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# Eosinophilic esophagitis: latest insights from diagnosis to therapy

Alain Schoepfer,[1] Carine Blanchard,[2] Heather Dawson,[3] Alfredo Lucendo,[4] Aurelio Mauro,[5] Camillo Ribi,[6] Ekaterina Safroneeva,[7] Edoardo V. Savarino,[8] and Roberto Penagini[5]

[1]Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois/CHUV and University of Lausanne (UNIL), Lausanne, Switzerland. [2]Nestlé Research Center, Vevey, Switzerland. [3]Institute of Pathology, University of Bern, Bern, Switzerland. [4]Department of Gastoenterology, Hospital General de Tomelloso, Tomelloso, Ciudad Real, Spain. [5]Division of Gastroenterology, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi of Milan, Fondazione IRCCS Cà Granda – Ospedale Maggiore Policlinico, Milan, Italy. [6]Division of Allergy and Clinical Immunology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. [7]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [8]Division of Gastroenterology, Department of Surgery, Oncology and Gastroenterology – DiSCOG, Azienza Ospedaliera di Padova, Padova, Italy

Address for correspondence: Alain Schoepfer, M.D., Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois/CHUV and University of Lausanne (UNIL), Rue de Bugnon 44, 07/2409, 1011 Lausanne, Switzerland. alain.schoepfer@chuv.ch

**Eosinophilic esophagitis (EoE) represents a chronic, local immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. Other systemic and local causes of esophageal eosinophilia should be excluded. Clinical manifestations or pathologic data should not be interpreted in isolation. EoE was first described as a distinct disease entity in 1993. Most patients are diagnosed with underlying food allergies. The first diagnostic and therapeutic guidelines were published in 2007 with a first update in 2011. In 2017, new international guidelines were published based on the GRADE methodology. These guidelines provide, among many other topics, insights on the role of proton pump inhibitor-responsive esophageal eosinophilia. Over the last two decades, considerable progress was made by stakeholders regarding the understanding of EoE's pathogenesis, genetic background, natural history, allergy workup, standardization of assessment of disease activity, evaluation of minimally invasive diagnostic tools, and new therapeutic approaches. This brief review provides further insights into latest diagnostic and therapeutic advances.**

**Keywords:** eosinophilic esophagitis; proton pump inhibitor-responsive esophageal eosinophilia; food allergy; dysphagia; guidelines; patient-reported outcomes

## Introduction

Eosinophilic esophagitis (EoE) was first described as distinct entity in the early 1990s, independently by Attwood and Straumann.[1,2] Current incidence rates of about one new patient in 10,000 inhabitants per year and current prevalence rates of approximately one patient per 2000 inhabitants have been reported in industrialized countries.[3–9] A group of international EoE experts published in 2007 the first consensus definition.[10] In the updated 2011 version, EoE was defined as "a chronic, immune/antigen-mediated, esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation."[11] Of note, other conditions associated with esophageal eosinophilia should be excluded before EoE can be diagnosed.[12] The EoE guidelines of the pediatric gastroenterologists (ESPGHAN) closely followed the 2011 guidelines.[13] Guidelines were updated for the third time in 2017 by an international group that consisted of gastroenterologists, allergists/immunologists, pediatricians, ear-nose and throat surgeons, pathologists, and epidemiologists.[14] Authors used the AGREE II methodology and provided recommendations to 45 clinically relevant questions using the GRADE

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methodology. The following section is going to highlight some key points of the updated 2017 guidelines.

