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EXPERT REVIEWS

Eosinophilic esophagitis: a practical approach to diagnosis and management

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Eosinophilic esophagitis (EoE) has emerged as a common cause of dysphagia and food impaction in children and adults. A trial of proton pump inhibitor (PPI) therapy is a mandatory diagnostic first step, given that at least one third of patients with suspected EoE will have PPI-responsive esophageal eosinophilia. Once EoE is diagnosed, short-and long-term therapeutic decision making may rely on patient symptoms, phenotype (inflammatory vs fibrostenotic) and preferences. Currently, the most reliable therapeutic targets are mucosal healing and caliber abnormalities resolution. Topical steroids followed by endoscopic dilation are recommended in symptomatic narrow caliber esophagus/strictures, whereas either topical steroids or dietary therapy are good short-term options for mucosal inflammation. Maintenance anti-inflammatory therapy is necessary to prevent esophageal fibrotic remodeling and stricture formation.

KEYWORDS: eosinophilic esophagitis • esophageal stricture • proton pump inhibitor-responsive esophageal eosinophilia • six-food elimination diet • topical steroids

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [1]. Since the first descriptions in the early 1990s [2,3], it has become an emerging cause of esophageal symptoms all over the world, being currently the second cause of esophageal inflammation after gastro-esophageal reflux disease (GERD) and the leading cause of dysphagia and food impaction in children and young adults. Furthermore, its incidence has steadily risen [4] and consistent prevalence rates have been recently reported in Europe and the USA, ranging from 44 to 56 cases per 100,000 inhabitants [5,6], comparable to that of Crohn's disease in western countries.

Major advances in the diagnosis and management of EoE have been accomplished over the last 7-year period, with updated consensus guidelines in 2007, 2011 and 2013 [1,7,8]. The aim of this review is to summarize key considerations for diagnosis and therapy of EoE from a practical standpoint, providing a panoramic view of the disorder regarding diagnostic issues, pharmacological and non-pharmacological treatments and short- and long-term therapeutic targets. Systematic reviews of clinical, endoscopic and histological features along with therapeutic armamentarium have been described elsewhere [1,7–9].

Diagnosing EoE: a stepwise process

Current consensus diagnostic criteria for EoE, including clinical, histological and differential diagnosis issues are summarized in FIGURE 1. All patients with clinical suspicion of EoE should undergo a stepwise diagnostic approach, namely, esophageal biopsies, confirmation of esophageal eosinophilia ≥15 eosinophils/high power field on histology and preclusion of other potential causes of esophageal eosinophilia, especially proton pump inhibitor (PPI)-responsive esophageal eosinophilia (PPI-REE).

Esophageal biopsies should be taken regardless of endoscopic findings: endoscopic findings are not a diagnostic criteria for EoE

Endoscopy with esophageal biopsy remains the only reliable diagnostic test for EoE. Recently, a novel classification has been reported aiming at defining common nomenclature and scoring severity for activity of the disease [10]. Major endoscopic EoE features are rings, furrows, exudates, edema, besides the presence of narrow caliber esophagus, feline esophagus, stricture

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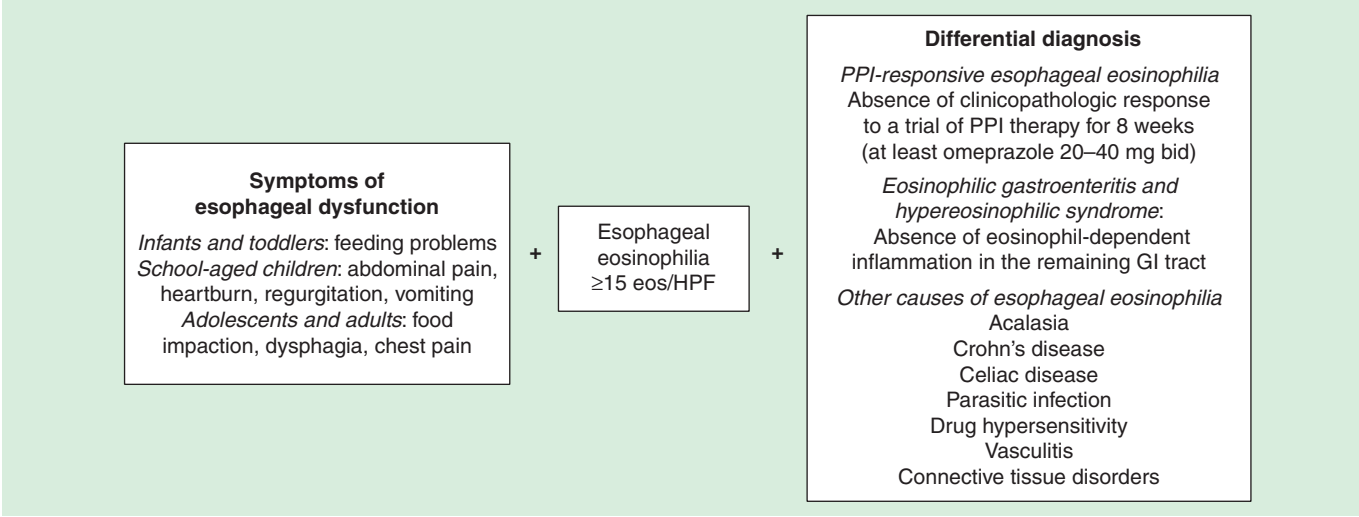

Figure 1. Stepwise diagnostic approach for eosinophilic esophagitis. *Typical endoscopic findings are not a diagnostic criteria for eosinophilic esophagitis.*
PPI: Proton pump inhibitor.
Data taken from [1,2].

and crepe paper esophagus (Figure 2). Nonetheless, these findings are not pathognomonic for EoE and have been described in other esophageal disorders. Conversely, esophageal eosinophilia has been reported in up to 10% of patients with a rigorous normal endoscopic pattern [11]. Furthermore, a recent meta-analysis comprising 100 studies reporting EoE endoscopic features concluded that the sensitivity, specificity and predictive values of endoscopic findings in EoE were insufficient to make diagnostic decisions [11]. As such, clinical suspicion and not endoscopic findings should lead us to esophageal biopsies.

