Treatment of Eosinophilic Esophagitis
How Should We Manage the Disease?

Sonia González-Castillo, MD, Ángel Arias, BSc, and Alfredo J. Lucendo, MD, PhD, FEBG

Abstract: Eosinophilic esophagitis (EE) is a chronic clinicopathologic syndrome and is the latest inflammatory disease of the esophagus described in literature. It seems to have a multifactorial etiology. Its causes include exposure to food or airborne allergens that affect individuals who may be genetically predisposed and exposure to the acid could also modulate the inflammatory response at esophageal level. However, we currently do not know how each of these possible etiologic factors contribute to the development of the disease that is essential to define specific treatment. We have used 3 different therapeutic approaches that were effective in patients with EE: various antiinflammatory drugs that are useful in treating asthma, controlling the exposure to allergens, particularly with respect to dietary changes and dilation of the esophagus. Although none of these treatments have absolute advantages, they can efficiently control the symptoms and inflammation in a large number of patients. Each treatment option should be assessed on a case-by-case basis in accordance with the experience of each center, the patients' characteristics, their sensitivity to allergens and their preferences. This article provides the latest information on the different treatment options for patients with EE, analyzing the advantages and disadvantages of each pathology and it offers practical recommendations on how to manage these patients who are being more frequently diagnosed.

Key Words: eosinophilic esophagitis, treatment, topical steroids, nutritional management, endoscopic dilation

(*J Clin Gastroenterol* 2010;44:663–671)

Eosinophilic esophagitis (EE) is a chronic clinicopathologic syndrome and is the latest inflammatory disease of the esophagus described in literature. It has become increasingly recognized in recent years since it was defined during the mid-nineties as a characteristic clinicopathologic syndrome different to eosinophilic gastroenteritis.[1] The number of reported cases and publications on the subject has increased exponentially and many cases have been brought to our attention from every continent, except Africa. Although the recognition of EE has led to a revolution in digestive allergic diseases, many of its physiopathologic and therapeutic aspects and matters concerning the natural history of the disease still remained unanswered today.

The accumulation of eosinophils in the esophagi of patients with EE seems to be directed by exposure to certain antigens, which it why it was considered an immunoallergic disorder and treated using drugs used for bronchial asthma.[2] More recently, it has been suggested that certain immune-regulatory genes could be a possible cause of EE[3] and gastroesophageal reflux (GER) could be involved in its physiopathology, although the coexistence of both has been considered as both the cause and effect.[4] EE could therefore be a disease with multifactorial causes, determined by the exposure of the esophageal mucosa's immunologic system to food or airborne allergens, modulated by the exposure of genetically predisposed individuals to acid. It would be essential to know how each of these possible etiologic factors contribute to the development of the disease to define specific treatment.

Although EE has gained importance in recent years, at present, there are no commonly accepted treatment strategies and the adequate management of these patients has been somewhat controversial. In addition, there are no randomized controlled studies available (except for 2 studies of pediatric patients[5,6] and a recent study on adults[7]) and it is difficult to control all the etiologic factors that may contribute to the development of EE. In addition, very little is known of the long-term effects of the different therapies in controlling inflammation of the organ and of their ability to modify the natural history of the disease.

The therapies tested include: (a) eliminating potential allergen triggers from the diet that could be a useful measure despite their disadvantages; (b) various drugs useful for the treatment of other inflammatory conditions but which have not been officially approved for EE, and (c) endoscopic treatment that aims to correct alterations in the caliber of the esophagus through dilation. This article reviews the efficiency and usefulness of the various therapies for EE documented in literature and aims to provide a rough guide for the practical management of the patients.

DIETARY MANAGEMENT AND CONTROL OF ANTIGENIC EXPOSURE

The first studies conducted on children with EE showed that allergies to certain components of the diet contributed significantly to its pathogenesis and that its symptoms and histopathologic findings improved in most cases once certain foods had been eliminated. After initial studies based exclusively on elemental diets in which all proteins were substituted,[8] other treatment approaches simply focused on eliminating the foods that triggered the disease. These strategies were based on using different allergy tests such as skin-prick testing (SPT) and atopic

From the Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso (Ciudad Real), Spain.

The authors did not receive any funding or financial support for this study.

The authors had no conflict of interest or affiliation with any of the institutions, organizations, or companies that might be mentioned in the manuscript.

Reprints: Alfredo J. Lucendo, MD, PhD, FEBG, Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos, s/n. 13700 Tomelloso (Ciudad Real), Spain (e-mail: alucendo@vodafone.es).

patch testing (APT) to detect food allergies in children[9,10] and both have been quite successful in guiding the management of these patients. However, because the involvement of a non-IgE, cell-mediated response in EE[11] is becoming more widely accepted, the use of these allergy techniques has been controversial, especially with regard to adult patients with EE for whom new specific studies should be conducted.

Elemental Diet

The elemental diet consists of feeding using a formula composed of essential amino acids and water and is therefore antigen free. It was first used with a group of children with EE attributed to GER in 1995 by Kelly et al[8] and led to complete clinical and histologic remission in 80% of the cases (and partial in the rest) over a 6-week treatment period, and the symptoms reappeared once to the children resumed their normal diets. This study established that childhood EE could be considered a food allergy. These results were corroborated by a study carried out in 2003 on 346 children diagnosed with chronic gastroesophageal reflux disease (GERD) who followed an elemental diet for 1 month. Of these, 51 presented EE, of which 49 showed clinical remission.[12] A large retrospective pediatric study of cases of EE published by Liacouras et al[13] showed significant improvement in clinical symptoms and esophageal eosinophilia in 160 of the 164 patients (97%), where food was completely eliminated using an amino-acid formula that worked successfully.

Aside from being the gold standard for the treatment of EE, elemental diets have a number of disadvantages in that they are expensive and have an unpleasant taste, which in many cases means that patients must be fed through a nasogastric tube (up to 80% of patients in the most recent study[13]). Another important disadvantage is that it cannot be used in chronic cases or for adults.