## Key points of updated international guidelines 2017

### *EoE diagnosis*

In the latest guidelines, EoE is defined (statement 1) as "a chronic, local immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically an eosinophil-predominant inflammation." Other systemic causes of local or systemic eosinophilia should be excluded. Clinical manifestations or pathologic data should not be interpreted in isolation. Of note, the 2017 guidelines no longer contain the proton pump inhibitor (PPI) trial that was considered necessary in the 2011 guidelines to distinguish EoE from gastro-esophageal reflux disease (GERD). In the 2011 guidelines, only patients unresponsive to PPI (or alternatively patients with a normal pH-metric study) could be diagnosed with EoE. This statement was based on the assumption that only GERD could respond to the acid-suppressive effect of PPI and that GERD and EoE were mutually exclusive disorders. This view has clearly changed with the recognition of the existence of "PPI-responsive esophageal eosinophilia (PPI-REE)" that was first described in 2011.[15] The term PPI-REE describes patients with clinical, endoscopic, histologic, and genetic features that are indistinguishable from EoE patients who experience a significant clinical and histologic improvement when put under PPI (single or double standard dose) for 8 weeks that is not related with underlying GERD.[16] Of note, no other disease entity than PPI-REE is defined on the basis of a response to particular drug. As such, the major change in the updated 2017 guidelines is the retraction of the term "PPI-REE" and the consideration of PPI therapy not as a diagnostic criterion for EoE but rather as a therapeutic agent. As such, the updated 2017 guidelines consider that clinical and histologic features of EoE may improve upon treatment with either PPI, swallowed topical corticosteroids (STCs), or elimination diets. As it is still unknown if the esophageal immune response in patients responding to PPI is triggered by GERD, food antigens, or the combination of both factors, the term "antigen" has been removed from the definition.

### *Noninvasive and semi-invasive tools to monitor EoE*

The relationship between symptoms in EoE and endoscopic and/or histologic activity is weak.[17] In one third of adult EoE patients in clinical remission, there is ongoing endoscopic and/or histologic activity.[18] Ongoing biologic activity is associated with esophageal remodeling and consecutive stricture formation which represent the main risk factors for long-lasting food bolus impactions that necessitate endoscopic removal.[19,20] Unfortunately, as of yet, no biomarker in blood or feces has been detected that would mirror the esophageal inflammatory activity. As such, EoE patients will have to undergo periodic endoscopic evaluation to monitor disease activity. New and innovative tools to monitor inflammatory activity of EoE include the esophageal string test and the esophageal sponge test.[21,22] Using the esophageal string test, eosinophilic granular proteins can be determined in the supernatant which correlate well with esophageal peak eosinophil counts. The esophageal sponge provides small tissue samples. The determination of esophageal peak eosinophil counts acquired by the sponge correlates well with standard esophageal biopsies. While both techniques represent attractive, minimally invasive tools to monitor the inflammatory activity of EoE, particularly in the pediatric population, they still need validation in larger patient cohorts.

As the potential interactions between EoE, GERD, and PPI are complex, the next section will provide further insights into this controversially discussed topic.

## Interaction between EoE, gastro-esophageal reflux disease, and PPI

Knowledge of the relationship between GERD, EoE, and response to PPIs is rapidly evolving. In 2007, the first Consensus Guidelines considered EoE and GERD to represent two mutually exclusive conditions.[10] The 2011 guidelines took into account that EoE and GERD can coexist in the same patient and that there exists an entity with clinical, endoscopic, and histopathology features similar to EoE that responded to PPIs, the so-called "PPI-REE".[12] Initially, this entity was considered to be outside of the spectrum of EoE.[11,23] In the following years, it was appreciated that PPI-REE and EoE also shared pathophysiological and genetic characteristics. Therefore, the 2017 guidelines

suggested that PPI-REE lies within the EoE spectrum.[14,24]

