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Emerging Therapeutic Strategies for Eosinophilic Esophagitis

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Opinion statement

Eosinophilic esophagitis (EoE) is recognized as an increasingly common cause of chronic and recurrent esophageal symptoms that significantly impact quality of life and may occasionally result in severe complications in both pediatric and adult patients. The disease is triggered and maintained by exposure to food antigens in most patients, with an additional role proposed for airborne allergens. Different diet-based approaches focused on restricting potentially offending foods have proven to be effective long-term therapies for EoE. Dietary therapy is thus an attractive, yet challenging treatment option that should be considered for all pediatric and adult EoE patients. However, limitations related to food restriction, patient willingness to undergo repeated endoscopies and biopsies, and the variable results of allergy testing imply that dietary management is for the most part currently restricted to highly motivated healthcare providers treating highly motivated patients reluctant to utilize drug-based therapy on a chronic basis. Pharmacological therapies for EoE mainly comprise swallowed topical steroids, especially fluticasone propionate and budesonide, which were originally developed to treat bronchial asthma and are now extensively used "off label" in EoE patients. In fact, topical steroids currently constitute the prevailing therapeutic option and will probably continue to do so in the near future; indeed, several randomized clinical trials are currently underway to test these drugs for approval as the first pharmacological agents for EoE patients. Immunomodulators and several anti-allergic agents must be further assessed as therapeutic alternatives for refractory cases or patients with complications. Endoscopic dilation represents the third pillar in the therapeutic management of EoE patients, since they frequently present reductions in the esophageal caliber as a result of collagen deposition and a progressive fibrous remodeling process promoted by chronic eosinophilic infiltration. Dilation provides

at least temporary symptom relief with similar complication rates to esophageal strictures from a different origin. However, although repeated endoscopic dilation has sometimes been used as the sole therapy for EoE, it best constitutes an adjuvant therapy along with dietary or pharmacological-based interventions, especially since dilation has no effect on the underlying esophageal inflammation. Current therapeutic management of EoE varies widely, with physician experience being a major explanatory factor. New evidence from ongoing research on EoE should thus seek to define a common treatment algorithm to optimize EoE patient management.

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory condition that has emerged over the past 2 decades as one of the most common causes of upper gastrointestinal (GI) symptoms in both children and adults. The disease has been defined by a consensus panel of experts as a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. As the disease is restricted to the esophagus, other causes of esophageal eosinophilia should be ruled out, especially proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) [1•].

The natural history of EoE has become more defined in the last few years. It is already known that in the absence of treatment, the esophageal inflammation and its derived symptoms usually persist from childhood into adulthood, significantly reducing the health-related quality of life (QoL) of affected individuals [2••, 3]. The natural course of the disease during adulthood is characterized by persistent dysphagia and structural esophageal alterations that generally have no impact on the nutritional status of the patient [4]. To date, no malignant potential has been associated with this disease, but retrospective studies have demonstrated that the duration of untreated disease directly correlates with the prevalence of esophageal strictures in a time-dependent manner [5•], in a similar way to that demonstrated in the natural history of Crohn's disease. In fact, fibrous remodeling and subepithelial collagen deposition have been demonstrated in both pediatric [6, 7] and adult [8, 9•] patients with the disease, similar to what occurs in bronchial asthma and other eosinophilic-associated inflammatory conditions. As such, diagnostic delay may result in esophageal strictures, leading to disease-inherent and procedure-related complications.

The prevalence of EoE has experienced an upward trend in developed countries during the past few years and it is now estimated to affect 43–56.7/100,000 child and adult inhabitants in both America and Europe [10–15]. As a result, EoE poses a large burden to the healthcare system, involving multidisciplinary services including gastroenterologists, dietitians, and allergists in the management of the disease, in addition to the costs derived from the frequent emergency room visits for food impaction or after complications [16]. Given the high prevalence of the disease, the cost-effectiveness of performing esophageal biopsies in patients with upper GI symptoms to rule out EoE have been demonstrated [17].

An increasing body of research has begun to define the pathogenesis of EoE, although even from its first descriptions, EoE has been associated with allergies. In fact, EoE patients commonly have a familial or personal atopic history, including asthma, rhinitis, conjunctivitis, or eczema [1•]. Food and aeroallergen sensitization determined by positive skin prick tests (SPT) have also been commonly described in patients of all ages [18–20], but the definitive definition of EoE as a characteristic food allergy was firmly established when (1) disease remission was achieved after exclusive feeding with an antigen-free amino acid elemental formula in a series of pediatric patients, followed by recurrence after resuming a normal diet [21••], and (2) acceptable remission rates (over 70 %) were achieved after empirically removing at least six major food groups from the diet.

Despite the exponential increase in our knowledge of EoE after two decades of research, many aspects of the disease remain unresolved, including therapeutic issues. Thus, some medications, food elimination di-

ets, and endoscopic dilation have all proven to be effective therapies with important limitations. This review focuses on the therapeutic aspects of EoE and aims to give both a critical overview of the currently available treatment alternatives as well as an update on developing therapies for the near future.

Treatment

- The classic EoE treatment goals are (1) resolution of clinical symptoms, and (2) achievement and maintenance of disease remission. These have been expanded in recent years to encompass other important aspects of chronic disorders and now include (3) prevention of fibrotic complications such as strictures, (4) avoidance of iatrogenic effects of medication, (5) maintenance of an adequate QoL, and (6) prevention of nutritional deficiencies from dietary treatment, especially in children.
- Despite the amount of research published on EoE, the management of the disease in clinical practice remains somewhat controversial [22]. A commonly accepted algorithm for treating patients is currently lacking, mostly because of limited information regarding the long-term effects of different therapies to modify the natural history of the disease and the associated subepithelial fibrosis [8, 22, 23•]. As a result, a wide variability, both in the standard of care of EoE patients and in adherence to proposed international guidelines, has been documented in clinical practice [24•, 25•].
- Although currently available EoE treatment strategies have often proved effective, there is no medication specifically approved for the disease. Off-label systemic and topical steroids are the oldest and most frequently prescribed medications for EoE patients of all ages. Most of these have been adapted from formulations designed for bronchial or intranasal delivery.
- Furthermore, no comparative studies on the efficacy of different therapeutic interventions (i.e., topical steroids compared to other drugs, dietary interventions, or esophageal dilation) have been published. Consequently, there is a great need for the development of specific drugs and formulations specifically for EoE patients.