Exclusion Diets

Another line of dietary treatment tested for EE consisted of eliminating foods that were more likely to trigger allergies, that is those which were more allergenic, despite the individual allergy test results. In 2006, 6 foods (cows' milk protein, soy, wheat, eggs, peanuts, and seafood) were excluded from a cohort of 35 pediatric patients diagnosed with EE, who were compared with another group of 24 patients also with EE following an elemental diet, both over a 6-week period.[14] Seventy-four percent of the patients following exclusion diets showed clinical improvement and a decrease in the esophageal infiltrate by eosinophils and 88% of those on elemental diets. These positive results were not subsequently reproduced in a small study carried out on adults using the same strategy, who reported a symptoms score decrease of 30%, accompanied by incomplete histologic resolution.[15] In conclusion, the empirical exclusion of the aforementioned 6 foods from the diet is an efficient treatment method that is well-tolerated in children with EE as it allows them to eat solid food, but not enough available information exists to be recommended as a sole treatment for adults.

Elimination of Specific Foods Based on Allergy Tests

The third type of dietary treatment for EE involved excluding foods that provoked allergic reactions. Food allergens can be identified through clinical history, by detecting specific IgE levels in the blood, or through SPTs and/or APTs. This can sometimes be complicated as the patient does not usually associate the consumption of certain foods with the development of symptoms of EE, given that its physiopathology seems to be mediated by a delayed hypersensitivity reaction, and if a patient suffers from food allergies, it does not necessarily mean that they are responsible for eosinophilic inflammation of the organ.

In 2002 Spergel et al[9] used SPTs and APTs on patients with EE for the first time to guide the elimination diet and obtained positive results especially with regard to the following food allergens in each test: in SPTs: milk, eggs, peanuts, seafood, peas, beef, fish, rye, wheat, and tomatoes; in APTs: wheat, corn, beef, milk, soy, rye, eggs, chicken, oats, and potatoes. Subsequently, for the first time as a treatment for patients with EE, the same study group eliminated the foods against which allergic reactions were observed during the allergy tests.[10] Of the 146 pediatric patients studied with EE, the corresponding allergy tests identified specific foods in 77 cases and after they were eliminated 77% managed to control the disease whereas 10% showed no improvement. Unfortunately, we do not have any data on studies conducted on adults using the same strategy.

The disadvantage of this treatment strategy is that it is difficult to reproduce the results obtained in other studies because allergy tests are not standardized. Also, most patients need to exclude more than one food type from their diet, which can lead to significant nutritional deficiency that would have to be compensated appropriately, especially in the case of children.

Food reintroduction is very important in the dietary management of EE patients, and should always be considered after taking normal esophageal biopsies from patients on elemental or elimination diets. Food reintroduction aims to improve patients' acceptance of a less restrictive diet and selectively identifies foods causing EE. For the latter reason, a reintroduction sequence must be planned, beginning with those unlikely to cause EE- foods, such as vegetables and fruit, followed by those which are most likely to cause EE, such as corn, chicken, wheat, beef, milk, soy, or eggs.[16] Endoscopic studies and biopsies should be carried out every 1 to 2 months to ensure that there is no inflammation, or as soon as the patient develops esophageal symptoms.

PHARMACOLOGIC TREATMENT FOR EE

Various matters should be taken into consideration when choosing pharmacologic treatment for EE (Table 1). As no drugs have been specifically approved for use in EE to date, we must resort to medication used for other allergic diseases. EE is also a chronic disease that can require long-term treatment, which is why each therapy must be evaluated both in terms of its efficiency and safety to avoid or minimize its possible adverse effects. Furthermore, none of the therapies currently available have been capable of modifying the course of the disease or totally curing its symptoms in the long term. Despite these problems, the need to provide treatment for patients with EE has led to the use of different drugs in recent years, as follows:

Proton Pump Inhibitors (PPIs)

These are not considered to be a specific treatment for EE but they are useful in distinguishing EE from

TABLE 1. Summary Table of Pharmacologic Treatment in Eosinophilic Esophagitis

Pharmacologic Treatment	Recommendations
Proton pump inhibitors (PPIs)	PPI should be used to distinguish between EE and GERD. Also can be recommended in some patients as a cotherapy
Systemic corticoids	Systemic corticosteroids should be used only in severe, refractory, or urgent cases of EE
Topical steroids	Topical steroides are used as first line treatment in both pediatric and adults
Mast cell stabilizers	Mast cells stabilizers have not shown clinical nor histologic improvement, so its use is not recommended
Antileukotrienes	Monteleukast does not improve clinical and histologic remission, although more studies are needed
Azathioprine/6-mercaptopurine	The good results of AZA or 6-MP need confirmation with further studies
MepolizumAb	Mepolizumab not improve clinical manifestations of the disease while reducing the number of eosinophils
Experimental therapies	OmalizumAb and InfliximAb not seem effective in the treatment of EE, although more studies are required
or Future therapies	Therapies using anti IL-13 or antieotaxin 3 antibodies, FGF-9, and Suplatast tosilate could be assessed in the future

GERD[17–19] and can also offer clear benefits for certain patients diagnosed with EE who have secondary symptoms of GERD, which are most likely owing to poor esophageal acid clearance[20] caused by motor alterations associated with eosinophilic inflammation of the organ.

However, 2 recent studies have shown that PPI-based therapies can be effective in the short term for some patients. In the first study, Ngo et al,[21] showed how 3 patients with EE (aged 5, 14, and 25) became asymptomatic after being treated with PPIs for 2 months and had normalized endoscopic findings and fewer eosinophils in the epithelial infiltrate. In the second study, Peterson et al[7] conducted the first prospective, randomized, controlled trial on adults comparing 15 patients treated with swallowed fluticasone to 15 other patients treated with esomeprazole over 8 weeks, and concluded that neither treatment was superior to the other and both led to a decrease in eosinophils and to an improvement of approximately 50% in dysphagia and partial histologic resolution. However, because the study was small, it could have prevented a greater difference from being identified. In view of these results, PPIs can be recommended as a cotherapy for some patients and not only to differentiate EE from GERD. Nevertheless, we do not know what effect gastric acid antisecretory treatment could have on the symptoms and histopathologic findings of EE over the medium and long term and cannot rule out that the symptoms may reappear after some time through continued airborne or dietary antigen exposure that causes for the disease.

