Eosinophilic esophagitis: New insights in pathogenesis and therapy

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Abstract
Eosinophilic esophagitis (EoE) is a clinico-pathological entity with esophageal symptoms and dense esophageal eosinophilic infiltration throughout the esophagus that may persist despite treatment with proton pump inhibitors. This eosinophilic infiltration is usually absent in the stomach, small intestine and colon, although there are a number of reports of patients with a multi-organ involvement. EoE is associated with abnormalities involving TH2-dependent immunity, with multiple environmental factors strongly contributing to disease expression. The layer of the esophagus affected by the eosinophilic infiltration causes the specific symptoms. Esophageal involvement results mostly in dysphagia for solids that can be severe enough to cause recurrent esophageal obstruction with typical endoscopic features suggesting esophageal remodeling and pathological changes of eosinophilic infiltration of the mucosa, sub-epithelial fibrosis and muscle hypertrophy. This disease is frequently associated with other allergic conditions such as allergic asthma, allergic dermatitis and eosinophilia. The treatment of patients with EoE depends on the severity of the symptoms and of the inflammatory process as well as to their response to a gradual step-up treatment. The first line of treatment consists of steroid containing local inhalers. If unresponsive they are then treated with oral steroids. Intravenous interleukin blockers seem to have a consistent positive therapeutic effect.

Key words: Eosinophilic esophagitis; Gastro-esophageal reflux disease; Esophagus; Esophagitis; Eosinophilia; Cytokines

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Core tip: Eosinophilic esophagitis is a clinico-pathological entity characterized by esophageal symptoms and dense esophageal eosinophilic infiltration throughout the esophagus. Our manuscript provides a deep description of the disease showing that many efforts have been made in the last decades in understanding
its pathogenesis paving the way to new therapeutic targets which are reviewed in the manuscript. For these reasons, the story would not appear to end herewith but deserves further attention and investigation.

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INTRODUCTION

One of the first reports of eosinophilic involvement of the esophagus dates from 1977 when Dobbins et al[4] described a man with dysphagia who had dense esophageal eosinophilia. However, it has been classified as a distinct clinical disease limited to the esophagus later[5,6]. It is now recognized as a chronic inflammatory disorder of the esophagus. It is characterized by dysphagia and gastro-esophageal reflux disease (GERD) symptoms, including vomiting, regurgitation, nausea and epigastric pain. Esophageal mucosal biopsy contains more than 15 to 20 eosinophils per high-power field in the absence of GERD disease. Occasionally it is associated with various other conditions including celiac disease[7].

PREVALENCE

In a 16-year follow-up study, an average annual incidence of 1.4% was reported[8]. The marked increase in incidence does not appear to be explained by a greater recognition of this disease since it is higher than the increased number of endoscopic procedures that are being performed[9]. The prevalence of eosinophilic esophagitis (EoE) is higher in cold climate zones of the United States than in tropical or arid zones suggesting a possible relationship between climate and the disease[10]. There is also a higher incidence of this disease in westernized countries and in urban areas of the United States with a significant Caucasian predominance of almost 90%[8-10].

More recent studies have updated the estimates of the incidence (7/100000) and prevalence (43/100000) of EoE[10] similar to the estimates reported from Olmsted County, Minnesota (incidence 9/100000; prevalence 55/100000) in patients identified retrospectively[11]. A similar prevalence estimate (52/100000) was derived from physician surveys. It is far more common in males than in females with a 3:1 to 3:2 ratios[12]. In some reports the incidence in males is even as high as 86% of patients. This gender difference remains unexplained and it contrasts with the higher incidence of allergic asthma in females than in males[8]. There is also an increased rate of family history of atopy in patients with EoE, and the disease tends to occur with familial clustering[12-14].

CLINICAL PRESENTATION

Patients with EoE complain of dysphagia mostly with solid foods. Food impaction tends to occur in the mid-esophagus unless the inflammatory process affects the esophageal innervation resulting in motility disorders consistent with achalasia or diffuse esophageal spasm. Fifty to eighty per cent of these patients have a prior history of atopic symptoms such as allergic rhinitis, asthma or atopic dermatitis and some of these allergic conditions are frequently associated with EoE clinical presentation, particularly allergic asthma and rhinitis[14,15]. Children generally present with non-specific symptoms of GERD, abdominal pain or failure to thrive; other present with dysphagia and esophageal food impaction[16].