Pharmacological treatment

- Pharmacological treatment of EoE patients has consisted mainly of several anti-inflammatory drugs commonly used in other allergic disorders.
- Immunomodulatory and biological therapies have also been assessed.

Topical steroids

- Several of the initially described cases of EoE were effectively managed with systemic steroids. Today, these have been replaced by topical steroids after demonstrating that the latter are just as effective in terms of histological and symptomatic remission, with fewer side effects.
- First used in a limited number of pediatric patients [26], topically administered (i.e., swallowed rather than inhaled) fluticasone propionate (FP) has been demonstrated through randomized, controlled trials (RCTs) to be highly effective in children [27], significantly superior to a placebo and comparable to oral prednisone [28•] in inducing disease remission. Similar results have also been observed in adults [29, 30•, 31•], among whom long-term efficacy has also been documented [8]. In addition, FP has been shown to induce reversion in gene transcriptional changes associated with EoE in both age groups [32•, 33].
- FP in EoE is usually administered with a metered-dose inhaler; the medication is "puffed" into the mouth and then swallowed. A liquid formulation of FP designed for intranasal delivery has also been assayed. Research on FP administered in melting tablets is currently underway.
- Viscous budesonide (a suspension of the drug in sucralose) has also emerged as an alternative to FP in order to improve proper esophageal delivery of swallowed nebulized formulations. First assessed in an RCT in children, for whom the "puff" and swallow sequence is more difficult, oral viscous budesonide proved highly effective in achieving histological and clinical remission of the disease, with no significant adverse events [34]. A subsequent RCT carried out in adult patients demonstrated that budesonide was also highly effective in inducing a rapid histological and clinical remission of the disease [9•]. Long-term low doses were only partially effective, although superior to a placebo [35]. Phase II clinical trials are currently evaluating both budesonide in oral suspension and in tablet form for use in EoE patients [36, 37].
- Ciclesonide, a relatively new inhaled corticosteroid used for asthma and allergic rhinitis, has also recently been added to the pharmacological arsenal for treating EoE [38]. This topical steroid, administered in a metered-dose inhaler, is a pro-drug that becomes active after being converted by esterases from the esophageal epithelial cells. Its advantages over FP and budesonide include much higher glucocorticoid receptor binding (up to 100 times greater) and fewer systemic side effects (osteopenia, adrenal suppression, oral candidiasis) from its low systemic bioavailability due to a high first-pass hepatic metabolism. In two recent small series consisting of four children each, the reported histological remission rates have been 100 % and 50 %, respectively [38, 39]. Both nonresponders in the latter study showed

prior unresponsiveness to oral viscous budesonide. Further research is needed to determine the potential role of ciclesonide in clinical practice.

Montelukast

- Leukotriene D4 is a well-known eosinophil chemoattractant. Montelukast, a leukotriene D4 receptor antagonist, provides anti-inflammatory effects and symptom improvement with minimal side effects in the management of asthmatic patients. An initial study of montelukast in eight adult EoE patients demonstrated a symptomatic response rate of 75 %, with five patients remaining asymptomatic on a maintenance regimen using high doses [40]. A small series of eight pediatric EoE patients reported symptomatic improvement in three out of eight patients (37 %) with montelukast maintenance therapy [41]. Unfortunately, no histological follow-up was carried out in these studies. As for adults, a recent study found that a 3-month course of montelukast failed to maintain clinical or histological response in EoE patients after a corticosteroid-induced histological remission [42•].
- A phase 3, comparative RCT comparing montelukast to swallowed, aerosolized FP is currently underway [43], with the results expected for 2015. Additionally, researchers plan to test the efficacy of montelukast compared to a placebo in reducing the number of eosinophils in children with EoE [44].

Proton pump inhibitors (PPIs)

- According to updated guidelines for the management of EoE [1•, 45••], either gastroesophageal reflux disease (GERD) or PPI-REE should be formally ruled out before giving a final diagnosis of EoE. In fact, clinical and histological remission upon PPI therapy have been demonstrated in up to 30–50 % of patients suspected of having EoE based on clinical, endoscopic, and histological features [46]. Besides its importance as a diagnostic tool, the rationale for using PPI therapy in EoE patients has recently been provided by several in vitro studies, which showed that PPI may inhibit Th2 cytokine (inteleukin [IL]-4, IL-5, IL-13)-induced esophageal epithelial expression of eotaxin-3 [47, 48, 49••]. Moreover, because EoE patients have been shown to be hypersensitive to locally perfused acid as compared to GERD patients, blocking physiological acid could result in symptomatic improvement in EoE patients [50].

Immunomodulators

- Because of the chronic nature of the disease, the vast majority of EoE patients experience disease recurrence after discontinuing their

medication since exposure to food(s) that trigger the disease remains. As a consequence, maintenance treatment with steroids or repeated courses should be considered after achieving disease remission. However, since steroid response is not universal and there are potential side effects of long-term use of steroids, the utilization of steroid-sparing drugs such as thiopurines has been of interest.

- The research published on azathioprine/6-mercaptopurine is limited to a case series of three steroid-dependent adult patients (two of them with EoE and one with eosinophilic gastroenteritis with esophageal involvement). The drug proved effective in maintaining the remission of symptoms and eosinophilic infiltration for periods of 3–8 years [51•]. Further studies are needed to define the role of thiopurines and other immunomodulatory drugs in patients with steroid-refractory EoE.
- Sirolimus (also known as rapamycin) was initially developed as an antifungal agent. Today it is considered to be an immunosuppressant and is widely used to prevent rejection in organ transplantation, especially in kidney transplants, by inhibiting the response to IL-2, thereby blocking activation of T and B cells [52]. This drug has also been shown to decrease cell proliferation and tumor growth. Indeed, the antiproliferative effect of sirolimus has been exploited to create a coronary stent coating that prevents restenosis following balloon angioplasty [53]. An off-label dose-escalation study has been designed to evaluate the effectiveness of sirolimus in decreasing blood and/or gut eosinophilis in adult patients with eosinophilic gastrointestinal disorders (EGID), including EoE [54].

