.[49] More recently, esophageal body compliance, contractile response, distensibility plateau, and maximum EGJ diameter were used to develop a composite score named C2D2 score (Table 1). In practice, each component of the C2D2 is scored as 0 for normal or 1 to 2 for increasing degree of abnormality, and subsequently summed. In the development study, the C2D2 score showed significant positive correlation with mucosal eosinophil count (rho = 0.24) and total EREFS score (rho= 0.47). In addition, a C2D2 score ≤3 had an odds ratio of 14.5 to predict future PPI response.[50] In conclusion, FLIP panometry is emerging as a promising tool for optimizing the assessment of EoE. In particular, FLIP could be of use in patients with persisting symptoms despite optimal therapy, to investigate the presence of providing an increased esophageal stiffness or reduced distensibility because of chronic esophageal fibrosis, which might indicate the need for esophageal dilation or escalation therapy.[23]

Table 1 C2D2 Score of PhysioMechanical Function in EoE

Feature	Score: Definition
Compliance	0: >450 mm^3/mmHg
	1: 300–450 mm^3/mmHg
	2: <300 mm^3/mmHg
Contractile response	0: Normal or borderline CR
	1: Impaired-disordered or spastic-reactive CR
	2: Absent CR
Distensibility plateau	0: >17 mm
	1: 14–17 mm
	2: <14 mm
Maximum EGJ **D**iameter	0: >16 mm
	1: 12–16 mm
	2: <12 mm

Abbreviations: DP, distensibility plateau; EGJ, esophagogastric junction; CR, contractile response.

Role of High-Resolution Manometry in the Assessment of EoE

EoE is a chronic inflammatory disease that causes a transmural inflammation to the esophageal wall and other structural changes that might alter the esophageal wall motility and compliance.[23,29,51] High-resolution esophageal manometry (HRM) is considered the gold standard modality for the assessment of esophageal motility and the lower esophageal sphincter functions.[52] The practice of HRM systems has permitted a more accurate assessment of esophageal and lower esophageal sphincter functions, with an improved ability to localize the lower esophageal sphincter. Notably, the development of HRM has permitted the creation of the Chicago Classification, currently at its fourth iteration, which is considered as a standardized working algorithm for analyzing and interpreting HRM studies.[53] A systematic review of the literature on esophageal motility patterns in EoE reported that, although heterogenous conventional and high-resolution manometry protocols and classifications were used in included studies, motility disorders are not infrequent in patients with EoE.[42] In 2009, Bassett et al[54] performed the first prospective esophageal motility study in EoE patients using conventional manometry. The authors reported that 23% of patients had non-specific motor disorder whereas 77% had normal esophageal motility. More recently, several groups have studied esophageal motility in EoE and reported inconsistent results; Ghisa et al,[40] in a retrospective study, assessed HRM findings of 109 EoE patients and reported that 38% of patients had abnormal findings. Achalasia and other obstructive disorders were found in 15% of cases. Similarly, Savarino et al[55] reported that 17% of 35 EoE patients had achalasia or other obstructive disorders. Overall, although various HRM studies on EoE patients have revealed inconsistent findings, achalasia and other esophageal obstructive disorders were not uncommonly reported. Accordingly, provocative measures during HRM, including the rapid drinking challenge, solid swallows, and a test meal could be helpful to disclose EGJ obstructive disorders in patients with EoE.[56–58] Finally, some groups have reported that pharmacological treatment of EoE may improve esophageal motility patterns at HRM.[59–61]

In summary, esophageal motility disorders are not uncommon among EoE patients, especially achalasia and obstructive disorders. Assessment of esophageal motility by means of HRM in EoE might be of paramount significance when evaluating symptomatic refractory cases, especially in patients in histological remission and without esophageal strictures.

Role of Endoscopy in the Assessment of EoE

A diagnostic EGD is required to obtain biopsies and assess the esophageal mucosa of patients with EoE. Inflammatory histological abnormalities of EoE have a patchy nature,[62] therefore current guidelines recommend performing at least 6 to 8 biopsies in at least 2 different sites of the esophagus, targeting visible mucosal alterations when present, since they are associated with higher peak eosinophil counts.[2,63,64] To optimize biopsy collection, we recommend the "turn-and-suction" technique. When adopting such technique, instead of advancing the biopsy forceps against the esophageal wall and subsequently closing it to collect the tissue sample, the biopsy forceps is drawn back to the endoscope tip in an open position. Subsequently, the endoscope is turned toward the esophageal wall while suctioning and gently advancing the scope, with simultaneous closure of the biopsy forceps to obtain the tissue. Using this technique, biopsy samples are taken in a perpendicular orientation to the esophageal wall, which allows to collect larger tissue samples.[65]