Esophageal biopsies: how many & from where?

Esophageal eosinophilia in EoE is frequently patchy and may vary from distal to proximal esophagus. Subsequently, it has been shown that increasing the number of biopsies increases the diagnostic yield for EoE, so when the number of biopsies reaches 6–9, diagnostic sensitivity approaches 100% [12,13]. Therefore, it is currently recommended taking at least 4–8 biopsies (2–4 biopsies from at least 2 different locations, most typically in the distal and proximal esophagus) [1,8]. It is reasonable to target esophageal biopsies to the areas with abnormal inflammatory findings (i.e., plaques, furrows, cobblestone pattern), since these areas are most likely to have eosinophilic infiltration, biopsying normal appearing areas as well has been recently advocated [14].

In addition to esophageal biopsies, biopsies of the gastric antrum and duodenum should be obtained once in all children to exclude other potential causes of esophageal eosinophilia. There are limited data to support routine gastric or duodenal biopsies in adults in the absence of endoscopic abnormalities or symptoms suggestive of celiac disease or eosinophilic gastroenteritis [1,8].

Histology: esophageal eosinophilia is not diagnostic for EoE either

On examination of biopsy specimens, an eosinophilic infiltrate in the esophageal epithelium with ≥15 eosinophils/high power field suggests the diagnosis of EoE [1,8]. This arbitrary threshold has consistently remained in guidelines as the most important histologic feature for EoE. Similar to clinical symptoms and endoscopic findings, esophageal eosinophilia alone is not diagnostic for EoE, and the biopsy findings must be placed in the clinical context [14].

Ruling out potential causes of esophageal eosinophilia

A plethora of disorders that may present with esophageal eosinophilia is summarized in Figure 1. However, the main differential diagnosis of EoE is by far PPI-REE. As a matter of fact, a PPI trial is currently a mandatory diagnostic criteria for EoE.

Proton pump inhibitor-responsive esophageal eosinophilia

PPI-REE refers to patients showing symptoms and histological findings suggestive of EoE who achieve complete remission on PPI therapy. The first case report of PPI-REE was published in 2006 and reported two children and an adult with clinical, endoscopic and histological data suggestive of EoE, in whom complete remission was accomplished on PPI therapy [15]. Interestingly, the authors literally concluded that '*while these patients presentation was highly suggestive of allergic esophagitis, their symptoms, and the gross and histologic esophageal abnormalities normalized following treatment with a PPI, implicating acid reflux as the underlying cause*'. In fact, 2007 consensus guidelines stated a response to PPI suggested a diagnosis of GERD, whereas normal pH monitoring suggested EoE [16]. The premise underlying this recommendation was that GERD, as an acid peptic disorder, was the only disorder that could respond to the acid suppressing ability of PPI treatment. All these rigid distinctions were questioned in a visionary review article, where the authors exhibited a number of potential mechanisms of interaction between GERD and EoE [17]. In fact, GERD is common in PPI-REE, albeit up to 30% of PPI-REE patients have been shown to have normal acid esophageal exposure time on esophageal pH monitoring [18].

In 2011, the first prospective series reporting clinicohistological remission in up to 50% of patients with an EoE phenotype on PPI therapy was published [19], and the description of the PPI-REE phenotype was acknowledged as one of the major advances in EoE research in the updated 2011 consensus recommendations [1]. Since then, several prospective studies from Europe and the USA have reported consistent rates of PPI-REE (30–40%) in adults with suspected EoE after a PPI trial [20–22]. Overall, PPI-REE is a common clinical phenotype, affecting at least a third of adult patients with suspected EoE, who will not require topical steroid or dietary therapy. This finding stresses the fact that a PPI trial should always be performed before a diagnosis of EoE is given, in order to rule out PPI-REE.

Can we currently distinguish PPI-REE & EoE without a PPI trial?

As a PPI trial has been established as a necessary intervention before a diagnosis of EoE is confirmed, it would be important to learn how to differentiate EoE from PPI-REE. Two recent studies have failed to find distinguishing clinical, endoscopic and histological features between EoE and PPI-REE [20,23]. Furthermore, eotaxin-3 and IL-5 and IL-13 expression is indistinguishable as well between EoE and PPI-REE [22]. Collectively, these findings suggest PPI-REE might be a sub-phenotype of EoE, only distinguishable after specific therapy. Undoubtedly, studies are needed to determine why a subset of patients among a group with a similar phenotypic expression respond to PPI therapy.