CRTH2 antagonists – OC000459

- The chemoattractant receptor expressed on Th2 cells (CRTH2) is overexpressed on Th2 lymphocytes, eosinophils, and basophils after allergen exposure, and mediates chemotaxis in response to prostaglandin D_2. OC000459 is a selective CRTH2 antagonist with proven effectiveness against eosinophilic asthma. A recent randomized, double-blind, placebo-controlled trial in 26 adult patients with steroid-dependent or steroid-refractory EoE [55•] showed that OC000459 induced a significant decrease in both esophageal eosinophilia (114.83 to 70.26 eos/HPF, $p=0.0256$) and symptoms, with a trend towards improvement in endoscopic abnormalities compared to a placebo. No major side effects were reported.

Biologics

- Biologic agents are monoclonal antibodies that target cytokines regulating critical pathways in a given disease. They have demonstrated efficacy against various inflammatory and autoimmune disorders.

Even though the molecular mechanisms leading to EoE have not yet been fully explained, several RCTs have assessed the ability of biologics to target certain cytokines known to be involved in the pathophysiology of EoE.

- After documenting that tumor necrosis factor (TNF)-α was upregulated in EoE [56•] and highly expressed by esophageal epithelial cells in patients with active EoE [57], three adults with steroid-dependent EoE received two doses of infliximab. The drug was not able to induce a resolution of the eosinophilic tissue infiltration, nor did it markedly reduce symptoms [58].
- IL-5 is a Th2-type cytokine with a master role in the biology of eosinophils, inducing eosinophil proliferation and maturation in the bone-marrow, migration into peripheral blood, and penetration into tissues. Moreover, the IL-5 gene is upregulated in the esophageal mucosa of EoE patients [33, 56•]; a central role for IL-5 has thus been defined in experimental murine models of EoE [59]. Furthermore, the blood lymphocytes of patients with EoE produce significantly higher levels of IL-5 following stimulation in vitro compared to normal controls [60]. In addition, the percentage of blood-circulating IL-5+ CD4 T cells correlates with the severity of esophageal tissue eosinophilia [61]. Taking all these findings into account, researchers have conducted RCTs to assay the anti-IL-5 monoclonal antibodies mepolizumab and reslizumab in both adult [62] and pediatric [63, 64] EoE patients. The drug significantly reduced tissue eosinophils, albeit not to normal levels. Unfortunately, clinical improvement was minimal.
- Omalizumab is an anti-IgE monoclonal antibody used to control asthma in severely allergic asthmatic patients [65]. It has also been assessed as a treatment for EoE in short case series [66–68] and in an RCT [69]. None of these studies reported any improvements in either esophageal eosinophilic infiltration or clinical symptoms after treatment.
- IL-13 is a Th2-type cytokine that constitutes a major regulator of the epithelial cell pathways involved in the pathogenesis of EoE. It does this through direct induction of a large number of EoE-associated genes, including eotaxin-3. IL-13 has thus been recognized as a potential therapeutic target for treatment of the disease [32•]. A phase 2, double-blind RCT has ascertained the safety and effect of an intravenously administered anti-IL-13 antibody (QAX576, Novartis, Switzerland) on the frequency and severity of symptoms in EoE patients [70], but the results have yet to be reported.

Other experimental agents

- Transforming growth factor (TGF)-β, which is produced by eosinophils, mast cells, and other inflammatory cells, has been described as

a key mediator in the pathophysiology of EoE, directly involved in esophageal fibrous remodeling in both pediatric [7] and adult patients [8]. A single-nucleotide polymorphism in the TGF-β gene has also been proposed as a susceptibility factor for the disease [7]. Losartan, an angiotensin II receptor-blocker, has been approved for the treatment of high blood pressure in children and adults, and has proven safe when administered to patients with normal blood pressure. Losartan may reduce the amount of TGF-β and thus constitutes a potential treatment for eosinophilic esophagitis. A phase 2 trial administering increasing doses of losartan to pediatric and adult EoE patients is currently underway to evaluate endoscopic, histological, and symptomatic improvement after a 5-year follow-up period [71].

Dietary treatment of EoE

- With all research indicating that EoE is a form of food allergy, various types of dietary interventions have been proposed to offer a potentially effective, drug-free treatment option for long-term remission of both symptoms and inflammatory infiltration. Initially assessed predominantly in pediatric series, more recent research has focused on adult patients and less restrictive dietary therapies.

Elemental diet

- EoE was first characterized as form of food allergy as early as 1995, when 10 children fed exclusively with an amino acid-based formula exhibited symptom relief and histological normalization [21••]. Since then, several pediatric studies have reproduced these results [42•, 72, 73, 74••]. The results show that overall, more than 90 % of patients rapidly reach peak eosinophil counts <15 per hpf, with symptoms improving in >96 % of cases.
- Elemental diet has also been recently evaluated in adult EoE patients [75•]. In one study, 29 patients were prospectively fed exclusively with an elemental formula, avoiding any kind of table food for a 4-week period. A pathological infiltration of >15 eos/hpf persisted in only one of the 18 adults who completed the study. The per-protocol efficacy of this study was 94.4 %, which decreased to 58.8 % when analyzed for intention to treat, indicating the poor tolerability of this approach in adults.
- Despite having demonstrated a higher effectiveness in inducing EoE remission than any other dietary intervention, its many drawbacks, including its unpleasant taste, high cost, low adherence rates [76], and the psychological and social implications of complete avoidance of table food, restrict the use of elemental diet in clinical practice to feeding infants and toddlers, among whom the restriction of not having any additional food is better tolerated,

and only for the length of time required for food reintroduction in order to identify specific dietary triggers.