The entire esophagus is often infiltrated with increased number of eosinophils (> 15 to 20 eosinophils per high power field (HPF)) a differential feature from the increased number of eosinophils found occasionally in the distal esophagus in patients with GERD of less than 15 eosinophils per HPF[16,17]. A recent study demonstrated that a cutoff value of at least 15 eosinophils per high-power field has a sensitivity of 100% and specificity of 96% for establishing the histologic diagnosis of eosinophilic esophagitis, irrespective of location of the sample (proximal or distal esophagus). As patients with lower levels of eosinophilia and phenotypic features of eosinophilic esophagitis have been described and GERD may be difficult to rule out, in some cases the diagnosis could be better established by biopsy of the proximal esophagus[17]. In addition the biopsies showed increased number of mast cells. Anyway, the relationship between patient symptoms and endoscopic features as well as histological severity of the disease is not known. A modest correlation was found between symptoms and histology in newly diagnosed, untreated patients differently form patients with longstanding EoE[18].

The eosinophilic infiltrate in GERD frequently but not always tends to respond to omeprazole probably because it blocks stat-6 that appears to be involved in eosinophilic chemotaxis in the esophagus[19]. Occasionally, the differential diagnosis between EoE and GERD can be quite difficult particularly in the pediatric population with both conditions having similar symptoms and endoscopic appearance of the esophagus. It is important to treat these patients initially with high proton pump inhibitors (PPI) doses before GERD is ruled out[20]. In some cases this differential diagnosis is helped by biochemical and genetic studies. Measurements of eotaxin-3 levels may be useful in the diagnosis of EoE since its levels are higher than in GERD[21]. Another biochemical test that may be helpful is the level of AOL-15. High levels are more common in biopsies from patients with EoE than from GERD and controls[22].
However, there is a group of patients with biopsies showing 15 eosinophils or higher per HPF who respond to PPI therapy. These patients have been labeled PPI responsive esophageal eosinophilia (PPIREE). They have similar clinical, endoscopic and pathological features of those with EoE[23]. It has been suggested that PPI reduces the eosinophilic infiltration in this subgroup of patients by restoring the mucosal integrity (erosions and ulcerations) that had facilitated the transport of antigenic proteins[24].

More advanced cases of eosinophilic involvement of the dysphagia for solid foods is caused by remodeling of the esophageal body due to extensive sub-epithelial fibrosis that tend to occur more frequently in adults[25]. The incidence of fibrostenotic disease increases with age and with the incidence doubling every 10 years of age.

**ENDOSCOPIC FINDINGS**

The mucosa of esophagus can appear normal particularly in the pediatric population. It is estimated that in one-third of pediatric patients with EoE the esophagus has a normal endoscopic appearance[15]. However, in most adult patients the endoscopic examination of the esophagus reveal various types of abnormalities such as longitudinal furrows, white nodule- or plaque-like exudates, transient or fixed corrugated rings (esophageal “trachealization”), crepe-paper mucosa due to a loss of the mucosal elasticity and strictures of variable length. Whitish exudates and longitudinal furrowing occur secondary to local edema and acute inflammation[26-28]. Hirano et al[28] reported a good inter-observer agreement in these patients when these three esophageal features rings, furrows, exudates were present.