Let us review the evidence for these similarities between EoE and PPI-REE. From a clinical point of view in both conditions, almost every patient suffers from dysphagia and quite frequently from food impaction. Reflux symptoms are present in about one third of patients with EoE and PPI-REE, respectively.[25,26] However, Savarino *et al.* showed that PPI-REE has more frequently clinical, endoscopic, and manometric features similar to those of GERD patients.[27] Furthermore, Podboy *et al.* have suggested that EoE patients have earlier onset of symptoms (29 versus 38 years), and, using x-ray barium swallow (which is more sensitive than endoscopy in order to detect a decrease in wall compliance), that they have more frequently long strictures (>8 cm, 51% versus 18% of patients), and a trend toward developing these long segment strictures after 20 years of dysphagia duration (73% versus 30%).[28] Regarding the classical endoscopic features, PPI-REE shows no difference from EoE.[25,26] As far as histopathology is concerned, the peak eosinophil count both in the proximal and distal esophagus is similar in the two conditions together with other features, that is, superficial distribution, degranulation, microabscess formation and, when lamina propria was present in biopsies, also subepithelial fibrosis.[25,26] Furthermore, gene expression of $T_H2$ immune biomarkers (interleukin-5 [IL-5] and IL-13) and of allergic inflammatory mediators (Eotaxin-3) was the same both in proximal and distal esophagus biopsies, with the exception of higher expression of IL-5 gene in proximal biopsies of EoE.[29] Recently, an EoE diagnostic gene panel has been developed.[30] When this panel was tested in PPI-REE patients before PPIs treatment, dysregulation was similar in the majority of these genes (around 80%).[30] These results have been recently replicated in Japan.[31]

Several groups have accumulated data that suggest that EoE and PPI-REE are part of the same disease. The effects of PPIs on esophageal inflammation, gene expression, and mucosal integrity in patients with PPI-REE are similar to the responses seen with topical steroids or diet therapy in patients with EoE.[32–34] Further evidence was added by the observation that some patients responded both to PPIs and either topical steroids or diet therapy prescribed on a different occasion.[35,36] Most of the available evidence in the literature has been obtained in adults. One group of pediatricians working at the Children Hospital of Philadelphia objects to the inclusion of PPI-REE within the EoE spectrum and suggests that they are two distinct entities with the same histopathological endpoint.[37] According to their experience, pediatric patients responding to PPIs were unresponsive to steroids or dietary restrictions. Furthermore, in their opinion, from a practical point of view, pediatric patients with reflux, dysphagia, or presumed EoE may never require endoscopy, thus unnecessary endoscopies would be performed if adhering to the 2017 guidelines. In conclusion, in agreement with the experts of the four European Scientific Societies taking part to the European Guidelines,[14] adult patients achieving clinical and histological remission on PPI therapy are part of the EoE continuum, rather than a separate entity. Responders and nonresponders to PPI therapy show overlapping phenotypic, genetic, and mechanistic features. However, more data are needed in the pediatric population.

## Allergy testing in eosinophilic esophagitis

EoE appears to be related to an atopic predisposition, which is characterized by the production of specific IgE toward common allergens. As of yet, the exact pathophysiology of EoE remains poorly understood. Recent studies stress that the mechanisms underlying EoE are similar to those of atopic dermatitis.[38] As in atopic dermatitis, histological changes in the mucosa of EoE patients include hyperplasia of basal layers and papillary elongation, as well as defects in the esophageal epithelial barrier.[39] Disruption of the mucosal barrier function may lead to passage of antigens and activation of innate immune cells, such as invariant NK T cells.[40] Also, several features such as upregulation of the cytokines IL-13[41] and thymic stromal lymphopoietin[42] among others are characteristic of an immune response driven by T helper-2 ($T_H2$) lymphocytes. EoE has long been considered an allergic disease, based on the prominent eosinophilia and $T_H2$ signature in the esophageal mucosa, the epidemiologic association with atopy and other allergic disease, the fact that some patients display positive allergy tests to food allergens and last but not least the success of dietary interventions in a majority of

patients. This section focuses on allergy tests aiming to identify allergic triggers in EoE.