Skin allergy testing-elimination diet

- This approach consists of testing for food allergies by means of skin prick testing (SPT) and atopy patch testing (APT), with subsequent elimination of foods that give a positive test result. In children, this strategy initially showed a 77 % rate of histological remission [77], although subsequent retrospective analyses have shown a reduced remission rate of 53 % [78]. It is worth noting that these results have not been extensively replicated at other centers. As for adults, elimination of wheat and rye in six sensitized EoE patients as measured through IgE and SPT did not lead to clinical or histological resolution [79]. A more recent series in 22 patients who underwent SPT and APT to 26 different foods showed a suboptimal 33 % histological response for this therapeutic strategy [80].
- A growing body of evidence points to the involvement of a cell-mediated delayed reaction against foods in the pathophysiology of EoE rather than a predominantly IgE-mediated reaction. As a result, the clinical utility of immediate IgE testing for dietary intervention in patients with EoE remains largely limited. In fact, food triggers can currently only be unequivocally identified by documenting disease remission after specific food antigen avoidance followed by EoE recrudescence upon specific food reintroduction [1•]. This is the strategy followed by the empirical elimination diets and food reintroduction protocols described below.

Empiric six-food elimination diet

- The elimination of the six foods most commonly associated with food allergies in children was proposed in order to overcome the disadvantages of elemental diets and allergy testing-directed food elimination. The original six-food elimination diet (SFED) excluded milk protein, soy, eggs, wheat, peanut/tree nuts, and seafood, and led to significant improvement of esophageal inflammation (<10 eos/hpf) and symptom relief in 74 % of the 35 children treated during a 6-week period [73]. These results have recently been confirmed in a retrospective series [74••].
- The high response rate to SFED documented in children has been reproduced in adults in two prospective American and European series [81, 82]. It is worth noting that the original list of restricted foods [73] was modified in all subsequent studies either to additionally exclude those foods with a positive SPT result [74••, 83] or according to geographical food sensitization patterns [82].

- After SFED-disease remission, the identification of specific food triggers was carried out by means of sequential, single-food reintroduction under endoscopic and bioptic monitoring [82, 84] to document food-challenge-induced disease recurrence. Cow's milk, wheat, and eggs were shown to be the major food triggers identified in all studies; however, the prevalence of the remaining foods varied among different studies, prompting researchers to design empirical elimination diets tailored to the staple diet and sensitization patterns of patients from each region [82].
- Two studies evaluating the sustained efficacy of avoiding specific food triggers in adult EoE demonstrated that disease remission was maintained for up to 3 years in every patient who followed the diet [82, 85].
- Finally, an interventional study to compare the efficacy of SFED versus either swallowed FP or budesonide in pediatric patients with active EoE is currently underway [86].

Empiric four-food elimination diet

- All of the studies on six-food elimination diets in children [87] and adults [82, 83] have revealed a major role as causative food allergens for cow's milk, wheat, eggs, and soy/legumes, with a minor role for nuts and fish/seafood. Therefore, one can speculate that a four-food elimination diet including the aforementioned common food triggers could improve patient adherence to dietary restrictions and reduce both the number of endoscopies and the overall time necessary for completing the food reintroduction process. Several ongoing prospective studies on this novel dietary approach in children and adults are showing promising preliminary results, with remission rates ranging from 46–75 % [88–90].

Other diet-based therapies for EoE

- Exclusive elimination of cow's milk protein, the most common food trigger for EoE [74••, 82, 84, 91], has been retrospectively assessed in a pediatric EoE series [92]. Disease remission (<15 eos/hpf) was documented in 65 % of patients and symptom improvement was observed in all cases after the elimination of milk alone. The unexpected high efficacy of this strategy, which may have been influenced by patient inclusion bias, needs to be confirmed in further research.
- A gluten-free diet has been used in some case reports and case series of EoE patients [93–97], most of whom had co-existing celiac disease, with uneven results regarding its effect on the esophageal eosinophilic infiltrate. The precise association between both diseases should be clarified before defining this diet's possible role in treating EoE patients.

Endoscopic dilation

- Esophageal dilation is a mechanical procedure that has been demonstrated to effectively improve symptoms in the majority of EoE patients at least in the short term, according to a recent meta-analysis [98••]. However, it has no effect on the underlying inflammatory process [99]. Because early reports on dilation treatment in patients with EoE described a higher than expected complication rate, it came to be considered a risky procedure [100].
- Endoscopic dilation has mostly been used in adult EoE patients, among whom esophageal stenosis with reductions in the esophageal caliber are usually observed. When performed by an experienced specialist, esophageal dilation is a safe procedure, as demonstrated by case series-based studies [99, 101, 102] and a meta-analysis [98]. There are, however, several proven risk factors for complications, including a long history of dysphagia, high eosinophil density, younger patient age, repeated procedures, and luminal narrowing in the upper and middle esophageal thirds [103, 104].

Allergy immunotherapy

- Allergy immunotherapy (AIT) is a well-established and effective treatment for allergic rhinitis and asthma that can induce tolerance to environmental allergens. EoE patients frequently present aeroallergen sensitization [20, 105]; in fact, seasonal variation in EoE diagnosis and symptoms has been reported, with both increasing during the months with higher environmental pollen concentrations [106–108]. AIT has thus been proposed as a treatment modality for patients with EoE and aeroallergen sensitization. In one off-label, interventional study, AIT was offered to patients who were then evaluated with the aid of a questionnaire, laboratory tests, and endoscopic and bioptic evaluation of changes in the disease before and after treatment [109]. It is important to note that an increasing number of studies have reported the development of EoE after milk [110] and egg [111] oral immunotherapy. Although data on long-term food tolerance induction are still scarce [87], the possibility of a change in the immune response pattern from a Th2 to Th1-type allergy should be considered. At this time, however, AIT for the treatment of EoE should only be considered in a research protocol.