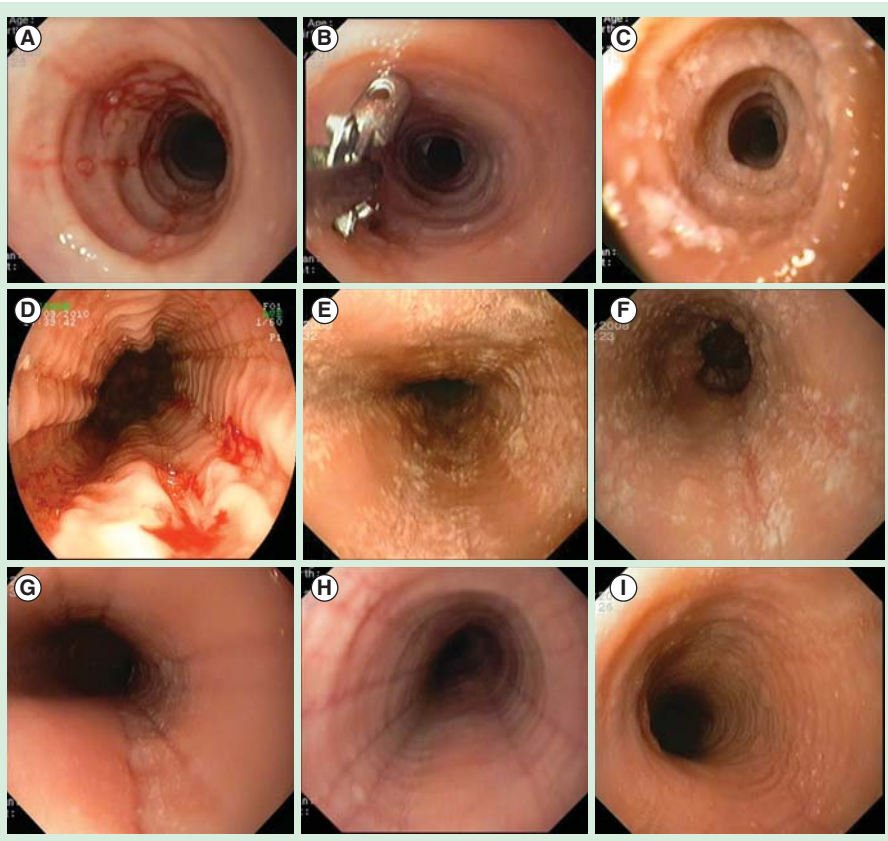

Figure 2. Typical endoscopic patterns suggestive of eosinophilic esophagitis (notice fibrostenotic and inflammatory features usually coexist). *Fibrostenotic features*: **(A)** multiringed esophagus; **(B)** narrow caliber esophagus; **(C)** stricture showing trachealization of the esophagus; **(D)** esophageal corrugation. *Inflammatory features*: **(E)** whitish exudates; **(F)** exudates and erythema; **(G)** longitudinal furrows and exudates; **(H)** longitudinal furrows; **(I)** cobblestone mucosa.

Natural history of EoE

EoE has been demonstrated to be a chronic disease with persistence of symptoms and inflammation over years [24]. Furthermore, long-standing eosinophilic inflammation may increase the risk of esophageal remodeling with subsequent stricture formation. A recent study nicely showed how the prevalence of esophageal strictures correlates with the duration of untreated disease [25]. Of note, both swallowed topical corticosteroids [26–28] and dietary allergen [29] avoidance can prevent and even reverse this esophageal remodeling process.

Patients should be counseled that the disease is chronic and that there is a high likelihood of stricture formation if untreated or recurrence after discontinuing treatment. As such, maintenance anti-inflammatory therapy, either with topical corticosteroids or diet, should be considered in all EoE children and adults.

End points of therapy

Treatment of EoE is focused on improving both patient symptoms and histology on esophageal biopsies as well as correcting or preventing complications such as esophageal strictures or food impactions. At the present time, we lack a validated instrument to measure and assess EoE symptoms. The development and validation of a symptom assessment instrument for pediatric and adult EoE patients is a challenge for a number of reasons. EoE symptoms typically change from the childhood to adulthood and dysphagia may not only depend on the existence of caliber abnormalities or active mucosal inflammation, but also on the consistency of the ingested food, behavioral modifications, such as food avoidance, food modification or an altered eating pace. Ideally, the goal would be complete symptom resolution and normalization of the esophageal epithelium with elimination of all eosinophils, but in practice, symptom improvement and histologic response do not always correlate, Moreover, histological remission might be achieved with medical therapy, but esophageal strictures may not respond.

As such, the most reliable therapeutic targets from a practical standpoint remain mucosal inflammation healing and resolution of esophageal caliber abnormalities. The first goal should be