The rationale of allergy testing in EoE is primarily the search for the responsible food allergen, with the aim of defining a more targeted elimination diet. Most of the techniques have focused on testing for IgE-mediated allergy, which is the most common and comprehensive type of hypersensitivity. Skin-prick-tests (SPTs) rely on the application of putative allergens on the subject's intact skin, and then by pricking the skin through the preparation using a hand-held lancet. As in IgE-mediated food allergy, SPT with fresh food is more sensitive than with commercial allergen preparation. SPTs are minimally invasive and relatively inexpensive. SPTs, however, do not accurately assess non-IgE-mediated allergy. Atopy patch tests (ATPs) aim at eliciting delayed responses to food allergens applied directly to the skin surface. ATPs have been primarily developed to test children with atopic dermatitis and food-induced exacerbations, but remain unstandardized to date. In EoE, ATPs have low sensitivity, particularly in adults.[43] One explanation for the poor performance of these tests in EoE may be that allergen penetration into the skin is dependent on the epithelial barrier function. APTs are also quite cumbersome and time-consuming.

In recent years, component-resolved diagnostics (CRD) has improved allergy testing. The technique relies on the detection of sIgE to a single allergen molecule (e.g., α-lactalbumin as a protein component of cow milk). Testing for sIgE to (mostly recombinant) allergen components is more precise, but less sensitive than using an assay to the "whole" allergen source. One prospective study relying on CRD in EoE was stopped prematurely, when 14 of 15 patients tested positive to allergens failed to achieve endoscopic remission after targeted eviction.[32] Interestingly, nine out of 15 (60%) patients tested positive with CRD expressed sIgE to pathogenesis-related plant proteins (PR-10), which are contained in most plant-derived fresh foods and pollens. Hypersensitivity to PR-10 makes a targeted elimination quite impossible and it is therefore possible that the limited sensitivity of CRD is not the only reason for the failure of this study. Total serum IgE is unreliable for allergy diagnosis. *In vitro* basophil activation which also aims at assessing immediate-type hypersensitivity has shown very low sensitivity in EoE.[44] Increased levels

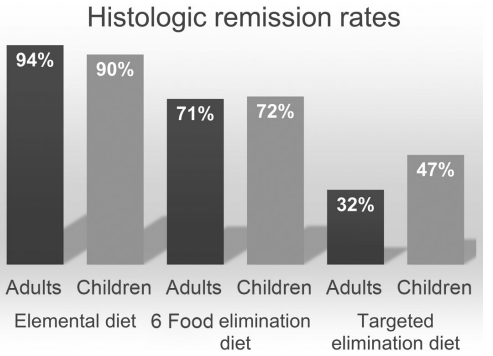


**Figure 1.** **Histologic success rates of food elimination diets in adults and children with eosinophilic esophagitis.**

of food-specific IgG4 were found in the serum and esophageal tissue of patients with EoE, but appeared not to be correlated with disease activity.[45] Also, measurement of food-specific IgG4 failed to predict food triggers in EoE.[45] Testing for specific IgG4 in allergic diseases is controversial, as expression of such antibodies to food allergens is common and an increase in titers is usually observed during tolerance induction.[46] Table 1 lists the studies that have examined the predictive value of allergy tests to predict food triggers in children and adults with EoE.[32,44,47–50] Figure 1 shows histologic remission rates in adults and children with EoE achieved by three common dietary strategies (elemental diet, 6-food elimination diet, and targeted elimination diet based on skin testing).[51] The figure shows that targeted elimination diets based on SPT are less effective than empiric elimination diets. Determination of sIgE performs slightly better than SPT or ATP in predicting food triggers in EoE.[49] Some have advocated to check for sIgE to the usual trigger foods milk, wheat, egg, soy/legumes/peanut, tree nuts, fish, and shellfish and perform targeted elimination diet in case of positive test results to one or a few foods.[52] This approach may fail in patients with airborne EoE triggers such as swallowed pollens or pollen-food syndrome. Based on the current performance of allergy tests, others do not recommend targeted elimination diet in EoE.[46] In other non-IgE-mediated food hypersensitivity, endoscopic application of putative triggers such as wheat and milk directly to the digestive mucosa with real-time assessment of intraepithelial lymphocyte recruitment has shown promising results.[53] Whether such techniques are applicable to EoE