Unresolved aspects & suggestions for future research

- EoE is a chronic disease that recurs upon discontinuation of treatment. As such, maintenance therapy should be considered in all patients. As long-term therapies, steroids are hampered by their potential long-term side effects whereas dietary interventions may impair social functioning and quality of life, especially in children and adolescents.

- The choice of a maintenance therapy will depend, to a large extent, on patient preference, provider experience, and local expertise.
- Diet therapy can be enhanced in the short term through less restrictive schemes and less invasive methods of monitoring response to treatment.
- New steroid formulations will most likely reduce the rate of steroid-refractory patients, many of who are probably not receiving an appropriate dose of the drug to the esophageal mucosa due to the drug delivery system, which relies on inhalation-designed devices. As for true steroid-dependent or refractory patients, multiple ongoing trials are evaluating drugs involving specific immunological targets in the pathogenesis of EoE. While the rationale for these drugs is plausible (avoidance of long-term steroids and ability to modify the natural course of the disease), histological and clinical responses have been much more modest than those accomplished with steroids or diet.
- Currently, remission of both symptoms and esophageal eosinophilia remain the gold standard for assessing the efficacy of available therapies, even though dissociation between clinical and histological activity is common in EoE. A better understanding of predictors of therapeutic success in patients with fibrostenotic (i.e., esophageal distensibility) and inflammatory (i.e., genetic biomarkers) phenotypes is crucial for the proper selection of effective long-term therapies for EoE. Aspects concerning health-related QoL will also be a major factor in deciding on future therapeutic modalities for this disease.

Compliance with Ethics Guidelines

Conflict of Interest
Alfredo J. Lucendo and Javier Molina-Infante declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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

These expert committee-consensual guidelines for management of EoE in children and adults is an update of those published in 2007. As a reference document, it revises and discuses all the available relevant information on EoE, providing recommendation for further research.

2.•• DeBrosse CW, Franciosi JP, King EC, et al. Long-term outcomes in pediatric-onset esophageal eosinophilia. J Allergy Clin Immunol. 2011;128:132–8.

After EoE patients were retrospectively identified through a review of pediatric esophageal biopsy specimens up to 1999, they were contacted 15 years later and asked to participate in a questionnaire-based study; quality of life was significantly lower among patients compared with control subjects, while

EoE symptoms persisted throughout time.

3. Lucendo AJ, Sánchez-Cazalilla M. Adult versus pediatric eosinophilic esophagitis: important differences and similarities for the clinician to understand. Expert Rev Clin Immunol. 2012;8:733–45.
4. 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;125:1660–9.
5.• Schoepfer AM, Safroneeva, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation, in a time-dependent manner. Gastroenterology. 2013;145:1230–6.

A retrospective analysis of a database demonstrated that the duration of untreated disease directly correlated with the prevalence of esophageal fibrotic strictures in adult EoE patients.

6. Chehade M, Sampson HA, Morotti RA, et al. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2007;45:319–28.
7. Aceves SS, Newbury RO, Dohil R, et al. Esophageal remodeling in pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2007;119:206–12.
8. 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;128:1037–46.
9.• Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology. 2010;139:1526–37.

This RCT is the first evaluation of budesonide in adult EoE patients; a 15-day course of treatment achieved histological and clinical remission of EoE, with no serious side effects.

10. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med. 2004;351:940–1.
11. 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;128:1349–50.
12. Arias A, Lucendo AJ. Prevalence of eosinophilic oesophagitis in adult patients in a central region of Spain. Eur J Gastroenterol Hepatol. 2013;25:208–12.
13. Soon IS, Butzner JD, Kaplan GG, et al. Incidence and prevalence of eosinophilic esophagitis in children. J Pediatr Gastroenterol Nutr. 2013;57:72–80.
14. Dellon ES, Jensen ET, Martin CF, et al. The prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol. 2013. doi:10.1016/j.cgh.2013.09.008.
15. Spergel JM, Book WM, Mays E, et al. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. J Pediatr Gastroenterol Nutr. 2011;52:300–6.
16. Lucendo AJ, Friginal-Ruiz AB, Rodriguez B. Boerhaave's syndrome as the primary manifestation of adult eosinophilic esophagitis. Two case reports and a review of the literature. Dis Esophagus. 2011;24:E11–5.
17. Miller SM, Goldstein JL, Gerson LB. Cost-effectiveness model of endoscopic biopsy for eosinophilic esophagitis in patients with refractory GERD. Am J Gastroenterol. 2011;106:1439–45.
18. DeBrosse CW, Collins MH, Buckmeier Butz BK, et al. Identification, epidemiology, and chronicity of pediatric esophageal eosinophilia, 1982–1999. J Allergy Clin Immunol. 2010;126:112–9.
19. Roy-Ghanta S, Larosa DF, Katzka DA. Atopic characteristics of adult patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2008;6:531–5.
20. Castro Jiménez A, Gómez Torrijos E, García Rodríguez R, et al. Demographic, clinical and allergological characteristics of Eosinophilic Esophagitis in a Spanish central region. Allergol Immunopathol (Madr). 2013;10. doi: 10.1016/j.aller.2013.04.004.
21.•• Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995;109:1503–12.

The first demonstration of EoE as a characteristic form of food allergy came after documenting disease remission after exclusive feeding with an amino acid-based elemental formula in a series of pediatric EoE patients. This seminal research established the first gold standard against which to compare further treatment options while simultaneously demonstrating that food allergies cause esophagitis.

22. González-Castillo S, Arias A, Lucendo AJ. Treatment of eosinophilic esophagitis: how should we manage the disease? J Clin Gastroenterol. 2010;44:663–71.
23.• 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;67:1299–307.

This retrospective research demonstrated that subepithelial collagen deposition associated with eosinophilic inflammation reverted after dietary or steroid treatment in children with EoE.

24.• Spergel JM, Book WM, Mays E, et al. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. J Pediatr Gastroenterol Nutr. 2011;52:300–6.