With regards to mucosal assessment, the EREFS score is the only validated endoscopic scoring system describing endoscopic features of EoE.[18] EREFS items include five major findings (Edema, Rings, white Exudates, linear Furrows, and Stricture) that are scored 0 to 9, while the presence of 'crepe-paper esophagus' is considered an adjunctive finding (Figure 1).[18] The EREFS score has shown moderate to substantial intra- and inter-observer agreement and should be used in clinical practice to standardize the endoscopic assessment of EoE.[66]

Dellon et al investigated the diagnostic utility of EREFS findings and their change in response to treatment.[67] The investigators found that, compared to healthy controls, EoE patients had significantly higher EREFS scores. Accordingly, based on receiver operating characteristic analysis, the EREFS score identified patients with EoE with an area under the curve of 0.94. In addition, another study found that inflammatory features of the EREFS score, including exudates and linear furrows, were associated with the highest concentration of eosinophils, while

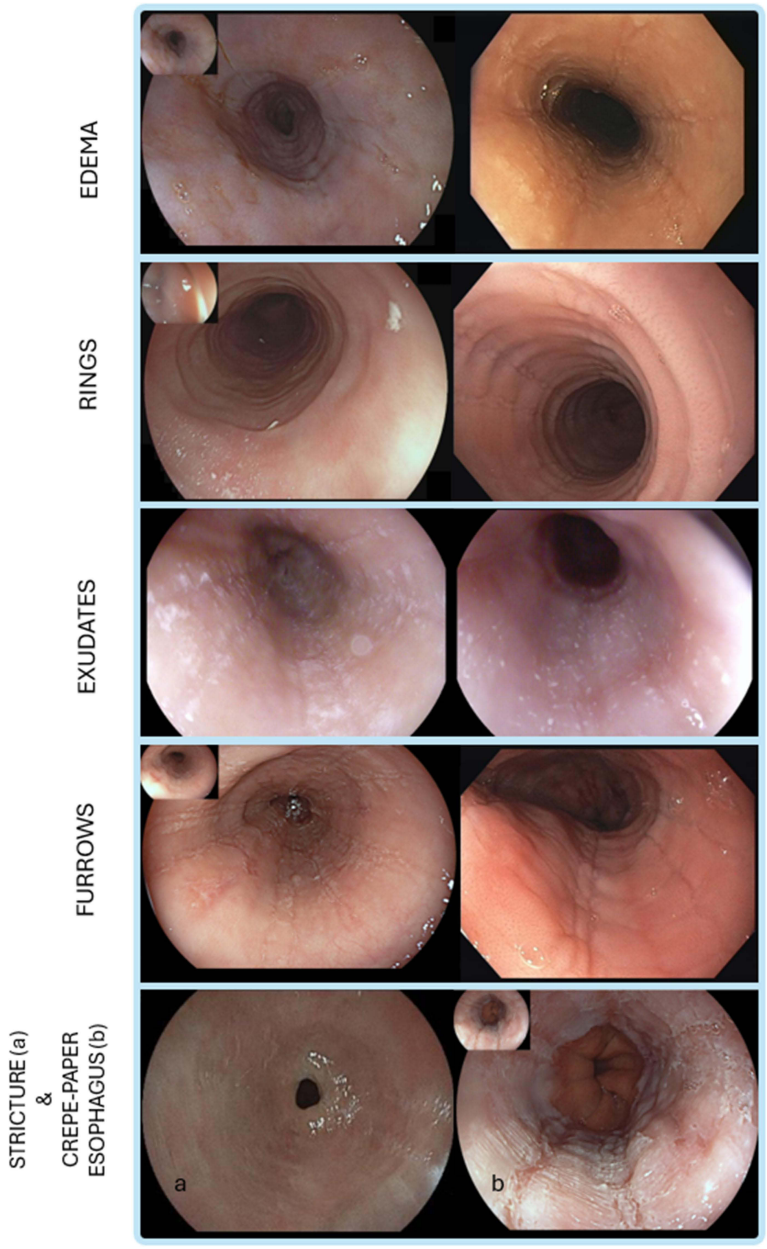

Figure 1 Examples of the different components of the EoE endoscopic reference score. Edema refers to the loss of normal vascular markings on the esophageal surface. Rings are circumferential ridges that are not modified by esophageal peristalsis. Exudates are white spots on the esophageal mucosa. Furrows are longitudinal red lines with variable depth. Stricture is a discrete luminal narrowing that may be non-negotiable with the endoscope (bottom left **a**). Crepe-paper esophagus refers to the frail and whitish appearance of the esophageal mucosa, similar to that of crepe-paper (bottom right **b**).