Systemic Corticoids

Various studies in the past have shown that systemic corticoids are efficient in controlling the symptoms and esophageal inflammatory infiltrate in EE, but because this is a chronic illness, systemic steroids are not recommended owing to their adverse effects in favor of other safer therapies. Prednisone has been one of the most widely used drugs since the first cases of the disease came to light. Other studies have shown that oral dosages of methylprednisolone[22] of between 0.5 and 1.5 mg/kg/d were also highly effective, although the symptoms and the esophageal eosinophilic infiltrate reappeared several months after the treatment was discontinued.

A recent study compared a systemic corticosteroid (prednisone) with a topical corticosteroid (fluticasone propionate), which were equally effective and showed a rapid clinical and histologic response, although the adverse effects were greater in the group treated with systemic corticosteroids and the symptoms reappeared after the treatment was discontinued.[6] For these reasons, systemic corticosteroids should only be recommended in severe, refractory, or urgent cases of EE.

Topical Steroids

This has been the front-line treatment chosen in many cases of EE[23] and, in particular, fluticasone propionate is the most widely used. Since it was first used in EE,[24] numerous studies[5,22,25–35] have shown that it is as efficient in children and adults as systemic steroids, but has minimum side effects, the most common being pharyngeal-esophageal candidiasis.

The study by Konikoff et al,[5] which consisted of a randomized, double-blind, placebocontrolled trial using fluticasone propionate in pediatric patients with EE is the only study of its kind, and showed that 50% of the patients treated with fluticasone (880 μg divided twice daily over 3 months) experienced histologic remission, a decrease in the number of eosinophils (65.9 vs. 1.4 eosinophils/HPF) and in the number of $CD8^+$ lymphocytes, compared with the placebo group, especially in the proximal third of the esophagus.

The dosages of fluticasone propionate used in the different articles published on EE range from 176 μg/d in children to 1 mg/d in adults (2 dosages given), over a period of 6 to 12 weeks. The main disadvantage of this treatment is that it is difficult to administer (normally by inhaler and must be applied on the tongue and then swallowed to treat EE). Consequently, it is very important to teach patients how to take the drug correctly and inform them that they should not eat or drink for at least 30 minutes afterward. We have a liquid form of fluticasone, which was originally intended for nasal administration, making it easier to swallow. To facilitate correct administration, particularly in the case of children, Aceves et al,[36] used a viscous budesonide solution that gave positive results in 80% of the patients, showing a decrease in the number of eosinophils and remission of symptoms, and no safety issues relating to the drug were reported. The budesonide dosages used for these children were 1 to 2 mg/d in a volume of 8 to 12 mL, taken once per day.

Mast Cell Stabilizers

Although disodium cromoglycate has been used for eosinophilic gastroenteritis owing to its resistance to gastric acidity,[37] no clinical or histologic improvement was observed in a study of 14 children with EE who were given dosages of 100 mg/d (divided into 4 dosages) over 1 month,[13] and, accordingly, we do not have enough evidence to recommend the use of this treatment for EE.

Antileukotrienes

Montelukast, a leukotriene receptor antagonist used to treat bronchial asthma was used in a small group of 8 patients with EE who were given high dosages (up to 100 mg/d).[38] After several weeks of treatment, 7 patients showed remission of symptoms but none had significant histologic improvement. After the treatment was discontinued the symptoms reappeared. In a more recent study[39] the gene expression levels of the cysteinyl leukotrienes in the esophageal epithelium were determined and no differences were detected between children with EE and normal controls. It seems obvious that Montelukast does not achieve clinical and histologic remission of EE, although further studies are required to determine whether or not Montelukast is efficient in maintaining steroid-induced remission.

Azathioprine/6-mercaptopurine

Like in inflammatory bowel disease, thiopurinic immunomodulators were tested on steroid-dependent patients to control eosinophilic inflammation of the esophagus. In this study conducted by Netzer et al,[40] 3 steroid-dependent adults with EE were treated with AZA or 6-MP (2 to 2.5 mg/kg/d), showing remission of symptoms and of the eosinophilic infiltrate that remained stable over the course of the therapy (3 to 8 y) without requiring steroids. After the treatment was discontinued, the disease recurred in 2 patients.

Further research based on a larger number of cases is required to evaluate the efficiency of the treatment.

Experimental Therapies or Future Therapies

Knowledge of the molecular mechanisms giving rise to the development of EE has led to the use of monoclonal antibodies against cytokines that mediate the physiopathology of the disease. We already have some experimental studies that evaluate the use of these possible therapies.

MepolizumAb

This is a humanized monoclonal antibody against Interleukin (IL)-5, a TH2 cytokine that plays a key role in the proliferation, differentiation, survival, and activation of eosinophils, whose expression is increased[41,42] both in humans[43] and in animal models of EE.[44] MepolizumAb had been successfully used in the treatment of hypereosinophilic syndrome,[45,46] although rebound eosinophilia was detected after the therapy was discontinued. In 2006 Stein et al[47] showed that it was useful for EE, as it reduced the eosinophilia in periferic blood and had no side effects having treated 4 patients with the disease. Straumann et al[48] recently conducted a double-blind, randomized, placebo-controlled clinical trial on adult patients with EE, which showed a significant reduction in mean esophageal eosinophilia (−54%) compared with the placebo group (−5%) 4 weeks after the treatment began and there was no further decrease after additional doses were administered. The expression of molecules associated with esophageal remodeling (TGF-β and tenascin C) was reversed, but these changes showed minimal symptomatic improvement in EE patients.

OmalizumAb

This is a monoclonal anti-IgE antibody that was not effective in treating EE in any of the few studies conducted.[49,50]

InfliximAb

Recent studies showed an increase in the expression of tumor necrosis factor (TNF)-α in patients with EE. InfliximAb is an anti-TNF-α antibody. A study of 3 patients treated with InfliximAb (5 mg/kg over 4 or 6 wk) did not show an improvement of symptoms or eosinophilia[51] although further studies are required using more patients to confirm these results.