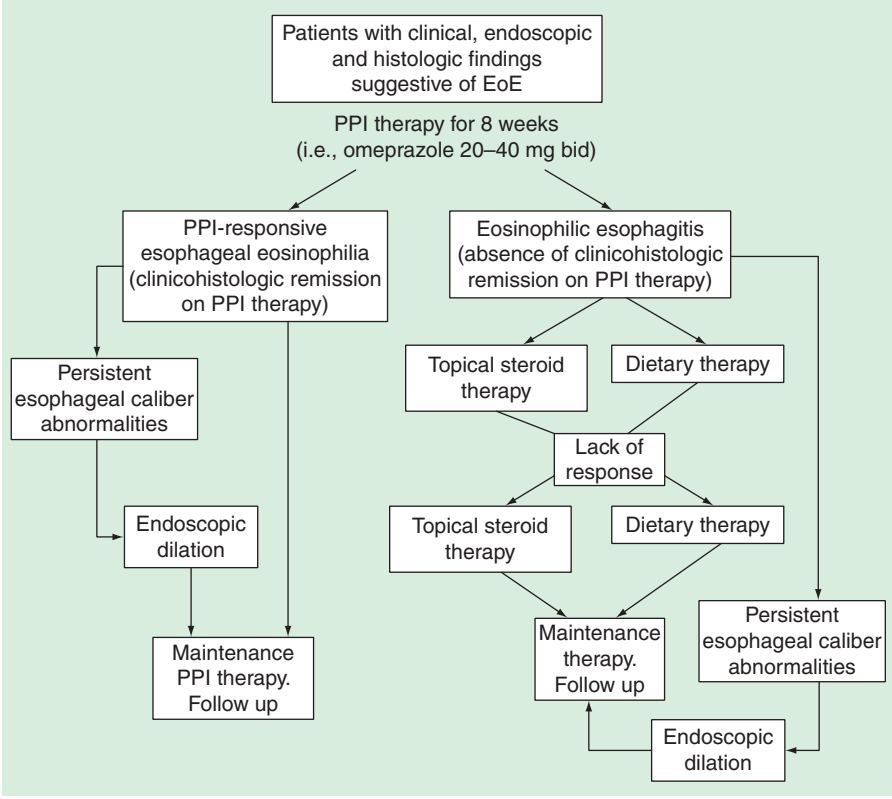

Figure 3. Proposed diagnostic and therapeutic algorithm for eosinophilic esophagitis in children and adults.
EoE: Eosinophilic esophagitis; PPI: Proton pump inhibitor.

treated with medical therapy and the second one treated with endoscopic dilation. The choice of short- and long-term medical therapy (corticosteroids vs dietary therapy) should be discussed with the patient and may depend on the age, the disease severity, the patient's lifestyle and preferences, the ability of the patient to continue the medication, treatment side effects and adverse impact on quality of life and family resources [1,8,9]. A follow-up endoscopy after an initial course of therapy should be carried out to document histologic response.

Treatment of EoE: the 3 Ds (drugs, diet, dilation)

Although there are as yet no US FDA-approved medications or devices to treat EoE, solid data supporting all treatment categories have been published over the last decade. In Figure 3, we suggest a diagnostic and therapeutic algorithm for EoE covering both inflammatory and fibrostenotic phenotypes.

Drugs: corticosteroids

As for medical therapy, swallowed topical corticosteroids have proven efficacious in reducing esophageal eosinophil counts and in improving EoE-related symptoms in several trials, whereas alternative drugs, such as biologics, immunomodulators or leukotriene antagonists, have shown limited results [1,8,9]. Novel anti-eosinophil drugs represent a field of intense research [30].

Topical corticosteroids have been proven to be an effective therapy for EoE, and are a first-line therapy for both adult and children, with response rates ranging from 50 to 80% [1,8,9]. The medications, available as multi-dose inhalers, nasal drops or aqueous nebulizer solutions for use in asthma or rhinoconjunctivitis, should be swallowed instead to coat the esophagus and provide topical medication delivery. Dose ranges and specific instructions for administration are presented in Table 1.

Topical steroids have been found to be safe drugs as minimal absorption is expected from the esophageal mucosa (bioavailability <1%), albeit it is clear that the pharmacodynamics of the topical steroids in EoE is unknown and whether the drug has a topical or systemic effect on the esophagus is yet to be explored. There have been no reports of adrenal suppression associated with the initial course of topical steroid administration, but long-term safety data are needed for a variety of potential steroid-related side effects [1,8,9]. No data on growth impairment or bone density in children are available. The rate of candidal esophagitis with topical steroids has ranged from 0 to 32% in prospective studies, although the majority of these cases were asymptomatic and incidentally detected during follow-up endoscopy and were related to nebulized administration.

Dietary therapy

Dietary management should be considered for every patient with EoE, even when we lack specific predictors of response in each patient. Its major limitations arise from the absence of non-invasive surrogate markers for the disease [31] and the subsequent necessity for repeated endoscopies with biopsies. Thus, this treatment option is preferable for highly motivated patients who are reluctant to adhere to drug-based therapies on a chronic basis [32]. Table 2 summarizes characteristics of the major dietary treatments for EoE currently available.

Elemental diet

The ability of dietary modifications to induce remission of EoE in children was initially demonstrated back in 1995, when the infiltration of the esophagus with a high density of eosinophils was still considered as a refractory form of GERD [33]. A series of 10 children were exclusively fed with an elemental formula, in which all proteins are eliminated and the nitrogen source is exclusively provided by single amino acids, thus lacking any antigenic capacity: eight patients showed total resolution with the other two exhibiting improvement of symptoms in parallel with normalization of esophageal histology, after 8 weeks of treatment. Several studies later corroborated the high efficacy of elemental diets, that according with a recent meta-analysis of

13 studies including 429 patients (411 children and 18 adults), has proven superior to that of any other type of dietary intervention in inducing histological remission of EoE achieving an overall efficiency of 90.8% (95% CI: 84.7–95.5%) [34]. However, the many disadvantages of exclusively feeding with elemental diets in clinical practice, including its unpleasant taste (which requires nasogastric tube in many cases), limitation in social activities due to the complete avoidance of any kind of table food, its high cost that is not covered by some insurance plans and high non-adherence rates make this option unfeasible in most patients and for chronic use. The only realistic utility of elemental diet in clinical practice is to feed infants and toddlers, among whom the restriction of having no additional food may be better tolerated, and only during the length of time required for food reintroduction with the goal of identifying specific dietary triggers.