linear furrows and normal appearing mucosa were not commonly associated with >15 eos/HPF. Interestingly, rings alone, in the absence of linear furrows or white exudates were found in both histologically active and inactive EoE patients.[68] It must be noted, however, that approximately 11% of EoE cases present with a normal esophagus.[66] Accordingly, a metanalysis on 4678 EoE patients reported a low sensitivity (ranging 15–48%) and sub-optimal specificity (ranging 90–95%) of endoscopic features in the differential diagnosis of EoE.[69] Other non-validated endoscopic signs of EoE include the "tug-sign"[70] and the "pull sign",[71] that is the feeling of substantial resistance when pulling on the forceps to remove the biopsy sample in EoE compared to non-EoE patients, as well as the Ankylosaurus back sign,[72] that is a linear arrangement of pale nodules with the appearance of the back of an Ankylosaurus dinosaur. A prospective cohort study on 83 EoE patients and 121

controls demonstrated that the pull-sign had 98% specificity and 97% positive predictive value for a diagnosis of EoE,[71] while a retrospective study showed that the Ankylosaurus back sign, when present, was associated with erosive esophagitis in PPI-responsive EoE.[72]

More recently, advanced imaging techniques have been used to improve the diagnostic yield of the endoscopic assessment of EoE. In a retrospective study on 189 patients referred for upper endoscopy for dysphagia or food bolus impaction, a high-definition virtual chromoendoscopy system (ie, iSCAN; Pentax EC-3490Fi; Pentax, Tokyo, Japan), could predict a histologically confirmed diagnosis of EoE with sensitivity of 97.6% and specificity of 89.5%.[73] In another study, magnifying endoscopy with narrow-band imaging (ME-NBI) was used to assess NBI signs of EoE. The investigators found that the absence of sub-mucosal vascularity (absent cyan vessels), the presence of beige-coloured mucosa and dot-shaped intra-papillary capillary loops was significantly more prevalent in histologically confirmed EoE and lymphocytic esophagitis compared to GERD.[74] However, it must be noted that larger prospective studies are needed to validate the utility of advanced endoscopic imaging in the setting of EoE.

The EREFS score has proven utility also in the monitoring of response to treatments in EoE. Several RCTs have reported a significant reduction of EREFS scores in treatment responders compared to non-responders.[3] Accordingly, a recent post-hoc analysis of a comparative RCT between slurry budesonide and oral fluticasone therapy identified an EREFS score of 2 or less as a threshold to determine endoscopic response in EoE.[75]

Treatment of Eosinophilic Esophagitis Using Licensed Drugs

EoE is a relatively young disease, and despite a large amount of RCTs investigating EoE-specific drugs,[9] budesonide orally disintegrating tablet (BOT) and dupilumab are the only drugs currently approved for the treatment of EoE in Europe,[76,77] while budesonide oral suspension (BOS) and dupilumab represent the only approved drugs for EoE in the United States.[78,79] In an RCT on 88 patients with EoE, BOT 1 mg twice daily showed efficacy as an induction of remission treatment for active EoE, with 57.6% of patients taking the active drug achieving clinical and histological remission compared to 0% of those in the placebo group ($p<0.0001$).[80] Subsequently, in a maintenance of remission study, both BOT 1 mg and 0.5 mg twice daily maintained persistent remission in 75.0% and 73.5% of patients, respectively, at week 48, compared to 4.4% of patients in the placebo group ($P < 0$ 0.001 for both comparisons).[81] More recently, in an RCT on 318 patients with EoE, BOS 2 mg twice daily achieved significantly higher rates of histological and clinical remission compared to placebo (53.1% vs 1.0%; $p<0.001$ and 52.6% vs 39.1%, $p=0.2$, respectively) after 12 weeks of treatment.[82] In addition, in a randomized withdrawal study where EoE patients in remission were randomized to continue BOS 2 mg daily or placebo, significantly more patients taking active drug maintained clinical and histological remission at week 36 (83.3 vs 50.0%, respectively; $p=0.03$).[83] Similarly, in another RCT on 81 patients with EoE, dupilumab 300 mg once weekly demonstrated superiority compared to placebo, with 60.0% of patients taking the active drug achieving histological remission after 24 weeks of treatment compared to 5% of patients taking placebo ($p<0.001$). In addition, dupilumab also proved efficacy in the maintenance of remission in EoE, since results observed at week 24 of treatment were maintained or even improved at week 52.[84] A recent network meta-analysis confirmed that all approved drugs are more efficacious for the induction of remission and have a comparable safety profile compared to placebo in patients with EoE.[3] Among approved drugs, BOT 1mg twice daily, dupilumab 300 mg weekly, and BOS 1mg twice daily or 2mg twice daily were significantly more efficacious than placebo for achieving histological remission defined as <15 eos/HPF. In terms of symptoms improvement, BOT 1mg twice daily and BOS 2mg twice daily were significantly more efficacious than placebo. With regards to improvement of endoscopy findings based on the EREFS score, BOT 1mg twice daily, and BOS 1mg twice daily or 2mg twice daily ranked first and second, while dupilumab could not be included in the analysis because the data reported in the trial were non-extractable.[3] Despite these data confirm that all licenced drugs are effective in patients with EoE, it must be noted that the trials included in the network meta-analysis had significant heterogeneity in eligibility criteria and assessment instruments, hampering the establishment of a hierarchy to inform a therapeutic algorithm in active EoE. Recent guidelines have recommended both topical corticosteroids and dupilumab as possible first-line treatments based on treatment efficacy, although topical steroids may be prioritized because of lower costs. However, according to patient-specific