Anti IL-13

High levels of IL-13[52] and eotaxin-3[43,53] were observed in the esophageal mucosa of patients with EE and therapies using anti IL-13 or anti-eotaxin 3 antibodies could therefore be assessed in the future.

Fibroblast Growth Factor (FGF-9)

FGF-9 is involved in homeostasis and proliferative response to damage. In a recent study,[54] an increase was observed in FGF-9 levels in the esophageal epithelial cells of EE patients owing to the release of major basic protein by the eosinophils, indicating that FGF-9 could play an important role in EE and be a new therapeutic target for study.

Suplatast Tosilate

This is an antiallergic agent that inhibits the production and degranulation of mastocytes, the production of TH2 cytokines (IL-4, IL-5), IgE production and the local accumulation of eosinophils.[55] Asthma studies were carried out on animal models[56] yielding good results. Although this drug has had positive results in eosinophilic gastroenteritis,[57] new studies on patients with EE are required to learn about its mechanism of action and results.

ENDOSCOPIC TREATMENT: BENEFITS AND CONTROVERSY

The esophageal mucosa is extremely fragile in cases of EE. A high rate of tears and lacerations of the mucosa has been reported, which is probably caused by efforts made by patients to induce vomiting and dislodge impacted food. The chronically maintained esophageal inflammation alone could alter the elasticity and resistance of the layers of the esophageal wall to the extreme that a simple brush of the endoscope could cause mucosal rents. Cases of spontaneous esophageal perforation[58] and Boerhaave syndrome[59] have even been reported following the simple passage of the endoscope[60] in patients with EE, which means that the various endoscopic procedures should be gently carried out on them.

The clinical manifestation of EE that most frequently leads to diagnosis in adult patients is food impaction in the esophagus and this complication must be urgently resolved. A study of 251 Swiss patients with EE showed that 34.7% required extraction of the impacted bolus using flexible or

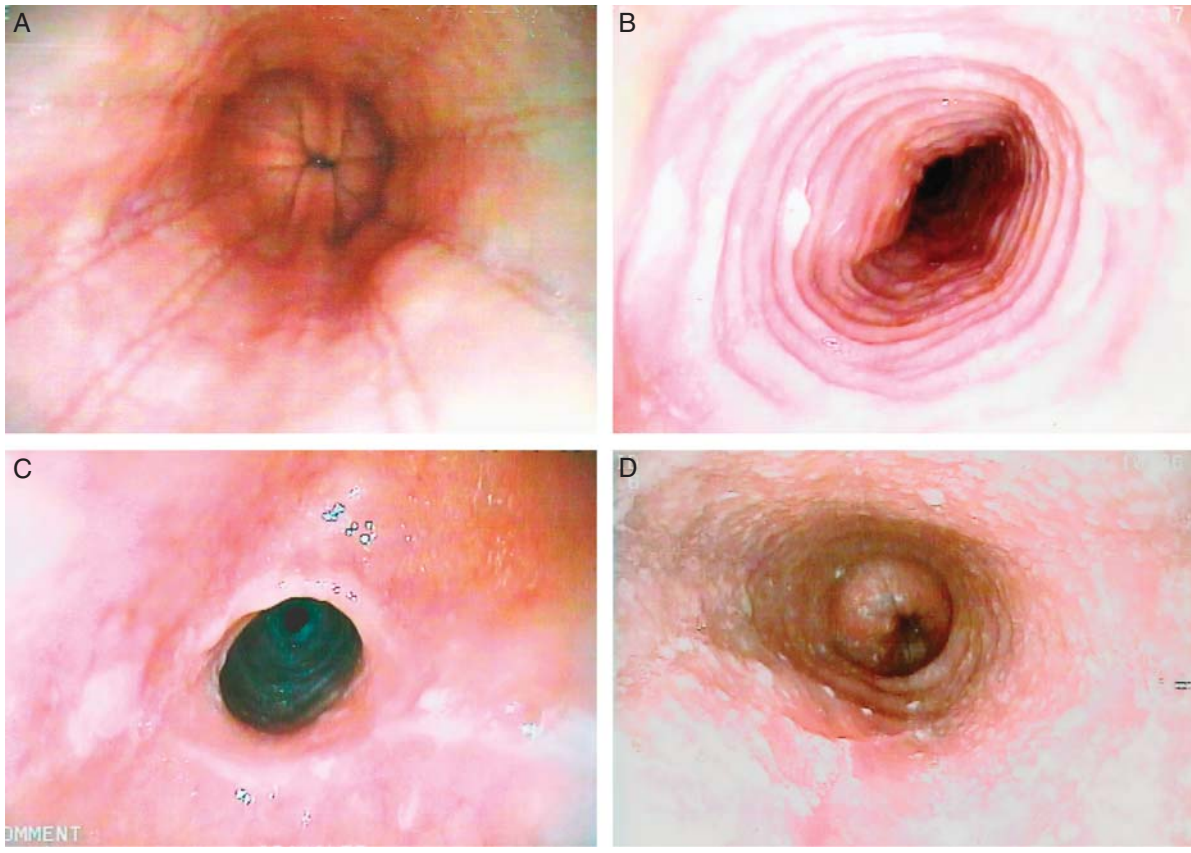

FIGURE 1. Several endoscopic appearances of eosinophilic esophagitis. A, Normal-caliber esophagus with longitudinal linear furrows and smooth mucosa. B, Ringed esophagus, with multiple simultaneous contraction rings along the organ. C, Concentric stenosis in the mid third of the esophagus, obstructing the passage of the endoscope. D, Esophageal mucosal surface covered in cotton-like exudates mimicking candiadiasis, but biopsy finds them to be multiple eosinophil-containing microabscesses.

rigid esophagoscopy in which a 20% rate of transmural perforations was observed[61] using the latter technique meaning that bolus removal by rigid endoscopy is a high-risk procedure and should not be used for EE patients.