**MOTILITY DISORDERS ASSOCIATED TO EOE**

Patients with EoE exhibit a variety of esophageal functional disorders depending upon the esophageal layer involved by the chronic inflammatory process. Motility disorders occur when this process affect muscle or neuronal cells. Since the initial studies there have been at least 22 published series or case reports in which the results of esophageal manometry have been reported, 19 adult and 3 pediatric studies. These esophageal motility studies have included a total of 144 patients, 115 adults and 29 children[29]. One study examined the esophageal motility features in 48 EoE patients, 48 GERD patients and 50 controls. Motility disorders were more frequent in EoE patients than in controls; the observed abnormal motility features were similar in EoE and GERD patients[30]. It has been suggested that this motor pattern is probably due to an impaired response to neural stimulation probably due to impaired acetylcholine release since the muscle response to this neurotransmitter is normal and in more advanced cases to reduced esophageal compliance due to extensive sub-epithelial fibrosis[31]. Furthermore, previous conventional motility studies assessing esophageal motor function in patients with EoE have reported few cases of achalasia, diffuse esophageal spasm, nutcracker esophagus and high amplitude contractions[29]. One patient with dysphagia and manometric abnormalities consistent with achalasia responded to treatment with prednisone[32].

**NATURAL HISTORY**

EoE is a chronic condition that usually starts in childhood. In some patients it may become clinically apparent in adulthood when they begin to complain of dysphagia. Swallowing difficulties are due to remodeling of the esophagus, strictures and motility disorders. Strictures are uncommon in children suggesting that over time the chronic infiltration with eosinophils leads to this complication in adults. This is particularly evident when there is a delay in the diagnosis that may lead to the remodeling of the esophagus and stricture formation[33]. In some cases, esophageal food impaction can be the initial presentation of the disease. Endoscopic procedures to relieve food impaction may lead to complications such as esophageal perforation and, even if rare, spontaneous transmural esophageal rupture (Boerhaave’s syndrome) has also been reported as a primary manifestation of EoE.

Most studies support a similar pathogenesis in both pediatric and adult populations suggesting that the clinical and pathological differences are the consequence of the evolution of the diseased process[34]. Occasionally heavy infiltration of eosinophils is found in the esophagus of patients complaining of symptoms originated in other segments of the upper gastrointestinal tract. However, a longitudinal study that followed 30 patients for up to 11 years and with a mean follow-up of 7.3 years revealed recurrent episodes of dysphagia but without nutritional abnormalities and without extension to other gastrointestinal segments or blood eosinophilia. Furthermore, in this study there was a partial spontaneous reduction of the eosinophilic count even in symptomatic patients[35]. However, the prognosis of this disease is still in its early stages, but there is no relation between esophageal cancer and EE described[36].

**PATHOLOGICAL ABNORMALITIES**

Pathological studies in patients with EoE reveal four abnormalities: Diffuse eosinophilic infiltration of the mucosa along the entire esophagus, increase basal cell hyperplasia, sub-epithelial fibrosis and muscle hypertrophy. Epithelial cells are highly hyperplastic in EoE patients[30]. In addition the epithelial layer shows a significant dilation of the intercellular spaces in patients with active disease compared to patients with inactive
The one that appears more frequently is the presence of high levels of eosinophils in the epithelial layer. The pathogenic effects of eosinophils include the promotion of basal cell proliferation and mast cell recruitment. The finding that eosinophils are mostly present in the epithelial layer of this disease is probably because most of the diagnostic studies are based on endoscopic biopsies that are relatively superficial. If deeper esophageal specimens are obtained eosinophils are frequently present in the muscularis mucosa and circular muscle layer. These deeper specimens also revealed the presence of mast cells that may contribute to some of the esophageal functional abnormalities. In atopic patients these mast cells contain IgE whereas they are IgE-negative in the non-atopic patients. These deeper specimens also show various degrees of sub-epithelial fibrosis and muscle hypertrophy that in some patients can be quite prominent resulting in short and long strictures.

Occasionally the differential diagnosis of EoE is with erosive esophagitis due to gastro-esophageal reflux disease. Although most patients with GERD complain of heartburn, in some patients dysphagia may be the most prominent symptom. Biopsies from the esophagus of these patients may reveal increased number of eosinophils but almost always they are present only in the distal segment and they are fewer than 15 cells per HPF. This segmental eosinophilia resolves after treatment with PPI’s probably because it heals the inflammatory process and blocks the function of stat-6 that contributes to the eosinophilic infiltration into the esophagus in both disorders. In immunized squamous epithelial cells omeprazole had no effect on eotaxin-3 mRNA stability or on STAT6 phosphorylation and its nuclear translocation. Rather, omeprazole appears to block the binding of interleukin stimulated STAT6 and RNA polymerase II to the eotaxin-3 promoter lowering its expression. However, in few cases the differential diagnosis can be quite difficult. Therefore it is possible that in these patient’s determinations of eotaxin-3 mRNA and protein levels that strongly correlate with tissue eosinophilia may be able to differentiate between these two entities.