clinical scenarios, especially in case of Th-2-mediated comorbidities amenable of dupilumab treatment such as asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyps, dupilumab may also be considered a first-line treatment.[11]

Treatment of Eosinophilic Esophagitis Using off-Label Drugs

Historical off-label treatments for EoE include PPIs and aerosolized/swallowed topical steroids originally designed for the treatment of asthma. PPIs can reduce the inflammatory burden of EoE via two main mechanisms: one is the reduction of the acid refluxate, which favors the restoration of the mucosal barrier and limits environmental allergens exposure;[17,85,86] the other is the reduction of eotaxin-3 levels, an eosinophil chemoattractant.[87] In an early meta-analysis of mostly retrospective observational studies, although there was a significant publication bias in favour of studies reporting histologic responses to PPIs, PPIs were found to be useful for the induction of histological remission and clinical response in up to 50.5% and 60.8% of patients, respectively. Of note, twice daily administration of full-dose PPIs may achieve better outcomes compared to lower doses, and patients with a stricturing phenotype may respond less to PPIs.[88] These early findings were recently confirmed in a more recent European multi-centre population-based study conducted on 630 patients with EoE, in which PPIs achieved histological remission in 48.8% and decreased symptom scores in 71% of patients.[89] Importantly, in a recent study on 305 patients with EoE, it has been shown that twice-daily PPI dosing can achieve better outcomes compared to once-daily dosing regardless of total daily dose. In particular, omeprazole 20mg twice daily achieved significantly better outcomes compared to omeprazole 40mg once daily, with 52.8% vs 10.0% of patients achieving histological response, respectively.[90] In addition, PPIs could also be of use for maintaining histological remission in patients who are intolerant to or develop adverse events under topical steroid treatment.[86] Off-label topical steroids include aerosolized and subsequently swallowed budesonide or fluticasone. Administered doses of fluticasone usually vary between 880 and 1760 mcg/day for induction and 440–880 mcg/day for maintenance of remission, while for budesonide a dose of 2 mg/day and 1mg/day is usually employed for induction and maintenance of remission, respectively.[1] In a recent multi-centre population-based study conducted on 866 patients, doses ≥800 mcg/day achieved combined clinical and histological remission in 65% of patients.[91] Despite having shown utility in patients with EoE, off-label topical steroids are significantly less efficacious than approved EoE treatments based on a recent network meta-analysis.[3] Based on available evidence, current guidelines suggest that PPIs may be preferred in patients with concomitant GERD-like symptoms and that the use of off-label topical steroids should be limited to settings where other options are not available.[11] However, it must be noted that, due to lower costs, PPIs may still represent a first-line treatment in resource-limited settings, especially in mild disease phenotypes without esophageal stricturing or in cases with overlapping GERD symptoms.

Dietary Treatment of Eosinophilic Esophagitis

Seminal reports have demonstrated that food allergens trigger the inflammatory cascade of EoE, and that food avoidance can lead to histological remission.[29,92,93] The most common foods that are responsible for triggering an eosinophil-predominant inflammation in patients with EoE are dairy/milk, wheat/gluten, egg, soy/legumes, and seafood.[94] Accordingly, a possible treatment for EoE consists in the elimination of specific foods or groups of foods from the diet. Available dietary regimens include elemental diets and empirical elimination diets, while allergy tests-directed elimination diets are not superior to empiric elimination diets,[95] and are currently not recommended by clinical guidelines.[11,63] Elemental diets involve feeding with amino-acidic-based formulas while avoiding all kinds of table foods. Although elemental diets can be efficacious in more than 90% of patients, the complete restriction of food and poor palatability hamper their routine use in clinical practice.[96] Historical empiric dietary regimens were designed with a top-down approach and started with an initial large food restriction (ie, six-food elimination diet, SFED) followed by sequential reintroductions of foods with endoscopic assessment at each reintroduction. In contrast, the novel step-up strategy involves starting from the least restrictive regimen followed by sequential restrictions based on the histological response.[97] The step-up design has proven to be more cost-effective and should be preferred when initiating elimination diets.[11,98] An early study on 131 patients undergoing elimination diet showed that a two-, four-, and six-food elimination diet (TFED, FFED, SFED), could achieve histological remission in up to 43%, 60%, and 79% of patients, respectively.[98]