Alterations in the caliber of the esophagus including a narrowing of the lumen may be observed during the performance of endoscopies or other radiology techniques on EE patients (Fig. 1). From the earliest documented cases, mechanical dilation has been used as a treatment option for EE, in a similar manner to how it is used in other cases of rigid or fibrous esophageal stenosis resulting from the cicatrisation of prolonged inflammatory processes affecting the mucosa of the digestive tract (like in GERD or after caustication). The chronic inflammatory phenomena that take place in EE also determine subepithelial fibrous remodeling, as recently shown in childhood forms of the disease[62] and in animal models.[63] Also, in recent years, various studies have addressed the relationship between EE and GERD[4] proving that both diseases can coexist in the same patient, causing dysmotility of the distal third of the esophagus, poor acid clearance, and the possibility of lesions by reflux.[64]

In this context, various investigators have used hydropneumatic dilators or bougies to treat EE since the cases were first reported (Table 2). A study of the literature shows that esophageal dilation is an efficient treatment providing immediate symptomatic relief,[76,80] which is why many authors regard it as a front-line treatment.[69,70] However, endoscopic dilation has been warned to pose a higher risk of complications in patients with EE. It has been suggested that the long evolution of dysphagia, esophageal stenosis, and the high density of eosinophils are predictive factors of these complications during dilation.[81] Most of the cases of esophageal perforation described (spontaneous or after endoscopic procedures) only led to pneumomediastinum,[75,79] but in 2 cases, an emergency esophagectomy through thoracotomy and an esophagogastroplasty were required (in 1 case after esophageal bouginage[65] and in another after spontaneous rupture[82]). No patient fatalities have been reported, but to minimize complications, it would be practical to proceed slowly and carefully and dilate using smaller calibers than those used in various forms of stenosis.

Conversely, endoscopic dilation is a mechanical procedure that has no effect on the underlying inflammatory process,[78] and, accordingly, its efficiency could be limited over time. In published cases, the duration of the effect cannot be appropriately estimated owing to the short monitoring period, although it usually ranges from 3 to 12 months, and it is very usual for patients to undergo repeated dilations (up to 5 times[77,83]) to control their symptoms.

It could therefore be risky to use endoscopic dilation on these patients,[78] and it should be considered as an

TABLE 2. Summary of Published Cases of Dilations, Their Results, and Complications

Author and Year	Patients Studied	Efficiency	Repeated Sessions	Perforation	Other Complications
Riou et al 1996[65]	1 patient	Stenotic esophagus despite dilation	No	Yes	Pneumomediastinum and early mediastinitis, requiring subtotal esophagectomy
Morrow 2001[66]	1 adult	16 clinically improved	1 required repeated dilation	No	Deep mucosal tears Increased post endoscopy analgesia. Difficulty in inserting the endoscope
Vasilopoulos et al 2002[67]	5 adults	5/5 clinically improved	Yes (4 of them)	No	Two extensive esophageal tearing, chest pain and overnight hospitalization
Straumann 2008[68]	11 adults	A single dilation of 7 patients 50% reduction in symptoms 1 patient did not show improvement of symptoms	Yes (in 4 patients)	No	Severe mucosal tearing
Croese et al 2003[69]	17 adults	16/17 improved clinically	Mean 3.4 dilations per patient, (range 1-13)	No	Tears were recorded in 13 (87%)
Straumann et al 2003[70]	5 adults	5 asymptomatic for 3 to 24 mo	No	No	Development of disquieting lesions in response to the procedure
Nurko et al 2004[64]	7 children	5 total symptomatic relief 2 partial response	Not specified	No	No
Potter et al 2004[71]	13 adults	7/13 showed transient (< 3 mo) improvement	Repeated in 6 patients at least twice over the following year	No	Extensive esophageal trauma. Moderate chest pain. Overnight hospitalization
Langdon 2005[72]	11 (not specified)	Not specified	Not specified	Yes	2-3 d hospitalization, severe chest pain and odynophagia
Zimmermann et al 2005[73]	8 adults	8 temporary relief of dysphagia	4 patients with recurrent dysphagia (mean number of procedures, 2.5; range, 2-4) over an average period of 4.5 y (range 1-10 y)	No	No
Cantù et al 2005[74]	2 adults	Both cases	No	No	No
Eisenbach et al 2006[75]	1 adult	Asymptomatic	Repeated esophageal dilation	Yes	No
Zuber-Jerger et al 2006[76]	1 adult	Clinical improvement for 3 y	Yes, after dysphagia recurred.	No	No
Pasha et al 2007[77]	13 adults	11/13 clinically improved	Mean number of dilations was 2 (range, 1-5)	No	Superficial mucosal tears occurred in 31% of dilations
Schoepfer et al 2010[78]	10 adults	10/10 clinically improved over an average 6-month period	Mean number of dilations was 2.7 (range, 1-5)	No	Transient postprocedural odynophagia for 1-3 d
Rajagopalan and Triadafilopoulos 2009[79]	1 adult	Symptoms improved for 6 mo	2 dilations in a 6-week period	No	Severe pain during the subsequent 24-48-hour period

alternative treatment for patients with EE and esophageal stenosis when other measures have failed, especially topical steroids.[84,85]

PRACTICAL CONSIDERATIONS

The information at our disposal concerning the efficiency of the different treatments to control EE is based on a limited number of patients monitored over short periods of time. It consists of single treatment strategies that were not compared with a placebo group and mostly relate to pediatric cases of EE, the results of which are subsequently extrapolated to adults. We do not know the long-term consequences of eosinophilic inflammation, fibrous remodeling of the esophagus, or of its possible modification using different therapies. For these reasons, it

is difficult to recommend common guidelines for all patients. The experience of each center and the availability of techniques and studies also limit the treatment options and the objectives established in each case: merely to control the symptoms or resolve the epithelial inflammatory infiltrate. A group of EE experts recommended treating asymptomatic cases of EE to avoid the potential consequences of fibrous remodeling of the organ,[17] although these long-term consequences are not known. In any case, in the absence of treatment, we should consider EE to be a chronic disease with intermittent symptoms but persistent histologic inflammation over time, which affects patients' quality-of-life.[68]

Owing to the coexistence of GER in many cases of EE and the effect shown by acid secretion inhibitors in controlling symptoms, in the case of suspected EE, it would be appropriate to carry out a therapeutic test using PPIs over a period of 8 weeks before repeating the endoscopy and taking further biopsies. Aside from ruling out GERD as the cause of eosinophilia, this measure could correctly characterize the patients in whom EE and GERD coexist, which would be better than monitoring the pH of the esophagus.[86] We will only be able to propose specific treatment when the persistence of the eosinophilic inflammatory infiltrate and the symptoms deriving there from have been verified (Fig. 2).[66]

Given that swallowed topical steroids are very efficient and have few side effects (fluticasone propionate or budesonide), these drugs could be the number 1 alternative, both in children and adults with EE, provided that the relevant sensitivity studies to allergens are also conducted. The difficulty in swallowing these drugs when they are administered by inhalers (they are sold in the form of an aerosol spray to treat bronchial asthma), could impair their efficiency, especially in the case of children. The use of liquid formulas (liquid fluticasone is available for intranasal administration) or viscous compounded medication minimizes this problem. Owing to their safety profile and good tolerance, empirical treatment using montelukast could also be proposed in certain cases.