GENETIC VS ENVIRONMENTAL ETIOLOGICAL FACTORS

Evidence has been presented that both genetic and environmental factors contribute to the development of EoE. This disease is associated with a variety of mendelian genetic based disorders. The most frequent associations of EoE are with hereditary collagen disorders such as Marfan and Ehlers-Danlos syndromes with an incidence of about 1%. Genetic studies have also identified a number of abnormalities. The one that appears more frequently is the presence of a common single nucleotide polymorphism in the 3’ untranslated region of CCL-26 that encodes eotaxin-3 that is an over-expressed esophageal transcript in the EoE transcriptome. It is well known that CCL-26 mRNA and protein are overexpressed in the majority of these patients. Although other genetic abnormalities have been reported perhaps two that have been persistently demonstrated in unbiased manner are present in chromosome 5q22. It contains a single locus in the spanning of the thymic stromal lymphoprotein (TSLP) and of the WD repeat domain 36 (WDR36) genes that are significantly associated with EoE. TSLP mRNA is increased in esophageal tissues from patients with EoE, compared with controls. TSLP is a cytokine that is produced by keratinocytes and promotes the development of Th2 cells.

The genetic contribution of this disease, however, is limited despite of the higher incidence of EoE in members of the same families. Although EoE is observed in 1.8% to 2.4% of relatives depending on the relationship and sex with higher values for men, there is only a 40% concordance between monozygotic twins and 30% concordance between dizygotic twins. This latter low incidence suggests a strong environmental contribution to acquiring this disease. This conclusion is supported by the finding that although the nuclear-family heritability appeared to be high (72.0%), the twins cohort analysis revealed that this high levels are likely due to a powerful role of a common environment that occurs in 81.0% of the cases.

PATHOGENESIS

Epidemiologic studies and therapeutic trials have provided indirect evidence about the pathogenesis of this disease. Most patients with EoE (approximately 75% of cases) show signs of atopy, defined by reactivity to allergens by skin-prick testing (SPT) or by identifying specific serum IgE. The majority of these patients have evidence of either aeroallergen and/or food sensitization. This was illustrated by one subject that developed acute eosinophilic esophagitis after exposure to sublingual immunotherapy that included typical airborne antigens such as hazelnut, birch and alder. This esophageal response resolved clinically and endoscopically after the immunotherapy was discontinued. There is also experimental evidence in wild mice that repeated nasal inoculation with allergens such Aspergillus fumigatus triggers an eosinophilic infiltration of the esophagus. In contrast, these mice had no response when the allergen was inoculated in the oral cavity or in the stomach. Occasionally the specific trigger of the eosinophilic infiltration of the esophagus is a drug as illustrated in two patients found to have had an anticonvulsant hypersensitivity syndrome. The allergic component of EoE also is quite apparent from its strong association with other allergic diseases. About 70% of
EoE patients have current or past allergic diseases or positive skin pricks test especially to a variety of foods. However, despite these isolated reports the role of airborne antigens in the pathogenesis of human EoE is controversial and at best it may be a contributing factor in a small percentage of patients.

The immunoglobulin mediating this allergic reaction has not been conclusively determined. Fifty percent to seventy-five percent of patients with EoE are atopic, with a high prevalence of food-induced allergen-specific IgE[52]. This conclusion has been questioned after omalizumab an IgE antibody failed to improve the symptoms and reduce the eosinophilic infiltration in patients with EoE[53]. On the other hand a recent study shows that the most prominent immunoglobulin abnormality appears to be IgG4. There are abundant IgG4-containing plasma cells and serum levels of IgG4 appear to react to specific foods suggesting that EoE is more likely to be an IgG4 associated allergy[54].