A recent meta-analysis expanded early results, and showed that a one food elimination diet (OFED), TFED, FFED, and SFED could achieve histological remission in up to 51.4%, 45.7%, 49.4%, and 53.8% of patients, respectively.[99] More recently, an RCT on 129 patients with EoE found no difference in a milk-free dietary regimen compared to a SFED in terms of induction of histological remission (34% vs 40%, p=0.58),[4] corroborating that minimal restrictions and possible subsequent larger restrictions should be preferred in clinical practice.

The avoidance of trigger foods currently remains the only option targeting the cause, and not the effect, of the disease, and virtually represents a drug-free alternative to treat the disease. Food elimination diets are currently considered one of the possible first-line treatments for EoE, although they require the patient to be strongly motivated to ensure adherence. In this regard, to implement the use of dietary regimens in clinical practice, a rigorous management plan should be defined prior to starting the diet and should involve counselling on possible increased costs for shopping and negative impact on quality of life, as well as a professional dietitian to provide personalized education and tailor a nutritionally balanced and palatable diet.

On a final note, it must be acknowledged that the efficacy of elimination diets can be decreased by the unavoidable inhalation of aeroallergens during the pollen season in sensitized patients,[17] and that lack of long-term compliance represents a cause of treatment failure.[97,100]

Endoscopic Treatment of EoE

Untreated EoE progresses to fibrostenosis and esophageal remodeling with a reduction of the esophageal caliber, increasing the risk of food impaction.[25] Fibrostenosis is characterized endoscopically by esophageal rings, luminal narrowing, and strictures.[101] In this setting, endoscopy provides critical information to guide treatment and a barium esophagogram may complement endoscopy by increasing the yield for narrow-caliber esophagi and subtle strictures that may be missed at endoscopy.[102,103] In a recent Delphi consensus, an esophageal diameter of at least 16 mm was identified as the target threshold for the prevention of food impaction episodes.[10] Endoscopic dilatation (ED) is the standard of care in fibrostenotic EoE. ED in EoE can be safely performed using either pneumatic balloons or bougies.[104] Although recent meta-analysis reported no significant differences between the two techniques, bougies may be more practical to use in patients with severe and long strictures, while pneumatic balloons may be more viable for short strictures.[105] Savary bougies do not necessarily need fluoroscopy and provide a tactile sensation to the endoscopist that helps gauging the caliber and resistance of the stricture. In addition, bougies allow to dilate the entire lumen of the esophagus in patients with a narrow-caliber esophagus. Through-The-Scope (TTS) pneumatic balloon catheters are effective in the management of short strictures and allow to inspect the mucosa trauma in real-time during the procedure (Figure 2). However, TTS pneumatic balloon catheters can also be used to perform a panesophageal ED using the pull-through technique, that is retrieving the pneumatic balloon slowly and carefully following inflation.[106] Recently, a novel dilator device, the BougieCap (Ovesco Endoscopy AG, Tübingen, Germany) has been tested in patients with EoE.[107] The BougieCap is a single-use, dome-shaped, transparent hard plastic cap that is attached to the endoscope tip. In a prospective study on 57 patients, the ED with the BougieCap was technically effective in 100% of patients, although in one case the cap detached in the hypopharynx and had to be subsequently retrieved.[107] Regardless of the device and technique used for dilating EoE patients, a careful step-up approach with a "start low, go slow" method is advisable, usually with a maximum increase of 3 mm from initial diameter within the same session until a clear mucosal tear is observed.[108,109]

According to a meta-analysis of 27 studies, the efficacy of ED in EoE patients is high, with clinical improvement occurring in up to 95% (95% CI: 90%–98%, I2: 10%, 17 studies) of patients, while the safety profile is good, with perforations, bleeding, and hospitalisation occurring in 0.38% (95% CI: 0.18%–0.85%, I^2: 0%, 27 studies), 0.05% (95% CI: 0%–0.3%, I^2: 0%, 18 studies), and 0.67% (95% CI: 0.3%–1.1%, I^2: 44%, 24 studies) of patients, respectively.[110] ED is particularly effective in controlling persistent dysphagia in fibrostenotic EoE patients with strictures or narrowed esophageal lumen but has no anti-inflammatory effect on esophageal eosinophilic infiltrates.[103,111] In this regard, esophageal inflammation should be effectively treated before and following ED since this is associated with a decreased need for subsequent dilatations, healthcare costs, and improved quality of life.[112] A recent expert consensus agreed on the safety of performing ED to improve dysphagia in histologically