Because good results were obtained from children with EE who modified their diets (elemental diets and the exclusion of 6 foods), this treatment option should always be considered, in cooperation with a nutritional expert to guarantee a balanced diet to prevent nutritional deficiency. In adults, the elemental diet is not a feasible alternative and the few experiences involving food exclusion have not been widely studied, although perhaps it could be less effective given the increasing involvement of airborne allergens in the physiopathology of EE in adults.[15] At centers where food sensitivity studies can be conducted thoroughly, empirical elimination diets should be tested using the foods to which sensitivity is shown. It should be noted that these studies are not very standardized.

Although unresponsive cases to topical steroids—at least symptomatically—are not very common and when dietary treatment has not been effective, treatment using thiopurinic immunomodulators (azathioprine/6-mercaptopurine), drugs that are widely used in inflammatory bowel disease could be proposed for adolescents or adults, and although experience is limited,[40] they have been very efficient in inducing and maintaining remission of the inflammation.

As mentioned earlier, endoscopic dilation would only be considered in cases of persistent symptoms and of a reduction in the caliber of the esophagus that have failed to respond to the aforementioned therapies. It should also be carried out gently using medium-sized bougies.

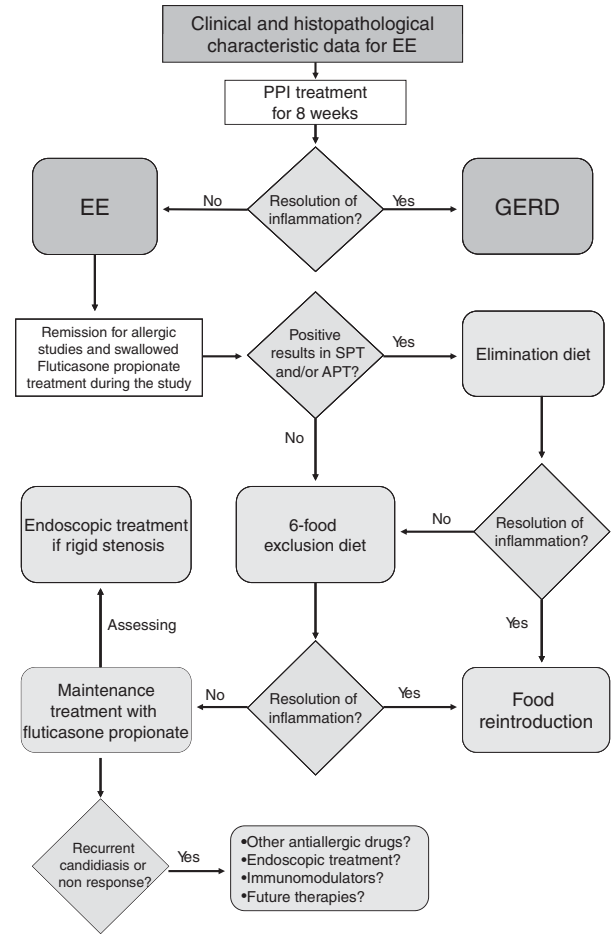

FIGURE 2. A possible algorithm for treatment of eosinophilic esophagitis (EE). APT indicates atopic patch tests; PPI, proton pump inhibitors; SPT, skin prick tests.

Mepolizumab is currently an experimental treatment whose safety profile and long-term effects are unknown and it should only be considered in studies or in symptomatic patients who have not responded to the earlier described options.

The various therapeutic approaches to EE suggest that none have absolute advantages. Options should therefore be chosen on a case-by-case basis once the patients' characteristics, their sensitivity to allergens and treatment preferences are known. The frequent association of other atopical manifestations in EE patients makes it essential to coordinate the work between gastroenterologists and allergologists, and involve nutritional experts in cases of significant food restriction, to provide comprehensive treatment for patients.

REFERENCES

1. Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia: a distinct clinicopathologic syndrome. *Dig Dis Sci*. 1993;38:109–116.