**Table 1. Studies that have assessed the value of allergy testing to predict food triggers in patients with eosinophilic esophagitis**

| Reference | Design | Patients | Intervention | Tests | Outcomes | Comment |
|---|---|---|---|---|---|---|
| Gonsalves *et al.*[47] | Prospective | Adult ($n = 20$) | Empiric 6-food elimination diet | SPT | **Food trigger correctly identified in 15%.** | Study over 6 years. Two foods reintroduced at a time. PPI use in some patients. |
| Lucendo *et al.*[48] | Prospective | Adult ($n = 42$) | Empiric 6-food elimination diet | SPT; sIgE | **$\kappa < 0.20$ for SPT and $< 0.38$ for sIgE (any individual food trigger).** SPT and sIgE no more likely to be positive in those responding to elimination compared to nonresponders. | PPI not used. Biopsy of esophagus 6 weeks post food reintroduction. |
| Philpott *et al.*[44] | Prospective | Adult ($n = 20$) | Empiric 6-food elimination diet | SPT; sIgE; APT; BAT | **Food trigger correctly identified in 5%** (milk only). | PPI in all. Sequential food reintroduction and biopsy at 2 weeks following reintroduction. |
| Rodriguez *et al.*[49] | Prospective | Adult ($n = 24$) | sIgE-directed diet versus empiric 6-food elimination diet (only if tested negative) | SPT; sIgE; APT | **Equivalence to empirical (elimination) diet** demonstrated (73% versus 53% with 6-FED). Mean number of foods avoided according to allergy tests ($n = 4$). | Not randomized. Groups according to test results. |
| Spergel *et al.*[50] | Retrospective and comparative | Pediatric ($n = 319$) | Comparative study, SPT + APT versus empiric 6FED ± milk | SPT; APT | **Equivalence to empirical elimination diet** demonstrated. Mean number of foods avoided according to allergy tests ($n = 5$). | Combination results of SPT and APT guide dietary therapy. That is, food excluded if test positive to either. On average, five foods excluded. |
| van Rhijn *et al.*[32] | Prospective | Adult ($n = 15$) | CRD-guided diet | CRD | **Food trigger correctly identified in 6%** (milk only). | Diet failed in 14 of 15 patients in interim analysis: trial abandoned at 8 weeks. |

Abbreviations: APTs, atopy patch tests; BAT, basophil activation test; CRD, component-resolved diagnostics; PPIs, proton pump inhibitors; sIgE, specific immunoglobulin E; SPTs, skin prick tests; 6FED, empiric 6-food elimination diet.

remains to be determined. Also, despite the failure of CRD microarray testing in EoE, more studies are needed to assess the sensitization profile to molecular allergens, in particular with the aim of distinguishing "genuine" food allergens from pollen-plant food cross-reactive triggers.

In conclusion, allergy testing has performed poorly in predicting food triggers in patients with EoE. Most of allergy testing has relied on determining sIgE to food and airborne allergens as in immediate-type hypersensitivity, while recent concepts underline that EoE shares similar features of a delayed-type hypersensitivity with atopic dermatitis. This may account for low sensitivity of IgE testing in EoE. Another major challenge in allergy testing is to distinguish between sensitization, that is, presence of specific immunologic markers of an immune reaction to an allergen without clinical symptoms upon exposure, and hypersensitivity, that is, presence of markers confirming a manifest allergy. Of note, the same controversy applies to atopic dermatitis, where a sensitization to food is frequently found, but with a much lower rate of confirmed food allergy. Standard allergy testing in EoE may be useful to characterize comorbid immediate-type respiratory allergic diseases such allergic rhinitis and asthma and food allergies. These tests may also be considered in selected cases to identify food and swallowed environmental allergens that trigger EoE.