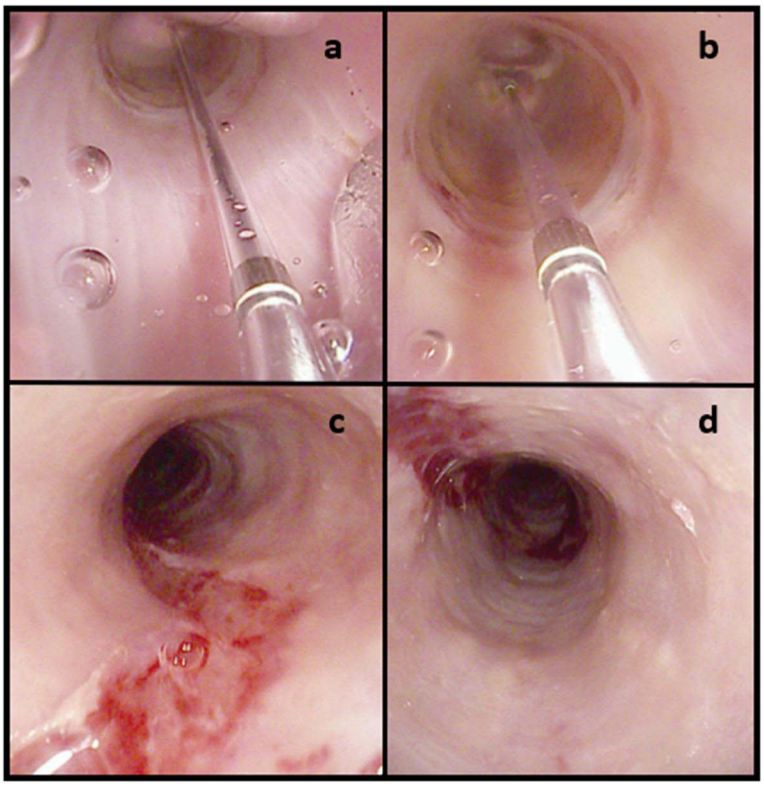

Figure 2 (**a** and **b**) Endoscopic dilatation with through-The-scope pneumatic balloon of a distal esophageal ring; panels (**c** and **d**) mucosal trauma after Savary dilatation in a narrow-caliber esophagus. In (**a** and **b**), the transparent pneumatic balloon is filled with saline and inflated, which allows to exert a radial pressure and obtain the dilatation of the esophageal stricture. (**c** and **d**) show the mucosal tear that results from the dilatation of the stricture. This is the intended outcome when performing stricture dilatations.

active EoE patients.[103] However, when clinically viable, it seems reasonable to achieve histological remission before performing ED in patients with EoE.[11] On a final note, Safroneeva et al found that ED modifies the association between symptoms and esophageal eosinophilia (eos/HPF)[113] and that such effect of ED can last longer than one year,[16] making the absence of symptoms less reliable for the assessment of histological disease activity in such patients.

Current Monitoring Strategies in Eosinophilic Esophagitis

The optimal assessment of long-term treatment response in EoE is multifaceted, encompassing the evaluation of endoscopic and histological findings, symptoms, and psychological aspects to accurately determine disease status and consider potential adjustments to therapy.[114] Recently, Von Arnim et al[10] provided international expert recommendations on long-term monitoring of EoE. The consensus group agreed on the need for a regular clinical follow-up of patients with EoE to ensure treatment compliance and monitor side effects. With regards to timing, the authors proposed that EoE patients with a confirmed clinical and histological remission should receive a clinical follow-up visit 12–24 months after the last endoscopy and that follow-up surveillance endoscopy could be performed 12–24 months after the last endoscopy in patients with a stable disease. Such recommendations were based on retrospective data showing that a gap in care longer than two years was associated with progression to fibrostenosis.[32] However, the optimal timing for patients monitoring is yet to be established. Several studies have shown that symptoms have modest accuracy for predicting histological response in EoE,[14] possibly because of confounding factors including symptom-specific anxiety and esophageal dysmotility.[19,20] Moreover, the EREFS score has proven sub-optimal responsiveness to histologic improvements and should not be used as the sole indicator of disease status in EoE.[115,116] In addition, despite increasing research on the topic, there are currently no validated non-invasive or minimally invasive biomarkers to monitor treatment