2. Furuta GT, Straumann A. Review article: the pathogenesis and management of eosinophilic esophagitis. *Aliment Pharmacol Ther*. 2006;24:173–182.
3. Lucendo AJ. Immunopathological mechanisms of eosinophilic esophagitis. *Allergol Inmunopathol (Madr)*. 2008;36:215–227.
4. Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol*. 2007;102: 1301–1306.
5. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized double-blind, placebo controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology*. 2006; 131:1381–1391.
6. 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;6:165–173.
7. Peterson KA, Thomas KL, Hilden K, et al. Comparasion of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. *Dig Dis Sci*. 2010;55:1313–1319.
8. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995; 109:1503–1512.
9. Spergel JM, Beausoleil JL, Mascarenhas M, et al. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol*. 2002;109: 363–368.
10. Spergel JM, Andrews T, Brown-Whitehorn TF, et al. Treatment of eosinophilic esophagitis with specific elimination diet directed by a combination of skin prick and patch test. *Ann Allergy Asthma Immunol*. 2005;95:336–343.
11. Lucendo AJ, Bellón T, Lucendo B. The role of mast cell in eosinophilic esophagitis. *Pediatr Allergy Immunol*. 2009;20: 512–518.
12. 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;98:777–782.
13. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol*. 2005;3:1198–1206.
14. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Ciln Gastroenterol Hepatol*. 2006;119: 1097–1102.
15. Gonsalves N, Ritz S, Yang G, et al. A prospective clinical trial of allergy testing and food elimination diet in adults with eosinophilic esophagitis (EE). *Gastroenterology*. 2007;132 (suppl 1):A6–A7.
16. Spergel JM, Shuker M. Nutritional management of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am*. 2008;18: 179–194.
17. 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;133:1342–1363.
18. Molina-Infante J, Ferrando-Lamana L, Mateos-Rodríguez JM, et al. Overlap of reflux and eosinophilic esophagitis in two patients requiring different therapies: a review of the literature. *World J Gastroenterol*. 2008;14:1463–1466.
19. Putnam PE, Rothenberg ME. Eosinophilic esophagitis: concepts, controversies, and evidence. *Curr Gastroenterol Rep*. 2009;11:220–225.
20. Nurko S, Teitelbaum JE, Husain K, et al. Association of Schatzki ring with eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr*. 2004;38:436–441.
21. Ngo P, Furuta G, Antonioli D, et al. Eosinophils in the esophagus—Peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol*. 2006;101:1666–1670.
22. Liacouras CA, Wenner WJ, Brown K, et al. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr*. 1998;26: 380–385.
23. King J, Khan S. Eosinophilic esophagitis: perspectives of adult and pediatric gastroenterologists. *Dig Dis Sci*. 2010;55: 973–982.
24. Faubion WA, Perrault J, Burgart LJ, et al. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr*. 1998;27:90–93.
25. Noel RJ, Putman PE, Collins MH, et al. Clinical and inmunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2004;2:568–575.
26. Arora AS, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis. *Mayo Clin Proc*. 2003;78:830–835.
27. Teitelbaum J, Fox V, Twarog F, et al. Eosinophilic Esophagitis in Children: inmunopathological analysis and response to fluticasone propionate. *Gastroenterology*. 2002;122:1216–1225.
28. Langdon DE. Fluticasone in eosinophilic corrugated ringed esophagus. *Am J Gastroenterol*. 2001;96:926–927.
29. Lucendo Villarin A, Carrion Alonso G, Navarro Sanchez M, et al. Eosinophilic esophagitis in adults, an emerging cause of dysphagia: description of 9 cases. *Rev Esp Enf Dig*. 2005; 97:229–234.
30. Martín-Muñoz MF, Lucendo AJ, Navarro M, et al. Food allergy and eosinophilic esophagitis: two cases studies. *Digestion*. 2006;74:49–54.
31. Lucendo AJ, Pascual-Turrión JM, Navarro M, et al. Endoscopic, bioptic and manometric findings in eosinophilic esophagitis before and after steroid therapy: a case series. *Endoscopy*. 2007;39:765–771.
32. Lucendo AJ, Navarro M, Comas C, et al. Immunophenotypic characterisation and quantification of the epithelial inflammatory infiltrate in eosinophilic esophagitis through stereology: an analysis of the disease's cellular mechanisms and the esophagus's immunological capacity. *Am J Surg Pathol*. 2007; 31:598–606.
33. Lucendo AJ, Castillo P, Martín-Chávarri S, et al. Manometric findings in adult eosinophilic oesophagitis: a study of 12 cases. *Eur J Gastroenterol Hepatol*. 2007;19:417–424.
34. Remedios M, Campbell C, Jones DM, et al. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest Endosc*. 2006;63:3–12.
35. Perrault J, Arora AS, Clawson ML, et al. Treatment of eosinophilic esophagitis with steoid lavage in adult patients (abstract). *Am J Gastroenterol*. 2001;96:S31.
36. Aceves SS, Dohil R, Newbury RO, et al. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2005;116:705–706.
37. Moots RJ, Prouse P, Gumpel JM. Near fatal eosinophilic gastroenteritis responded to oral sodium cromoglycate. *Gut*. 1998;29:1282–1285.
38. Attwood SE, Lewis CJ, Bronder CS, et al. Eosinophilic esophagitis: a novel treatment using Montelukast. *Gut*. 2003; 52:181–185.
39. Gupta SK, Peters-Golden M, Fitzgerald JF, et al. Cysteinil leukotriene levels in esophageal mucosal biopsies of children with eosinophilic inflamation: are they all the same? *Am J Gastroenterol*. 2006;101:1125–1128.
40. 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;19:865–689.
41. Yamazaki K, Murray JA, Arora AS, et al. Allergen-specific in vitro cytokine production in adult patients with eosinophilic esophagitis. *Dig Dis Sci*. 2006;51:1934–1941.
42. 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: 954–961.
43. Lucendo AJ, De Rezende L, Comas C, et al. Treatment with topic steroids downregulates IL-5, eotaxin-1/CCL11 and