Dietary elimination targeted by skin allergy testing

The attempt for identifying specific food triggers of EoE was first conducted by allergists, who used both skin prick testing and atopic patch tests on pediatric EoE patients to determine a suitable targeted elimination diet [35]. The avoidance of foods showing positive results on skin testing led to histological and clinical resolution in 49% of patients, after five foods on average were excluded from each child's diet. A retrospective cumulative analysis by the same researchers later documented complete resolution of the disease in that 53% of children with EoE who followed an allergy testing-directed exclusion diet; when allergy testing was combined with empirical elimination of milk, the histological remission rates increased up to 77% [36]. Unfortunately, this notable efficacy rates have not been replicated by other researchers, and results are especially disappointing among adult patients [37]. Criticism to targeted dietary elimination include that most of available data are based on a predominantly pediatric population, which might not be transferable to the adult population of EoE patients. Most importantly, the atopic patch tests methodology is not standardized and its interpretation is highly subjective and variable; as a result, data are poorly reproducible [38,39]. Subsequently, the summarized efficacy of skin allergy testing in a meta-analysis of 14 studies was 45.5% (95% CI: 35.4–55.7%) [34], calling into question whether this treatment should be widely recommended to EoE patients, and restricting its use to experienced centers where it has proven to be effective.

Empiric elimination diet

Aiming at overcoming the impracticability of elemental diets and the low sensitivity and specificity of allergy testing in identifying EoE food triggers, the alternative of empirically eliminating the six foods most commonly associated with food allergy in children (e.g., milk protein, soy, egg, wheat, peanut/tree nuts and seafood) achieved a significant improvement of both esophageal inflammation and symptoms in 74% of the 35 children in whom this intervention was initially assessed [40]. The results of this so-called six-food elimination diet (SFED) have been corroborated in subsequent studies carried out in both children and adults, which exhibit a fairly uniform efficacy rate of 72.1% (95% CI: 65.8–78.1%), as stated by a recent meta-analysis that combined result from 197 patients (75 children and 122 adults) retrieved from 7 studies [34]. Of note, the aforementioned 'classic' SFED had been extended by some authors to include foods that gave a positive result in allergy tests [37,41] or other common food allergens in the study population [42].

A single retrospective study in children showed histological remission and symptom improvement in 65% of children after the elimination of cow's milk from the diet [43]; since cow's milk protein is the most common food linked to EoE in all ages, this easy intervention should be considered especially for children.

Table 1. Topical steroid initial dosing for eosinophilic esophagitis treatment.

	Target population	Dosing (usually divided doses)
Fluticasone propionate[†,‡]	Children[§] Adults	88–440 µg/day 880–1760 µg/day
Budesonide[‡,¶]	Children[§] Adults	1 mg/day 2 mg/day

[†]If an inhaler is used, the patient should be instructed to puff the medication into their mouth during a breath hold, and then swallow it with a minimum amount of water, to minimize pulmonary deposition and risk for candidiasis.
[‡]Regardless of the form of administration (nebulized or swallowed), patients should fast at least 30–60 min after medication in order to minimize esophageal drug clearance.
[§]Specific doses in children will be determined by age, height or weight.
[¶]Oral viscous budesonide preparation consists of mixing 1–2 mg budesonide with 5 mg of sucralose.

Identification of food triggers for EoE & sustained effectiveness

According to the international consensus guidelines for EoE [1], food triggers can currently only be identified by documenting EoE recrudescence upon specific food reintroduction after disease remission has been achieved through specific food antigen avoidance. Thus, EoE patients should undergo to food reintroduction with the double aim of selectively identifying foods that trigger EoE, as well as improving their acceptance of and adherence to a less restrictive diet [32]. One or more independent foods can be responsible for EoE, so sequential food reintroduction ('food challenge') under endoscopic and bioptic monitoring has been used to identify EoE triggers after achieving disease remission by any dietary intervention in children [44] and adults [41,42]. No agreement exists on the sequence of food reintroduction; some researchers begin with food unlikely to cause EoE (e.g., vegetables and fruits, chicken and beef), in order to vary the patient's diet as soon as possible, while other do exactly the opposite (i.e., first reintroducing milk and wheat) alluding to their higher impact in normalizing a diet if the result is negative. Identified food triggers are quite similar across the various studies, with cow's milk, wheat and egg being involved in most of cases, regardless of patients' age and

Table 2. Available dietary interventions for eosinophilic esophagitis: major characteristics, advantages and disadvantages.

	Type of dietary treatment		
	Elemental diet	*Skin allergy testing-targeted elimination diet*	*Empiric six-food elimination diet*
Histological remission rate	>90%	35–56%	70–74%
Number of eliminated foods	All food groups are eliminated	Typically <6 food (5 foods on average in some studies)	The six food groups most commonly linked to food allergy
Common food triggers identified	Not available information	Milk, wheat, egg, soy	Milk, wheat, egg, legumes/soy, nuts, fish/seafood
Advantages	• Highest effectiveness • Fast response in time • Easy instructions • Minor risk of dietary contamination • Allergy testing is not needed	• Ability to remove less food from patients' diets • Exclusive removal of specific foods • Rapid normalization of diets • Moderate efficacy	• Exclusive removal of the most common antigens • Allergy testing is not needed • Moderately high efficacy • Rapid normalization of diet
Drawbacks	• Unpleasant taste, table food must be avoided • Often, gastric tube administration in children • High cost of elemental formula • Poor adhesion • Long-term supply • Long-term use in younger children may delay facial muscle development and speech	• High variability in response rates • Low sensitivity and specificity of allergy testing • Low standardization for atopy patch testing • Possible dietary contamination	• Risk of dietary contamination • Lack of standardization of protocol • Adequacy of diets to local customs should be assessed • Difficulties in reading/interpreting food labeling

geographical origin. Because EoE is a chronic disorder, foods identified as triggers for the disease should be avoided indefinitely [1]; after that, and even when a sustained drug-free response is achievable for most patients [42], data on the possibility of inducing food tolerance to offending food in the long term are scarce: the only available study on this topic provided disappointing results [44], with EoE universally reappearing after food reintroduction in every child who had been in remission for a period of up to 4 years.