The role of food in the pathogenesis of EoE is supported by the consistent observation that disease activity is responsive to elemental diets and resumption of unrestricted diets result in disease recurrence[55]. A prospective study in adult patients with EoE confirmed previous observations that a six-food elimination diet significantly improved their symptoms, endoscopic and histological abnormalities. Moreover, re-introduction of specific foods was frequently associated with recurrence of EoE with wheat in 60% of cases and milk in 50% of cases. In contrast, skin-prick testing of these foodstuffs predicted that only 13% of foods were associated with EoE. Even in patients without an associated allergic disease, EoE is likely caused by allergic reactions to certain foods since they still respond to an elemental diet. However, several studies have also suggested that aeroallergens may also play a role in the pathogenesis of this disease. This conclusion is supported by the fact that the severity of this disease may be affected by seasonal variations that correlated with pollen counts. Some of these studies have even suggested differences between younger from older patients with the former showing more IgE and patch sensitivity to certain foods whereas older children exhibiting greater IgE sensitization to inhalant aeroallergens[56].

This disease consists of highly reactive esophageal epithelial cells, high levels of cytokines, eosinaxes, particularly eotaxin-3, eosinophils and mast cells that mediate this type-1 hypersensitivity involving TH2 cells[57]. However, only a minority of EoE patients present with food anaphylaxis suggesting that the mechanisms involved in this condition are different from those causing the classical IgE-mediated mast cell and basophile activation. These conclusions also are supported by studies performed in experimental EoE in wild mice[58].

There is evidence that epithelial cells are capable of mediating this food-induced allergic reaction. In vitro studies have shown that esophageal epithelial cell lines act as antigen presentation cells in the presence of interferon-γ (IFNγ) by inducing the major histocompatibility complex (MHC) class II system. These findings suggest that the antigen presentation by esophageal epithelial cell may contribute to the pathophysiology of EoE[59].

Similarly to GERD patients with esophagitis[60,61], EoE is associated with high levels of cytokines particularly IL-3, IL-5, IL-13, increase production of eotaxin chemokines CCL11, CCL24 and CCL26 (or eotaxins 1, 2 and 3 respectively) that attract inflammatory cells, predominantly eosinophils[62,63]. Studies performed in esophageal rings showed that stimulation of the rings with IL-13 for 48 h resulted in a significant attraction of eosinophils into the lower chamber containing TH-2 lymphocytes while chambers containing only IL-13 did not[64,65]. These data demonstrate that IL-13 supports eosinophil migration and that CCL11 and CCL24 are also both important in promoting eosinophil infiltration[66,67]. Although patients with EoE have higher levels of several cytokines, the cytokines that are most consistently increased in this allergic disease are IL-5, IL-13 and eotaxin-3 (CCL26)[68,69]. Genome-wide microarray expression studies have shown that the gene-encoding eotaxin-3 is the most highly induced gene in EoE patients compared to healthy individuals[63]. Furthermore, a single-nucleotide polymorphism in the human eotaxin-3 gene seems to be associated with disease susceptibility and mice deficient in the eotaxin receptor were protected from experimental EoE[63,64]. Eosinophils are born from the bone marrow progenitor stem cells under the influence of interleukin-3 (IL-3), interleukin-5 (IL-5) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Eosinophils contain cytokines, GM-CSF, transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, RANTES (or CCL5)[67]. Eosinophils are also potent pro-inflammatory cells capable of causing severe host tissue damage[68,69].

There is also increasing evidence that suggests a strong role of mast cells in the pathogenesis of EoE. Although mast cells have been studied indirectly in EoE, the published data suggest that the number of mast cells present in the esophageal epithelium is higher with respect to controls and to patients with gastro-esophageal reflux disease[70,71]. However, history of anaphylactic reactions after exposure to allergens is uncommon in this patients. These findings suggest that the mast cells function in EoE may be dependent on T lymphocytes and that there may be a bi-directional crosstalk between mast cells and eosinophils. This relationship may contribute to EoE physiopathology. Furthermore, even though mast cells are present in healthy subjects, only the EoE patients have IgE-bearing mast cells. Their role in the pathogenesis of EoE was tested in experimentally induced EoE in wild-type mice, mast cell-deficient WWv mice, and mast cell-reconstituted WWv mice[58,72]. The results of these studies reveal that esophageal mast
Increased IL-13 supports eosinophil migration by stimulating the chemo attractants production and reactivity to allergens by skin-prick testing.