response in EoE.[117] Accordingly, endoscopy with biopsy, conducted 8–12 weeks after any treatment modification, is currently considered the benchmark for monitoring EoE, although robust evidence on the optimal timing is still lacking.[11,63] Therefore, regardless of endoscopic findings and symptoms, treatment response in EoE should always rely primarily on histological findings.[11] In this regard, treatments aim to reduce eosinophil counts below 15/HPF. However, this threshold is somewhat arbitrary, and recent studies suggest that even lower levels of eosinophils may be associated with ongoing disease activity.[118] More recently, the EoE histology scoring system (EoEHSS) has been introduced to improve the assessment of typical EoE histology findings beyond peak eosinophil counts per HPF.[119] The critical role of a comprehensive histologic analysis is underscored by the association of persistent symptoms with specific histologic features like basal cell hyperplasia despite low eosinophil counts.[120] In addition, the EoEHSS has shown excellent agreement between pathologists, can discriminate treated from untreated EoE patients better than the peak eosinophil count, and correlates with symptom scores of EoE.[121] Therefore, we feel that a thorough histological examination is pivotal to guide treatment adjustments, with the aim of achieving the minimal eosinophil presence and improvement of adjunctive histological findings to ensure disease remission.

A significant limitation of esophageal biopsy specimens is the inability to comprehensively capture the esophageal epithelium, as they often contain a minimal amount of the submucosa, including the lamina propria and muscularis.[122] In response to this challenge, esophageal panometry with FLIP has been introduced as an innovative tool for assessing esophageal distensibility/compliance and contractile response to distension, offering insights into the structural integrity and mechanical properties of the esophageal wall. FLIP could thus serve as an objective measure of structural changes in the esophagus, and the monitoring of changes in esophageal distensibility before and after treatment can help to evaluate the structural response to therapy, complementing histological and symptomatic assessments.[23]

While histological improvement is central, the correlation between eosinophil counts and patient symptoms is still imperfect. In fact, many patients report symptom resolution even when histological findings do not fully support this improvement.[15] Conversely, some patients continue to experience symptoms despite histological remission.[123] This discrepancy highlights the importance of incorporating PRO measures into the treatment response assessment, which could provide a quantitative measure of symptom severity and a subjective response to treatment.[124] PRO measures complement histological findings in EoE, and prompt clinicians to tailor therapeutic approaches. Indeed, despite the availability of validated PRO tools for adults with EoE (ie, DSQ, EEsAI), a comprehensive symptomatic management strategy is still missing.[125] Recently, Dellon et al developed the Index of Severity for Eosinophilic Esophagitis (I-SEE).[126] The I-SEE assesses three domains including symptoms and complications, inflammatory features (at endoscopy and histology), and fibrostenotic features (at endoscopy and histology). The score assesses the severity of EoE using a point scale of 0–6 for mild, 7–14 for moderate, and ≥15 for severe, and has recently been shown to decrease following successful treatment in adult EoE patients.[127]

EoE affects not only physical health but also significantly impacts psychological well-being, causing symptom-specific anxiety and esophageal hypervigilance, especially related to eating and fear of food impaction.[19] Anxiety and hypervigilance in EoE can be assessed using the validated esophageal and hypervigilance anxiety scale (EHAS).[38] Psychological factors of EoE patients can worsen symptoms or affect their perceived severity. Research by Carlson et al showed these factors predict dysphagia severity, highlighting the need for psychological evaluations in treatment assessment using tools such as the EHAS.[128] Recently, McCann et al validated a novel PRO tool, name EOE impact questionnaire (EoE-IQ), that measures health-related quality of life in patients with EoE.[129] The EoE-IQ contains 11 items that evaluate the impact of EoE on emotional functioning, social impact, school or work impact, and sleep disruption. The questionnaire has been shown to correlate with clinical and endoscopy outcome measures in patients with EoE.[129] In adult patients, health-related quality of life can be assessed using the EoO-QOL-A,[130] a valid and reliable disease-specific tool which includes five main domains: Eating/Diet Impact, Social Impact, Emotional Impact, Disease Anxiety, and Choking Anxiety. This questionnaire has demonstrated excellent internal consistency and test–retest reliability. However, its length and the fact that it has been validated only in English and Spanish have limited its use in clinical practice. For pediatric patients, the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS v2.0) is another validated PRO

questionnaire.[131] It comprises 20 items that measure four domains of EoE-specific symptoms: dysphagia, GERD, nausea/vomiting, and pain. The score ranges from 0 to 100 and aligns with clinical symptoms and histopathologic severity.

The assessment of esophageal hypervigilance, anxiety, and quality of life in EoE helps to identify conditioned responses that affect the gut-brain interaction, especially in patients with persistent symptoms or those reintroducing foods post-elimination diet.[19] Accordingly, an increased awareness of neurogastroenterology and disorders of gut–brain interaction is important in the setting of EoE.[132] Integrating psychological support and cognitive-behavioural techniques can enhance treatment success and adherence. In this regard, patients often adopt dietary and lifestyle changes to manage EoE, impacting their nutrition and quality of life,[133] emphasizing the importance of comprehensive strategies that include dietary, nutritional, and psychosocial evaluations to fully address the complexity of EoE.