Long-term difficulties in adhering to an elimination diet mostly depend on the type and number of food triggers involved in EoE. Key factors for improving adherence include finding appropriate substitutes for the eliminated foods, reconciling prolonged remission of EoE with a feasible diet and an adequate quality of life [45] and simplifying the food elimination study protocols. Cow's milk-based, extensively hydrolyzed formulas have been demonstrated to be well tolerated by most adult patients with milk-triggered EoE [46]. Ongoing research on less restrictive dietary options such as four-food elimination diets may simplify study protocols and reduce the number of endoscopies needed.

Endoscopic dilation

Dilation of esophageal strictures is effective for relieving dysphagia, but has no effect on underlying inflammation and subsequently should be reserved for patients with strictures or rings who have not responded to medical therapy. The goals should be dysphagia improvement, usually achieved in 75%, and a final esophageal diameter of 15–18 mm [47]. Medical therapy, usually topical steroids, should be used simultaneously to endoscopic dilation, in order to diminish esophageal mucosal inflammation. Dilation should be performed carefully since it has been associated with deep mucosal tears (Figure 4), which are definitely tell-tale signs of successful dilation. Therefore, it has been recommended that the progression of dilation per session be limited to 3 mm or less and the esophagus should be gently inspected after passing each dilator. Patients should be forewarned that chest pain may be present in 75% of patients after endoscopic dilation [48]. The risk of esophageal perforation is minimal and similar to that observed in other esophageal strictures. A 2013 meta-analysis that included 860 patients, of whom 525 underwent at least one dilation, and a total of 992 dilations found that there were only three perforations (2%, 95% CI: 0–0.9) and one hemorrhage (0%, 95% CI: 0–0.8) and bleeding [49].

Expert commentary

Noteworthy advances have been accomplished over the last decade, mostly focused on EoE diagnosis and therapy. Nonetheless, the etiology of EoE is the most unexplored field. EoE is well known to be a result of local interplay between genetic background, integrity of esophageal epithelium and external allergens, mainly food and airborne allergens. Not only the resolution of symptoms and the eosinophilic inflammation upon

food allergen avoidance in different dietary interventions [34], but also *de novo* onset of EoE after egg and milk oral immunotherapy [50,51] clearly support this hypothesis. As for aeroallergens, diagnosis of EoE has been shown to be directly connected to pollen load [52], with a seasonal variation pattern in newly diagnosed cases [53]. Moreover, recent *de novo* onset cases have been reported after exposure to large amounts of aeroallergens [54] or sublingual pollen immunotherapy [55]. These cases confirm aeroallergens as potential triggers of EoE and possibly responsible for EoE maintenance in patients unresponsive to dietary interventions such as SFED. Whether an airway exposure can induce EoE itself or and whether additional paths of induction exist (i.e., subcutaneous or systemic) remains to be elucidated. More importantly, we do not positively know the precise reason why these allergens now cause EoE and did not 30 years ago. In fact, hygiene conditions have remained the same in developed countries over the last two decades. It is tempting to speculate that genetic modification of food and crops, started in the early 1990s, or food processing changes might have been contributed to the development of this novel allergic disease.

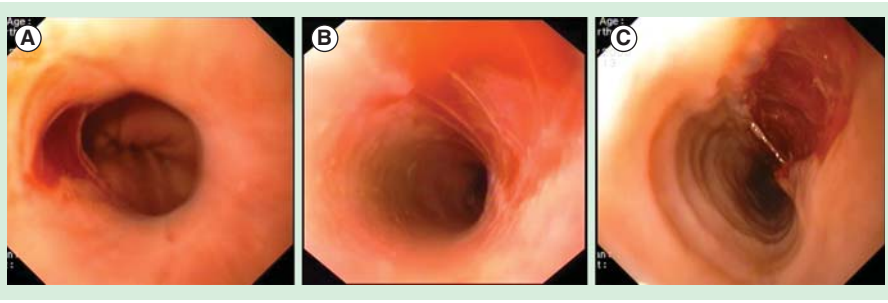

Figure 4. Different degrees of esophageal mucosal tearing after endoscopic dilation of strictures in eosinophilic esophagitis patients.

Five-year view

Etiology & pathogenesis

The development of an *EoE diagnostic panel*, based on molecular diagnosis, with a high sensitivity and specificity in discriminating pediatric and adult EoE patients from non-EoE patients, has been recently reported [56]. It will likely be helpful to determine which atopic patients and relatives might be at risk for EoE.

Diagnosis

Novel molecular tools, including genetic polymorphism and esophageal epithelial integrity assessment, are awaited to help us to distinguish EoE and PPI-REE at baseline, obviating the need of a PPI trial.

Novel minimally invasive devices for esophageal biopsy samples will likely lead to more convenient diagnosis and monitoring of EoE, obviating the need of multiple endoscopies. The string-test is an adaptation from the entero-test, a technique originally designed to detect gastric and small intestine pathogens, consisting of a capsule and a string. Two recent studies have shown promise for this modified technique in pediatric patients [57,58]. Patients had to swallow the capsule and the proximal string was taped to the cheek. After 12 h, the string was removed. Aiming at simplifying the procedure, preliminary results have shown that a 1-h exposure of the string might be sufficient for adequate sampling.