Increased number of mast cells in the esophageal epithelium might be the primary cause of obstructive symptoms, which could be attributed to epithelial cell proliferation and extracellular matrix remodeling. Leukotriene C4 is metabolized to LTD4 and LTE4 both of which stimulate smooth muscle contraction.

Leukotriene C4 may be a significant factor in promoting esophageal remodeling in eosinophilic esophagitis (EoE) patients. However, therapies that inhibit mast cell functions have been ineffective in treating EoE in contrast to their effectiveness in other respiratory tract diseases. It has been therefore suggested that mast cells may have a limited role in the pathogenesis of EoE.

While the natural history of EoE remains obscure, the fact that some patients develop esophageal narrowing and strictures is of concern, particularly as patients become adults. Obstructive symptoms seem to occur secondary to epithelial cell proliferation and extracellular matrix remodeling, processes linked to eosinophil-derived transforming growth factor-β (TGF-β) and leukotriene C4 may be an additional contributing factor since it is metabolized to LTD4 and LTE4 both of which stimulate smooth muscle contraction. This action may be quite important because obstructive symptoms may be also related to active smooth muscle contraction.

It is also conceivable that EoE is an allergic reaction of the esophageal mucosa to a variety of stimuli that may be mediated by different immunologic pathways. This complexity may explain the discrepancies in the therapeutic responses to specific immune suppressing agents. Therefore, these studies also raised a number of questions regarding this disease: (1) whether the eosinophilic response through nasal or oral cavity depends to a greater extent on the type of the allergen applied; (2) why the esophagus is singularly affected by this allergic reaction since other segments of the upper gastrointestinal tract like the pharynx appears to be spared despite of its contact with foods and aero allergens that could also trigger this reaction; and (3) whether its pathogenesis in humans have similar molecular processes to those induced experimentally in wild mice.

Possible mechanisms involved in EoE pathogenesis are summarized in Table 1.

### Table 1 Possible mechanisms involved in eosinophilic esophagitis pathogenesis

| Mechanism | Evidence | Ref. |
|-----------|----------|------|
| Atopy     | Reactivity to allergens by skin-prick testing | [46,47,49,50,52,54] |
| Food      | Disease activity is responsive to elemental diets | [55] |
| Aeroallergens | Severity of disease affected by seasonal variations which correlate with pollen counts | [56] |
| Chemo attractants | Increased IL-13 supports eosinophil migration by stimulating the chemo attractants production | [43,63,64,66,67,68,69] |
| Mast cells | Increased number of mast cells in the esophageal epithelium | [70,71] |
| TGF-β     | Obstructive symptoms seem to occur secondary to epithelial cell proliferation and extracellular matrix remodeling, processes linked to eosinophil-derived TGF-β | [61] |
| Leukotriene C4 | Leukotriene C4 is metabolized to LTD4 and LTE4 both of which stimulate smooth muscle contraction | [74] |

EoE: Eosinophilic esophagitis; IL-3: Interleukin-3; TGF-β: Transforming growth factor-β.

The treatment of patients with EoE depends on the severity of symptoms and of the inflammatory process as well as on their response to a gradual step-up treatment. It is a possible that with appropriate and persistent treatment the symptoms, endoscopic and histological abnormalities can be completely controlled in most patients, including reversal of the sub-epithelial fibrosis and fibro-stenotic complications. However, treatment needs to be maintained for prolonged periods since EoE is a chronic disease that tends to relapse once the treatment is discontinued.

Initially patients should be treated with PPIs since some patients may respond to this treatment either by reducing the acid secretion in patients with co-existent GERD, or, by means of other still undefined anti-inflammatory mechanisms. A small-randomized trial showed that EoE patients with coexisting GERD treated with esomeprazole, were significantly more likely to have resolution of esophageal eosinophilia as compared with fluticasone alone (100% vs 0%) and even in a few patients regardless of the presence of GERD. Treatment with esomeprazole, but not fluticasone, was associated with a significant improvement of dysphagia. As mentioned before PPIs also may be effective in small subgroup of patients that have been labeled PPI responsive.