## Treatment endpoints in EoE

There is increasing evidence that long-standing eosinophilic inflammation may lead to esophageal remodeling with consecutive stricture formation which are associated with the feared food bolus impactions that may need endoscopic disimpaction as an emergency procedure.[54,55] While there exist some data that long-term use of STCs reduces the risk for acute food bolus impactions that require endoscopic disimpaction, we still do not know which histologic threshold, expressed as peak eosinophil count/hpf, should be achieved to prevent stricture formation in the long-term run.[56] A recently published cohort study in 351 adult EoE patients showed that only 33 (9.4%) patients achieved a "deep remission" (defined as combined clinical, endoscopic, and histologic remission) under a daily dosage of 0.5 mg STCs.[57] When STCs were stopped in the 33 patients in "deep remission," the majority (81.8%) of patients experienced a clinical relapse after a median of 22.4 weeks.[57] Another challenge in the long-term management of EoE patients is related to the fact that the relationship between EoE-related symptoms and biologic (endoscopic and histologic) activity is only modest. In one third of adult EoE patients in clinical remission, there is still ongoing endoscopic and/or histologic activity to be observed.[18,58] As such, adult EoE patients will still have to undergo repetitive upper endoscopy in order to understand if a particular treatment strategy such as STC or elimination diets are effective regarding the biologic endpoints.

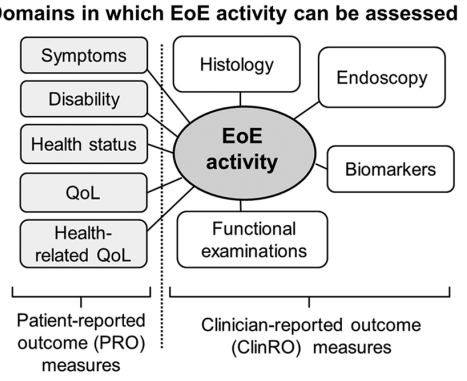


**Figure 2.** **EoE activity can be measured by patient-reported outcome (PRO) measures or clinician-reported outcome (ClinRO) measures. QoL, quality of life.**

Therapeutic endpoints in EoE include symptoms, EoE-related quality of life, histologic, and endoscopic alterations.[59] The term "endpoint" defines a particular therapeutic goal that should be reached. At present, physicians taking care of EoE patients do not have uniform therapy goals which is closely related to the sparse literature on this topic. When assessing the global activity of EoE, gastroenterologists attribute most weight to endoscopic activity and EoE-related symptoms and less weight to histologic alterations.[60] Of note, there is a complete lack of evidence which endpoints EoE patients consider to be clinically relevant.

Major progress has been made over the last decade to standardize the assessment of EoE activity in the domains of patient-reported outcomes (PROs, which include symptoms and quality of life) and biologic (endoscopic and histologic) activity (Fig. 2). EoE-specific and validated instruments are needed to assess EoE activity in the different domains for several reasons. First, they allow to standardize the process of EoE activity measurement and

**Table 2. Proposal for treatment targets in EoE**

| Domain | Treatment targets |
|---|---|
| Symptoms | ○ Asymptomatic patients<br>○ Absence of need of food modification, slow eating, or avoidance strategies |
| Quality of life | ○ Normal EoE-specific quality of life without social impairment |
| Endoscopy | ○ Absence of strictures<br>○ Absence of white exudates and/or furrows |
| Histology | ○ <15 peak eosinophils (to be further evaluated) |

thereby facilitate communication among the different stakeholders (physicians, researchers, patients, and pharmaceutical industry). This standardization will further allow EoE researchers to define clinically meaningful endpoints for use in clinical trials and observational studies. In addition, only by the use of standardized instruments to assess EoE activity, it will be possible to compare the efficacy of different therapeutic modalities such as drugs, elimination diets, or esophageal dilation. As such, the standardization of EoE activity measurement forms the basis for the later development of therapeutic algorithms to provide pediatric and adult EoE patients with the appropriate therapy. Validated instruments are now available to measure EoE-related symptoms and quality of life in adult and pediatric EoE patients.[59] In addition, validated instruments are also used to assess endoscopic and histologic activity.[61,62] Despite the recognition of many gray zones in the determination of clinically relevant endpoints, we would like to propose a working definition for treatment targets in EoE which is shown in Table 2.