The Cytosponge™ is an ingestible gelatin capsule containing a compressed mesh attached to a string. The capsule is swallowed and moves by peristalsis into the gastric cardia; after 5 min the capsule dissolves, releasing the sponge. The device then is retrieved, collecting a cytologic specimen from the esophageal mucosa. This device has been lately shown to be cost-effective for Barrett's esophagus screening [59] and these results are likely transferable to EoE monitoring. Several ongoing studies will soon give us an answer on this issue, with good preliminary results [60].

Therapy

Novel steroids formulations are being developed. Available topical steroids were not specifically designed for esophageal delivery. In a recent study, oral viscous budesonide provided a significantly higher level of esophageal contact time with the therapeutic agent than nebulized steroids, which correlated with lower eosinophil counts [61]. Furthermore, the esophagus might be a challenging target organ for topical drugs. It is mobile and clearance of esophageal content might be accelerated by saliva and gastroesophageal reflux. Preliminary results using effervescent tablets and viscous suspension have shown mucosa healing rates over 90% [62].

After demonstrating, it can provide many patients with a sustained remission while avoiding the use of drugs, a growing interest on the dietary treatment of EoE has emerged. The reluctance to undertake repeated endoscopies will be diminished by simplifying food elimination schemes through a four-food elimination diet, which will be provided to patients with acceptable remission rates while avoiding several endoscopic exams. We wait for no or minimally invasive markers of active esophageal inflammation that are urgently needed, since symptoms are not always reliable to infer disease activity. The possibility of predicting EoE triggers with no need of undergoing food reintroduction should be further explored.

As for conventional functional esophageal testing, high-resolution manometry or impedance/pH-monitoring have shown equivocal or even conflicting results. A novel device measuring compliance through a functional luminal imaging probe (EndoFlip®, Crospon, Carlsbad CA, USA) has shown promise to quantitatively assess the distensibility of the esophageal wall [63]. A recent study conducted in 70 EoE patients who underwent functional luminal imaging probe and underwent prospective follow-up, showed that patients with a history of food impactions exhibited significantly lower esophageal

distensibility than those with dysphagia alone. Decreased esophageal distensibility was also found to be associated with an increased risk of food impaction and need for dilation during the follow-up period. Therefore, this device has the potential to quantify the functional properties in EoE and could be helpful to go for endoscopic dilation in symptomatic patients even in the absence of esophageal strictures.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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Key issues

- Eosinophilic esophagitis (EoE) is an emerging immune allergen-driven esophageal disease, at least as prevalent as Crohn's disease in developed countries.
- Typical EoE endoscopic features or esophageal eosinophilia (≥15 eosinophils/high power field) are not diagnostic for EoE. Diagnosis of EoE is a stepwise process comprising symptoms of esophageal dysfunction and esophageal eosinophilia ≥15 eosinophils/high power field, unresponsive to an 8-week trial of proton pump inhibitor (PPI) therapy.
- PPI-responsive esophageal eosinophilia (PPI-REE) refers to patients with clinical, endoscopic and histologic features suggestive of EoE who achieve complete remission on PPI therapy. PPI-REE occurs in at least 30% of patients with suspected EoE and these patients will not need topical steroid or dietary therapy. Patients with PPI-REE are currently indistinguishable from EoE patients without a PPI trial, so they should be carefully monitored.
- Similar to inflammatory bowel disease, two different phenotypes have been described for EoE patients: inflammatory and fibrostenotic. The natural history of the disease has been suggested as a progression from the former to the later. Currently, the most reliable end points of therapy are mucosal inflammation healing and caliber abnormalities resolution.
- EoE is a chronic disease affecting young patients, who will need maintenance therapy to prevent esophageal fibrotic remodeling and subsequent stricture formation.
- Patients with a fibrostenotic phenotype (stricture, narrow caliber esophagus) should undergo endoscopic dilation, always preceded by medical therapy to treat mucosal inflammation.
- Either topical steroids or dietary therapy are good choices for patients with mucosal inflammation and no caliber abnormalities.

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Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128(1):3-20

• **Most recent update of consensus for diagnosis and therapy in eosinophilic esophagitis (EoE), emphasizing the description of proton pump inhibitor (PPI)-responsive esophageal eosinophilia (REE) and genetic markers for EoE.**

2. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993;38(1):109-16
3. Straumann A, Spichtin HP, Bernoulli R, et al. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings [in German with English abstract]. Schweiz Med Wochenschr 1994;24(33):1419-29
4. Hruz P, Straumann A, Bussmann C, et al. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. J Allergy Clin Immunol 2011;128(6):1349-50

• **A pioneer epidemiological analysis on changes in incidence and prevalence registered along the years in a series of EoE adult patients from a Swiss region.**

5. Dellon ES, Jensen ET, Martin CF, et al. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol 2014;12(4):589-96
6. Arias Á, Lucendo AJ. Prevalence of eosinophilic oesophagitis in adult patients in a central region of Spain. Eur J Gastroenterol Hepatol 2013;25(2):208-12
7. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007;133(4):1342-63
8. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013;108(5):679-92

• **This is the first guideline specifically addressing esophageal eosinophilia and PPI-REE as entities distinct from EoE. A comprehensive algorithm for diagnosis is provided, stressing the fact that PPI-REE might occur with pathological (acid mediated) or normal (unknown mechanism) pH monitoring.**

9. Dellon ES. Diagnosis and management of eosinophilic esophagitis. Clin Gastroenterol Hepatol 2012;10(10):1066-78
10. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62(4):489-95
11. Kim HP, Vance RB, Shaheen NJ, et al. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. Clin Gastroenterol Hepatol 2012;10(9):988-96

12. Gonsalves N, Policarpio-Nicolas M, Zhang Q, et al. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. Gastrointest Endosc 2006;64(3):313-19