TREATMENT

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EoE (PPI-REE) with symptomatic improvement and resolution of the esophageal eosinophilia\[76\]. However, a 24-hr-test performed prior to treatment to select patients that could be responsive to PPI therapy was unable to predict the response to PPI treatment. Neither positive nor negative tests were able to determine whether patients would respond to acid suppressing treatment\[77\]. The PPI responsive patients with EoE are genetically and phenotypically indistinguishable from patients that are unresponsive. Some studies have suggested that up to 30% to 40% of patients with EoE may be responsive to PPI’s. It is therefore recommended that PPI should be the first line of treatment.

The PPI unresponsive patients are then treated with steroid containing local inhalers or with intravenous interleukin blockers. Patients complaining of dysphagia due to strictures or impaired esophageal poor distensibility due to subepithelial fibrosis are treated with esophageal dilation using Savary or Malone dilators. Most of the reports indicate that the risk of perforation in patients with EoE is not different from these complications observed when this procedure is performed in patients with other types of esophageal strictures\[78,79\]. A meta-analysis confirmed the safety of this procedure with reported complication rate of less than 1%\[80\]. However, irrespective of the type of esophageal disorder this therapeutic procedure should be performed carefully.

Topical treatment is as effective as systemic corticosteroids. Topical fluticasone was just as effective as oral prednisone in terms of histological and symptomatic remission\[81\]. Its local anti-inflammatory effects induce the development of esophageal steroid responsive genes such as FK-506 binding protein and miRs and can even partially reverse the eosinophil transcriptome. Furthermore, there is an occasional discrepancy between clinical and histological improvement, defined by the reduction of the eosinophilic infiltration to normal levels. It is unclear, however, why symptoms may persist in some patients despite of the resolution of the inflammatory process. In some of these patients the symptomatic unresponsiveness may be due to the sub-epithelial fibrosis and muscle hypertrophy.

Topical corticosteroids improve symptoms and reduce esophageal eosinophilia and have become the “gold standard” of the pharmacotherapy of this disease. Anyway, due to lack of approved drugs for EoE, “off-label” drugs, designed for other allergic diseases, such as asthma or rhinitis are used. One-year treatment with fluticasone propionate caused a slight reduction in the sub-epithelial fibrosis although the differences did not reach significance probably because the number of patients included in the study was relatively small\[81\]. Moreover viscous steroids are more effective than nebulized steroids\[82\]. However even high doses of fluticasone have a 30% failure. Other therapeutic studies have shown that some patients have remained symptomatic despite the histological improvement defined by the reduction in the number of eosinophils\[83\]. Pediatric patients are more responsive probably because adult patients have a significant remodeling of the esophagus that may be responsible for the persistent dysphagia\[84\]. In addition, treating patients with EoE with this topical steroid for three months significantly down regulated the levels of cytokines IL-5 and eotaxin-3 although control levels were not reached\[85\].

Viscous budesonide has also been successfully used in both children and adults. Remission is usually obtained after 12-wk treatment. A control trial showed that budesonide 1 mg twice daily administered as viscous slurry was more effective in reducing the eosinophilic infiltration of the esophagus than the nebulized form\[85\]. This is due to greater mucosal contact time with former than with the latter as measured by esophageal scintigraphy\[82,86,87\]. However, the disease commonly recurs after the drugs are withdrawn. Therefore maintenance treatment with either steroid drug should be considered to avoid symptomatic recurrences and development of sub-epithelial fibrosis\[83\].

Those conclusions are supported by a meta-analysis that included seven clinical studies that treated a total of 226 patients\[88\]. Despite of the substantial heterogeneity of the studies it showed topical steroids induced a significant reduction in the number of eosinophils compared to controls. Subgroup analysis also showed that the reduction in eosinophil count was only present in patients who where previously treated with PPI’s used to rule out GERD. As mentioned in previous reports eleven out of 127 patients that received the oral steroid developed asymptomatic esophageal candidiasis\[89\]. Therefore, topical steroid therapy seems to be safe in general and, to date, there has been no evidence of adrenal suppression\[88\].