In summary, major achievements were made during the last decade to standardize assessment of EoE activity in the domains of PROs and biologic (endoscopic and histologic) activity. While good evidence is lacking to support claims, we propose as working definition for treatment goals in EoE an asymptomatic patient combined with a control of endoscopic and histologic activity.

## Treatment options in eosinophilic esophagitis

EoE is a chronic and progressive disease. When pharmacologic or dietary treatments for EoE are stopped, symptoms and/or esophageal eosinophilia typically recurs over a 3–6-month period.[11] There exist several reasons to treat active EoE. First, to reduce EoE-related symptoms and to improve EoE-related quality of life.[63,64] Second, in the long-term run, to reduce or prevent esophageal remodeling processes that are associated with stricture formation and food bolus impactions.[19,20]

Therapeutic options for EoE include drugs (PPI and STC), food elimination diets (elemental diet, targeted elimination diet, and empiric elimination diet), and esophageal dilation in case of strictures. In addition, several biologic therapies (monoclonal antibodies directed against key cytokines in EoE, e.g., IL-13 and IL-5) have been evaluated or are currently under evaluation. These biologic therapies may prove to be useful for patients failing conventional therapy strategies. Advantages and shortcomings of different therapeutic regimens are summarized in Table 3.[65] The European Medicines Agency just published a press release (mid-November 2017) that they approved budesonide effervescent tablets for treatment of adults with active EoE.[66] As such, this drug will be the first EoE-specific regimen to enter the market in European countries in 2018. The arrival of new compounds is eagerly awaited.

Among nonresponders to PPI who suffer from symptoms related to inflammatory activity, most patients will choose a therapy with STCs and only about 20% of patients will be willing to undergo a food elimination diet.[67] This is related to the fact that the use of STCs is better compatible with the daily lifestyle than food elimination diets which require motivated and disciplined patients. As of yet, there exist no data about the satisfaction of EoE patients regarding different therapeutic options. Such data are urgently needed to tailor individual therapies.

## Outlook

Despite the fact that EoE is considered to be still a "young" and rare disease, considerable progress has been made in a relatively short time interval with respect to our understanding of EoE's pathogenesis, molecular signature, natural history, as well as its endoscopic and histologic features. The assessment of EoE activity in the different domains (PROs and biologic activity) is about to be standardized. Developing and validating standardized EoE-specific instruments to assess disease activity

**Table 3. Assets and limitations of different therapeutic options in EoE**

| Therapy | Assets | Limitations |
|---|---|---|
| Drugs | | |
| - PPI | Effective (in 50% of patients) | No FDA-approved drugs yet on the market |
| - STC | Effective | Limited data on long-term safety |
| - Biologics | No dietary restriction needed<br>Antifibrotic<br>Favorable safety profile | Costs and availability |
| Diets | Nonpharmacologic, effective treatment option<br>Antifibrotic | Repetitive EGDs may be necessary (up to 10×)<br>Needs motivated patient |
| Dilation | Long-lasting symptom improvement | No influence on underlying inflammation<br>Postdilational pain |

Abbreviations: EGD, esophago-gastro-duodenoscopy; PPIs, proton pump inhibitors; STCs, swallowed topical corticosteroids.

represents a joint effort of multiple stakeholders, including physicians, researchers, patients, regulatory authorities, and pharmaceutical industry. This collaborative effort will continue with the ultimate goal to provide pediatric and adult EoE patients with much needed therapies that have undergone qualification review by regulatory authorities.

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## Competing interests

The authors declare no competing interests.

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