13. Shah A, Kagalwalla AF, Gonsalves N, et al. Histopathologic variability in children with eosinophilic esophagitis. Am J Gastroenterol 2009;104(3):716-21

14. Odze RD. Pathology of eosinophilic esophagitis: what the clinician needs to know. Am J Gastroenterol 2009;104(3): 485-90

15. Ngo P, Furuta GT, Antonioli DA, et al. Eosinophils in the esophagus: peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. Am J Gastroenterol 2006; 101(7):1666-70

16. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007; 133(4):342-63

17. Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. Am J Gastroenterol 2007;102(6):1301-6

•• **A visionary review that posed for the first time the possibility that a rigid distinction between EoE and gastro-esophageal reflux disease (GERD) based on PPI responsiveness was too simplistic, providing potential mechanisms for the complex interaction between both disorders. This 'ahead of its time' review proposed a PPI trial in all patients with a presumptive diagnosis of EoE, as we do today and, of note, called into question the premise that a response to PPI therapy precluded a diagnosis of EoE.**

18. Molina Infante J, Katzka DA, Gisbert JP. Review article: proton pump inhibitor therapy for suspected eosinophilic esophagitis. Aliment Pharmacol Ther 2013; 37(12):1157-64

• **This is the first systematic review in children and adults bringing together evidence on PPI-REE. Ten articles comprising 258 patients with suspected EoE (152 children, 106 adults) revealed that at least one-third of patients with EoE was actually PPI-REE patients. Histological remission after PPI therapy has been reported higher in adults than in children (23–40 vs 33–61%) and in patients with documented GERD when compared with those with no GERD on endoscopy/pH monitoring (70 vs 29%).**

19. Molina-Infante J, Ferrando-Lamana A, Ripoll C, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. Clin Gastroenterol Hepatol 2011;9(2):110-17

20. Dellon ES, Speck O, Woodward K, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. Am J Gastroenterol 2013;108(12):1854-60

21. Vazquez-Elizondo G, Ngamruengphong S, Khrisna M, et al. The outcome of patients with oesophageal eosinophilic infiltration after an eight-week trial of a proton pump inhibitor. Aliment Pharmacol Ther 2013; 38(10):1312-19

22. Molina-Infante J, Rivas MD, Vinagre-Rodriguez G, et al. Remission in proton pump inhibitor-responsive esophageal eosinophilia correlates with downregulation of eotaxin-3 and TH2 cytokines, similarly to eosinophilic esophagitis after steroids. Gastroenterology 2013;144(Suppl 1):S-484

23. Moawad FJ, Schoepfer AM, Safroneeva E, et al. Eosinophilic oesophagitis and proton-pump inhibitor-responsive oesophageal eosinophilia have similar clinical, endoscopic and histological findings. Aliment Pharmacol Ther 2014; 39(6):603-8

24. Straumann A, Spichtin HP, Grize L, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology 2003;125(6):1660-9

25. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013;145(6):1230-6

•• **The studies by the Swiss Group on EoE constitute the most compelling evidence on the natural history of EoE (references #24 and #25 in this review). Both studies have proven EoE to be a chronic disease, in which untreated esophageal inflammation may lead to fibrotic remodeling and stricture formation. Of note, both topical steroids and diets have shown to prevent or even reverse this process, so clearly maintenance therapy is warranted for EoE patients.**

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28. Lucendo AJ, Arias A, De Rezende LC, et al. Subepithelial collagen deposition, profibrogenic cytokine gene expression, and changes after prolonged fluticasone propionate treatment in adult eosinophilic esophagitis: a prospective study. J Allergy Clin Immunol 2011;128(5):1037-46

29. Lieberman JA, Morotti RA, Konstantinou GN, et al. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. Allergy 2012;6(10): 1299-130

30. Lucendo AJ, Molina Infante J. Emerging therapeutic strategies for eosinophilic esophagitis. Curr Treat Options Gastroenterol 2014;12(1):1-17

31. Rodríguez-Sánchez J, Gómez-Torrijos E, De-la-Santa-Belda E, et al. Effectiveness of serological markers of eosinophil activity in monitoring eosinophilic esophagitis. Rev Esp Enferm Dig 2013;105(8):462-8

32. Lucendo AJ, Arias A. Dietary management of patients with eosinophilic esophagitis. Curr Treat Options Allergy 2014. doi:10.1007/s40521-014-0012-2

33. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology 1995;109(5):1503-12

34. Arias A, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions in inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology 2014. doi:10.1053/j.gastro.2014.02.006

•• **The first systematic review and meta-analysis demonstrating that dietary treatment is an effective, drug-free therapy for achieving remission of eosinophilic infiltration in EoE patients. Comparisons on the various dietary treatment strategies provide varied efficacy rates, ranging from 90.8% for elemental diets to 45.5% for allergy testing-directed food elimination.**

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36. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol 2012;130(2):461-7

37. Henderson CJ, Albonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. J Allergy Clin Immunol 2012; 129(6):1570-8

- **The efficacy of the three major dietary-based therapies was compared in this retrospective pediatric cohort analysis; elemental diet was superior in inducing histologic remission compared with six-food elimination and skin tests-directed diets, these two last alternatives being equally effective.**

38. Molina-Infante J, Martin-Noguerol E, Varado-Arenas M, et al. Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis. J Allergy Clin Immunol 2012; 130(5):1200-2

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- **The development of a new molecular diagnostic test capable of identifying patients with EoE and distinguishing them from other conditions through a fast, objective and mechanistic method.**

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