This study, which aimed to define the national prevalence of EoE, found that EoE was most common in the northwestern US and urban areas. A considerable variability in diagnostic and initial therapeutic approaches was documented.

25.• Lucendo AJ, Arias A, Molina-Infante J, et al. Diagnostic and therapeutic management of eosinophilic oesophagitis in children and adults: results from a Spanish registry of clinical practice. Dig Liver Dis. 2013;45:562–8.

A nationwide prospective survey-based registry of pediatric and adult patients with EoE documented a wide variability in clinical practice regarding diagnostic and therapeutic management of patients. Physician experience and the availability of hospital facilities were the major explanatory factors.

26. Faubion Jr WA, Perrault J, Burgart LJ, et al. Treatment of eosinophilic esophagitis with inhaled corticosteroids. J Pediatr Gastroenterol Nutr. 1998;27:90–3.

27. Teitelbaum JE, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. Gastroenterology. 2002;122:1216–25.

28.• Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clin Gastroenterol Hepatol. 2008;6:165–73.

A RCT comparing systemic and topical steroid use demonstrated that both were effective in achieving histological and clinical remission of EoE; after discontinuation of treatment, disease recurred in both groups of patients.

29. Lucendo AJ, Navarro M, Comas C, et al. Immunophenotypic characterization and quantification of the epithelial inflammatory infiltrate in eosinophilic esophagitis through stereology: an analysis of the cellular mechanisms of the disease and the immunologic capacity of the esophagus. Am J Surg Pathol. 2007;31:598–606.

30.• Moawad FJ, Veerappan GR, Dias JA, et al. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. Am J Gastroenterol. 2013;108:366–72.

This RCT prospectively compared the histological and clinical response of adult EoE patients to aerosolized swallowed FP vs. esomeprazole. Both drugs provided a similar histological response for esophageal eosinophilia, but esomeprazole was superior to FP in achieving clinical improvement, particularly in patients with established GERD.

31.• Peterson KA, Thomas KL, Hilden K, et al. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. Dig Dis Sci. 2010;55:1313–9.

A prospective RCT conducted in adult EoE patients demonstrated that an 8-week course of esomeprazol 40 mg every morning produced no differences in the degree of eosinophil esophageal infiltration reduction or dysphagia improvement compared with aerosolized, swallowed FP 440 mcg twice a day. The authors proposed GERD as a relevant pathogenic agent for EoE.

32.• Blanchard C, Mingler MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. J Allergy Clin Immunol. 2007;120:1292–300.

This research demonstrated the central role that IL-13 plays in the pathogenesis of EoE, since cultures of esophageal epithelial cells reproduced an EoE characteristic transcriptome when stimulated with IL-13. After treatment with corticosteroids, changes in the gene expression reverted to normal. The authors proposed IL-13 as a potential therapeutic target in EoE.

33. Lucendo AJ, De Rezende L, Comas C, et al. Treatment with topical steroids downregulates IL-5, eotaxin-1/CCL11, and eotaxin-3/CCL26 gene expression in eosinophilic esophagitis. Am J Gastroenterol. 2008;103:2184–93.

34. Aceves SS, Bastian JF, Newbury RO, et al. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. Am J Gastroenterol. 2007;102:2271–9.

35. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2011;9:400–9.

36. OBS in adolescent and young adults with EoE: a phase ii, randomized double-blind placebo controlled study with an open label extension. Available from: http://clinicaltrials.gov/ct2/show/NCT01642212?term=budesonide+eosinophilic+esophagitis&rank=7 [Cited 25 September 2013].

37. Dose-ranging study of oral viscous budesonide in pediatrics with eosinophilic esophagitis. Available from: http://clinicaltrials.gov/ct2/show/NCT00762073?term=budesonide+eosinophilic+esophagitis&rank=4 [Cited 25 September 2013].

38. Schroeder S, Fleischer DM, Masterson JC, et al. Successful treatment of eosinophilic esophagitis with ciclesonide. J Allergy Clin Immunol. 2012;129:1419–21.

39. Lee JJ, Fried AJ, Hait E, et al. Topical inhaled ciclesonide for treatment of eosinophilic esophagitis. J Allergy Clin Immunol. 2012;130:1011–2.

40. Attwood SE, Lewis CJ, Bronder CS, et al. Eosinophilic oesophagitis: a novel treatment using Montelukast. Gut. 2003;52:181–5.

41. Stumphy J, Al-Zubeidi D, Guerin L, et al. Observations on use of montelukast in pediatric eosinophilic esophagitis: insights for the future. Dis Esophagus. 2011;24:229–34.

42.• Lucendo AJ, De Rezende LC, Jimenez-Contreras S, et al. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. Dig Dis Sci. 2011;56:3551–8.

This prospective observational study treated adult patients with montelukast at usual doses after having induced histological and clinical remission of EoE with FP. Disease recurrence occurred in every recruited patient within the first 3 months of treatment, demonstrating the unsuitability of montelukast as a steroid-sparing drug.

43. Eosinophilic esophagitis treatment: montelukast vs fluticasone. Available from: http://clinicaltrials.gov/ct2/show/NCT01702701?term=%22fluticasone%22+and+%22eosinophilic+esophagitis%22&rank=3 [Cited 25 September 2013].

44. A trial of montelukast for maintenance therapy of eosinophilic esophagitis in children. Available from: http://clinicaltrials.gov/ct2/show/NCT01458418?term=%22eosinophilic+esophagitis%22&rank=32 [Cited 26 September 2013].

45.•• 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;108:679–92.

The most recent guidelines for diagnosing and treating EoE patients have been recently published. Evidence levels are provided for each statement.

46. Molina-Infante J, Katzka DA, Gisbert JP. Review article: proton pump inhibitor therapy for suspected eosinophilic oesophagitis. Aliment Pharmacol Ther. 2013;37:1157–64.

47. Cortes JR, Rivas MD, Molina-Infante J, et al. Omeprazole inhibits IL-4 and IL-13 signaling signal transducer and activator of transcription 6 activation and reduces lung inflammation in murine asthma. J Allergy Clin Immunol. 2009;124:607–10.