Conclusion

EoE is a complex condition with histological, symptomatic, endoscopic, and psychological aspects that should be addressed by clinicians to optimally manage the condition. In this review, we summarized established and novel assessment tools that should be implemented in clinical practice to optimize care and improve patients' outcomes. We also provided an overview of available licensed and off-label drug treatments, most recent dietary strategies, and ED strategies. In Figure 3 we provide a summary of available tools for an optimal assessment and management of patients with EoE. Given the increasing incidence of the disease in parallel with the advent of new drugs for its treatment, a standardised and shared approach is highly recommended to improve the clinical management of EoE.

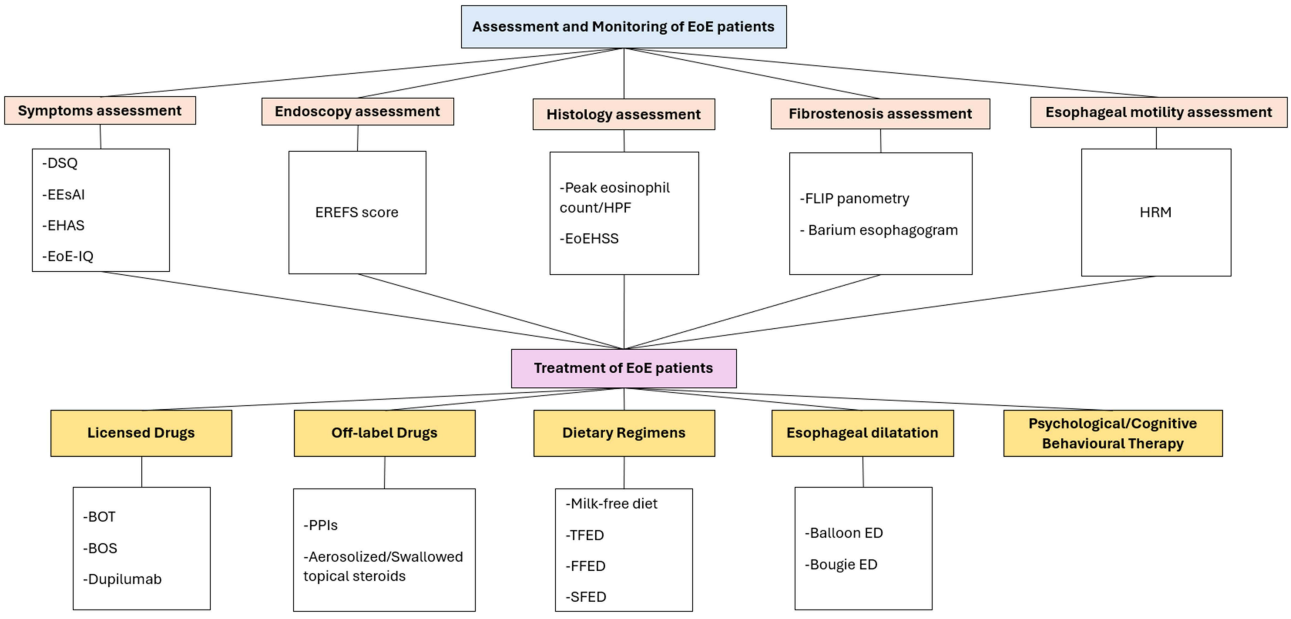

Figure 3 Summary of optimal assessment and management of patients with EoE shows the summary of available options to improve the assessment, monitoring, and treatment of patients with EoE.

Abbreviations: EoE, eosinophilic esophagitis; DSQ, dysphagia symptom questionnaire; EEsAI, eosinophilic esophagitis activity index; EHAS, esophageal hypervigilance and anxiety scale; EoE-IQ, eosinophilic esophagitis impact questionnaire; EREFS, EoE endoscopic reference score (edema, rings, exudates, furrows, stricture); HPF, high-power field; EoEHSS, EoE histology scoring system; FLIP, functional lumen imaging probe; HRM, high-resolution manometry; BOT, budesonide orally disintegrating tablet; BOS, budesonide oral suspension; PPIs, proton pump inhibitors; TFED, two-food elimination diet; FFED, four food elimination diet; SFED, six-food elimination diet; ED, esophageal dilatation.

Data Sharing Statement

No additional data available.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Guarantor of the article: Edoardo V. Savarino. Pierfrancesco Visaggi and Matteo Ghisa joint first authorship.

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