eotaxin-3/CCL26 gene expression in eosinophilic esophagitis. *Am J Gastroenterol*. 2008;103:2184–2193.
44. Mishra A, Hogan SP, Brandt EB, et al. IL-5 promotes eosinophil trafficking to the esophagus. *J Immunol*. 2001;168: 2464–2469.
45. Kim YJ, Prussin C, Martin B, et al. Rebound eosinophilia after treatment of hypereosinophilic syndrome and eosinophilic gastroenteritis with monoclonal anti-IL-5 antibody SCH55700. *J Allergy Clin Immunol*. 2001;114:1449–1455.
46. Garrett JK, Jameson SC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hipereosinophilic syndromes. *J Allergy Clin Immunol*. 2003;113:115–119.
47. Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol*. 2006;118:1312–1319.
48. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomized, placebo-controlled, double-blind trial. *Gut*. 2010;59:21–30.
49. Foroughi S, Foster B, Kim N, et al. Anti-IgE treatment of eosinophilic-associated gastrointestinal disorders. *J Allergy Clin Immunol*. 2007;120:594–601.
50. 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 Inmunopathol (Madr)*. 2008;36(extraordinario 1):68–69.
51. Straumann A, Bussmann C, Conus S, et al. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. *Gastroenterology*. 2008;122:425–427.
52. Blanchard C, Mingler MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: trasncriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol*. 2007;120:1292–1300.
53. Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest*. 2006;116:536–547.
54. Mulder DJ, Pacheco I, Hurlbut DJ, et al. FGF9-iduced proliferative response to eosinophilic inflammation in oesophagitis. *Gut*. 2009;58:166–173.
55. Sano Y, Yamada H. Progress in suplatast tosilate research. *Clin Exp Allergy*. 2007;37:970–972.
56. Myou S, Fujimura M, Kurashima H, et al. Effects of suplatast tosilate, a new type of anti-allergic agent, on airway cough hypersensitivity induced by airway allergy in ginea-pigs. *Clin Exp Allergy*. 2001;31:1939–1944.
57. Shirai T, Hashimoto D, Suzuki K, et al. Successful treatment of eosinophilic gastroenteritis with suplatast tosilate. *J Allergy Clin Inmunol*. 2001;107:924–925.
58. Prasad GA, Arora AS. Spontaneous perforation in the ringed esophagus. *Dis Esophagus*. 2005;18:406–409.
59. Cohen MS, Kaufman A, Dimarino AJ Jr, et al. Eosinophilic esophagitis presenting as spontaneous esophageal rupture (Boerhaave's syndrome). *Clin Gastroenterol Hepatol*. 2007;5:A24.
60. Kaplan M, Mutlu EA, Jakate S, et al. Endoscopy in eosinophilic esophagitis: 'feline' esophagus and perforation risk. *Clin Gastroenterol Hepatol*. 2003;1:433–437.
61. Straumann A, Bussmann C, Zuber M, et al. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. *Clin Gastroenterol Hepatol*. 2008;6:598–600.
62. Aceves SS, Newbury RO, Dohil R, et al. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol*. 2007;119:206–212.
63. Mishra A, Wang M, Pemmaraju VR, et al. Esophageal remodeling develops as a consequence of tissue especific IL-5-induced eosinophilia. *Gastroenterology*. 2008;134:204–214.
64. Nurko S, Teitelbaum J, Husain K, et al. Association os Schatzki ring with eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr*. 2004;38:431–441.
65. Riou PJ, Nicholson AG, Pastorino U. Esophageal rupture in a patient with idiopathic eosinophilic esophagitis. *Ann Thorac Surg*. 1996;62:1856.
66. Morrow JB, Vargo JJ, Goldblum JR, et al. The ringed esophagus: histological features of GERD. *Am J Gastroenterol*. 2001;96:984–989.
67. Vasilopoulos S, Murphy P, Auerbach A, et al. The small-caliber esophagus: an unappreciated cause of dysphagia for solids in patients with eosinophilic esophagitis. *Gastrointest Endosc*. 2002;55:99–106.
68. Straumann A. The natural history and complications of eosinophilic esophagitis. *Gastrointestinal Endosc Clin North Am*. 2008;18:99–118.
69. Croese J, Fairley SK, Masson JW, et al. Clinical and endoscopic features of eosinophilic esophagitis in adults. *Gastrointest Endosc*. 2003;58:516–522.
70. 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: 1660–1669.
71. Potter JW, Saeian K, Staff D, et al. Eosinophilic esophagitis in adults: an emerging problem with unique esophageal features. *Gastrointest Endosc*. 2004;59:355–361.
72. Langdon DE. Response to Straumann et al: primary eosinophilic esophagitis. *Gastroenterology*. 2005;127:364.
73. Zimmermann SL, Levine MS, Rubesin SE, et al. Idiopathic eosinophilc esophagitis in adults: the ringed esophagus. *Radiology*. 2005;236:159–165.
74. Cantù P, Velio P, Prada A, et al. Ringed oesophagus and idiopathic eosinophilic oesophagitis in adults: an association in two cases. *Dig Liv Dis*. 2005;37:129–134.
75. Eisenbach C, Merle U, Schirmacher P, et al. Perforation of the esophagus after dilation treatment for dysphagia in a patient with eosinophilic esophagitis. *Endoscopy*. 2006;38: E43–E44.
76. Zuber-Jerger I, Ratiu N, Kullman F. Long-lasting effect of endoscopic dilation of an esophageal stenosis due to eosinophilic esophagitis. *J Gastrointestin Liver Dis*. 2006;15: 167–170.
77. Pasha SF, DiBaise JK, Kim HJ, et al. Patient characteristics, clinical, endoscopic, and histologic findings in adult eosinophilic esophagitis: a case series and systematic review of the medical literature. *Dis Esophagus*. 2007;20: 311–319.
78. 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;105:1062–1070.
79. Rajagopalan J, Triadafilopoulos G. Ring(s)-related esophageal meat bolus impaction: biopsy first, dilate later. *Dis Esophagus*. 2009;22:E–16.
80. Roberts-Thomson IC. Gastrointestinal: eosinophilic esophagitis. *J Gastroenterol Hepatol*. 2005;29:1299.
81. Cohen MS, Kaufman AB, Palazzo JP, et al. An audit of endoscopic complications in adult eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2007;5:1149–1153.
82. Liguori G, Cortale M, Cimino F, et al. Circumferential mucosal dissection and esophageal perforation in a patient with eosinophilic esophagitis. *World J Gastroenterol*. 2008;14: 803–804.
83. Schoepfer AM, Gschossmann J, Scheurer U, et al. Esophageal strictures in adult eosinophilic esophagitis: dilation is an effective and safe alternative after failure of topical corticosteroids. *Endoscopy*. 2008;40:161–164.
84. Lucendo AJ, De Rezende L. Endoscopic dilation for treatment of eosinophilic esophagitis: a strategy with a high perforation risk. *Endoscopy*. 2007;39:376.
85. Straumann A, Rossi L, Simon HU, et al. Fragility of the esophageal mucosa: a pathognpmonic endoscopic sign of primary eosinophilic esophagitis? *Gastrointest Endosc*. 2003;57: 407–412.
86. Molina-Infante J, Ferrando-Lamana L, Fernandez-Bermejo M, et al. Eosinophilic esophagitis in GERD patients: a clinicopathological diagnosis using proton pump inhibitors. *Am J Gastroenterol*. 2009;104:2856–2857.