48. Zhang X, Cheng E, Huo X, et al. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. PLoS One. 2012;7:e50037.

49.•• Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut. 2013;62:824–32.

The anti-inflammatory capacities of PPIs are demonstrated in this research, in which epithelial cell cultures of eosinophilic esophagitis were stimulated by Th2 cytokines to produce eotaxin-3. PPIs blocked the cytokine-stimulated synthesis of eotaxin-3 by acting on the promotor sequence of the gene at a concentration equivalent to therapeutic doses.

50. Krarup AL, Villadsen GE, Mejlgaard E, et al. Acid hypersensitivity in patients with eosinophilic oesophagitis. Scand J Gastroenterol. 2010;45:273–81.

51.• Netzer P, Gschossmann JM, Straumann A, et al. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. Eur J Gastroenterol Hepatol. 2007;19:865–9.

This short case series is the only published evidence of the utility of tiopurins for maintaining long-term remission in steroid-dependent or refractory EoE and eosinophilic gastroenteritis with esophageal involvement. Disease recurred in every patient after discontinuation of therapy.

52. Halleck F, Duerr M, Waiser J, et al. An evaluation of sirolimus in renal transplantation. Expert Opin Drug Metab Toxicol. 2012;8:1337–56.

53. Dasari TW, Patel B, Saucedo JF. Systematic review of effectiveness of oral sirolimus after bare-metal stenting of coronary arteries for prevention of in-stent restenosis. Am J Cardiol. doi:10.1016/j.amjcard.2013.05.074.

54. Sirolimus for eosinophil-associated gastrointestinal disorders. Available from: http://clinicaltrials.gov/ct2/show/NCT01814059?term=%22eosinophilic+esophagitis%22&rank=45 [Cited 26 September 2013].

55.• Straumann A, Hoesli S, Bussmann C, et al. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. Allergy. 2013;68:375–85.

This RCT assessed the effectiveness of a CRTH2 antagonist for inducing remission in steroid-dependent or resistant adult EoE patients. After an 8-week treatment, the study drug exerted a modest, but significant, anti-eosinophil and clinical effect compared to placebo.

56.• Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. J Clin Invest. 2006;116:536–47.

The importance of eotaxin-3 as a critical effector molecule for EoE was underscored by this research, which also identified a single-nucleotide polymorphism in the eotaxin-3 gene as a potential risk factor for the disease. A characteristic conserved transcriptome was also defined for EoE through genome-wide microarray expression analysis, opening new possibilities for molecular diagnosis in EoE patients.

57. Straumann A, Bauer M, Fischer B, et al. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. J Allergy Clin Immunol. 2001;108:954–61.

58. Straumann A, Bussmann C, Conus S, et al. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. J Allergy Clin Immunol. 2008;122:425–7.

59. Mishra A, Hogan SP, Brandt EB, et al. IL-5 promotes eosinophil trafficking to the esophagus. J Immunol. 2002;168:2464–9.

60. Yamazaki K, Murray JA, Arora AS, et al. Allergen-specific in vitro cytokine production in adult patients with eosinophilic esophagitis. Dig Dis Sci. 2006;51:1934–41.

61. Bullock JZ, Villanueva JM, Blanchard C, et al. Interplay of adaptive th2 immunity with eotaxin-3/c-C chemokine receptor 3 in eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2007;45:22–31.

62. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. Gut. 2010;59:21–30.

63. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology. 2011;141:1593–604.

64. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2012;129:456–63. 463.
65. McKeage K. Omalizumab: a review of its use in patients with severe persistent allergic asthma. Drugs. 2013;73:1197–212.
66. Echeverría Zudaire L, Fernández Fernández S, Rayo Fernández A, et al. No eficacia de omalizumab (Xolair) en el tratamiento de un paciente con esofagitis eosinofílica. Allergol Immunopathol (Madr). 2008;36(extraordinario 1):68–9.
67. Foroughi S, Foster B, Kim N, et al. Anti-IgE treatment of eosinophilic-associated gastrointestinal disorders. J Allergy Clin Immunol. 2007;120:594–601.
68. Rocha R, Vitor AB, Trindade E, et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. Eur J Pediatr. 2011;170:1471–4.
69. Fang JC, Hilden K, Gleich GJ, et al. A pilot study of the treatment of eosinophilic esophagitis with omalizumab. Gastroenterology. 2011;140:5.
70. Efficacy and safety of QAX576 in patients with eosinophilic esophagitis. Available from: http://clinicaltrials.gov/ct2/show/study/NCT01022970?term=%22eosinophilic+esophagitis%22&rank=22 [Cited 26 September 2013].
71. Testing effectiveness of losartan in patients with EoE with or without a CTD. Available from: http://clinicaltrials.gov/ct2/show/record/NCT01808196?term=%22eosinophilic+esophagitis%22&rank=39 [Cited 26 September 2013].
72. Markowitz JE, Spergel JM, Ruchelli E, et al. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol. 2003;98:777–82.
73. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2006;4:1097–102.
74.•• Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2012;129:1570–8.
A retrospective analysis of a large series of pediatric patients with EoE documented that an elemental diet, a six-food elimination diet, and a skin allergy testing-directed elimination diet were effective in inducing disease remission of EoE. Although the skin allergy testing-directed diet was as effective as the six-food elimination diet, the negative predictive values of foods most commonly reintroduced in single-food challenges were not sufficient to support the dietary advancement plans based solely on skin test results.
75.• Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. Am J Gastroenterol. 2013;108:759–66.
The first evaluation of exclusive feeding with an elemental diet in adult patients with EoE demonstrated it to be as highly effective as in children. However, adherence to the diet posed a problem
76. Hommel KA, Franciosi JP, Gray WN, et al. Behavioral functioning and treatment adherence in pediatric eosinophilic gastrointestinal disorders. Pediatr Allergy Immunol. 2012;23:494–9.
77. Spergel JM, Andrews T, Brown-Whitehorn TF, et al. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. Ann Allergy Asthma Immunol. 2005;95:336–43.
78. 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;130:461–7.
79. Simon D, Straumann A, Wenk A, et al. Eosinophilic esophagitis in adults–no clinical relevance of wheat and rye sensitizations. Allergy. 2006;61:1480–3.
80. Molina-Infante J, Martin-Noguerol E, Alvarado-Arenas M, et al. Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis. J Allergy Clin Immunol. 2012;130:1200–2.
81. Gonsalves N, Yang GY, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology. 2012;142:1451–9.
82. Lucendo AJ, Arias A, Gonzalez-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. J Allergy Clin Immunol. 2013;131:797–804.
83. Gonsalves N, Yang GY, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology. 2012;142:1451–9.
84. Kagalwalla AF, Shah A, Li BU, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. J Pediatr Gastroenterol Nutr. 2011;53:145–9.
85. Gonsalves N, Doerfler B, Hirano I. Long term maintenance therapy with dietary restriction in adults with eosinophilic esophagitis [abstract]. Gastroenterology. 2011;140(5, Suppl 1):S-180–1.
86. Dietetic versus topical steroids for pediatric eosinophilic esophagitis. Available from: http://clinicaltrials.gov/ct2/show/record/NCT01846962?term=fluticasone+and+eosinophilic+esophagitis&rank=7 [cited 25 September 2013].
87. Kagalwalla AF, Shah A, Li BU, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully

treated with empiric elimination diet. J Pediatr Gastroenterol Nutr. 2011;53:145–9.

88. Gonsalves N, Doerfler B, Schwartz S, et al. Prospective trial of four food elimination diet demonstrates comparable effectiveness in the treatment of adult and pediatric eosinophilic esophagitis. Gastroenterology. 2013;144 suppl 1:S-154.
89. Molina-Infante J, Sanchez-Rodriguez J, Arias A, et al. An optimized four-food elimination diet (dairy, gluten, egg and legumes) might be as effective as six-food elimination diet for adult eosinophilic esophagitis: preliminary results. Eosinophilic Esophagitis: A Novel Chronic-Inflammatory Disease of the GI Tract. 2013, September 6–7, 2013, Graz, Austria.
90. Amsden K, Schwartz S, Chehade M, et al. Effect of four food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Eosinophilic Esophagitis: A Novel Chronic-Inflammatory Disease of the GI Tract* 2013, September 6–7, 2013, Graz, Austria.
91. 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;130:461–7.
92. Kagalwalla AF, Amsden K, Shah A, et al. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2012;55:711–6.
93. Al-Hussaini A, Al-Idressi E, Al-Zahrani M. The role of allergy evaluation in children with eosinophilic esophagitis. J Gastroenterol. 2013. doi:10.1007/s00535-012-0741-6.
94. Quaglietta L, Coccorullo P, Miele E, et al. Eosinophilic oesophagitis and coeliac disease: is there an association? Aliment Pharmacol Ther. 2007;26:487–93.
95. Verzegnassi F, Bua J, De AP, et al. Eosinophilic oesophagitis and coeliac disease: is it just a casual association? Gut. 2007;56:1029–30.
96. Ooi CY, Day AS, Jackson R, et al. Eosinophilic esophagitis in children with celiac disease. J Gastroenterol Hepatol. 2008;23:1144–8.
97. Leslie C, Mews C, Charles A, et al. Celiac disease and eosinophilic esophagitis: a true association. J Pediatr Gastroenterol Nutr. 2010;50:397–9.
98.•• Moawad FJ, Cheatham JG, Dezee KJ. Meta-analysis: the safety and efficacy of dilation in eosinophilic oesophagitis. Aliment Pharmacol Ther. 2013;38:713–20.

Dilation in patients with eosinophilic esophagitis was demonstrated to be a safe procedure with a low rate of serious complications (<1 %). It resulted in at least short-term improvement of symptoms in the majority of patients.

99. Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. Am J Gastroenterol. 2010;105:1062–70.
100. Lucendo AJ, De Rezende L. Endoscopic dilation in eosinophilic esophagitis: a treatment strategy associated with a high risk of perforation. Endoscopy. 2007;39:376.
101. Dellon ES, Gibbs WB, Rubinas TC, et al. Esophageal dilation in eosinophilic esophagitis: safety and predictors of clinical response and complications. Gastrointest Endosc. 2010;71:706–12.
102. Ally MR, Dias J, Veerappan GR, et al. Safety of dilation in adults with eosinophilic esophagitis. Dis Esophagus. 2013;26:241–5.
103. Cohen MS, Kaufman AB, Palazzo JP, et al. An audit of endoscopic complications in adult eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2007;5:1149–53.
104. Dellon ES, Gibbs WB, Rubinas TC, et al. Esophageal dilation in eosinophilic esophagitis: safety and predictors of clinical response and complications. Gastrointest Endosc. 2010;71:706–12.
105. Simon D, Marti H, Heer P, et al. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. J Allergy Clin Immunol. 2005;115:1090–2.
106. Almansa C, Krishna M, Buchner AM, et al. Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. Am J Gastroenterol. 2009;104:828–33.
107. Moawad FJ, Veerappan GR, Lake JM, et al. Correlation between eosinophilic oesophagitis and aeroallergens. Aliment Pharmacol Ther. 2010;31:509–15.
108. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. J Allergy Clin Immunol. 2003;112:796–7.
109. Allergy Immunotherapy in the Management of Eosinophilic Esophagitis (AIMEE). Available from: http://clinicaltrials.gov/ct2/show/NCT01685034?term=allergy+immunotherapy+and+eosinophilic+esophagitis&rank=1 [Cited 25 September 2013].
110. Sanchez-Garcia S, Del Rodriguez RP, Escudero C, et al. Possible eosinophilic esophagitis induced by milk oral immunotherapy. J Allergy Clin Immunol. 2012;129:1155–7.
111. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. Ann Allergy Asthma Immunol. 2011;106:73–4.