Specific treatments have also been developed in an attempt to inhibit immune mechanisms presumed to be involved in this disease. These therapies have been directed toward inhibition of IgE and IL-5 induced immunological abnormalities. While these approaches are often effective, no pharmaceutical agents have yet been approved by the Food and Drug Administration. The effect of omalizumab, an antibody against IgE, was evaluated in a double blind placebo controlled study in patients with EoE. This antibody, however, did not alter symptoms of eosinophilic esophagitis or eosinophil counts in biopsy samples compared with placebo\[94,95\].

The therapies against IL-5 were selected because this cytokine plays a pivotal role in innate and acquired immune responses and eosinophilia. In humans, the biologic effects of antibodies against IL-5 are best characterized by the reduction in the levels of eosinophils due to this cytokine involvement in the mechanisms of eosinophil development and activation.
These findings have led to therapeutic trials using humanized antibodies against IL-5 or the IL-5R. However, probably due to the heterogeneity of this disease the symptomatic improvement induced by mepolizumab has not been consistent and not all patients respond to this form of treatment. In addition there have been discrepancies between the symptomatic improvement and the reduction of the esophageal eosinophils. It is more effective in reducing eosinophilic infiltration than in improving patients’ symptoms.

Straumann et al. performed a placebo control study that enrolled few patients showed that mepolizumab reduced the number of eosinophils in the esophagus and reversed the esophageal remodeling. Moreover the safety profile was acceptable even at higher doses. It was partially supported by a double blind study performed in children using increasing doses of 3 infusions of mepolizumab of 0.55, 2.5, or 10 mg/kg every 4 wk over a 12-wk period followed by no treatment until week 24. After 3 mo, this antibody induced a mild to moderate symptomatic improvement associated with reduction in the number of eosinophils to normal levels (less than 20 per HPF) but only in 31.6% of the patients. A sub analysis of the esophageal biopsies obtained from these children examined the effect of this antibody on eosinophils and mast cells. Forty per cent of patients responded with reductions in eosinophils and 77% in the number of mast cells. Moreover prior to treatment eosinophils and mast cells were found in couplets that were significantly reduced after therapy. This treatment appears to be well tolerated.

This clinical trial was supported by a larger study showing that mepolizumab, assessed by immuno-fluorescence, induced a marked reduction in the mean esophageal eosinophilia (P = 0.03). Mepolizumab induced a 54% reduction in the eosinophil numbers of the esophageal mucosa compared to only 5% reduction in the placebo group 4 wk after initiation of treatment. Mepolizumab also reduced the number of mast cells in the esophageal mucosa.

Another IL-5 antibody reslizumab was studied in double-blind placebo controlled study. Reslizumab or placebo was administered to 226 children and adolescent with EoE. Four infusions of 1, 2 and 3 mg were administered at weeks 0, 4, 8 and 12 wk. Peak eosinophil count was reduced by 59% to 64% from baseline in the antibody treated group and 24% in the placebo treated group. Symptomatic improvement was observed in the antibody and placebo treated groups but were not significantly different.

The limited percentage of patients that respond to these antibodies raise a number of questions regarding patient selection and the immune mechanisms involved in this disease. The selection of topical corticosteroid-refractory patients in these studies may have had a negative impact on the clinical results and possibly because targeting a single molecule IL-5 may prove insufficient to optimally control symptoms and disease progression, particularly in the adults who already have develop sub-epithelial fibrosis and strictures. These complications may also explain the discrepancy between symptomatic improvement and reduction of eosinophilic infiltration.

There is also increasing evidence that most patients with EoE respond to elemental diets or to specific dietary restrictions. However, even in pediatric patients these dietary restrictions are limited by the usefulness of predicting therapeutic response using skin-prick testing and atopy patch testing for food allergies. Moreover, it is still uncertain how to formulate the optimal dietary restrictions for the management of this disease.

Although these elemental/amino acid-based formula diets have shown to be effective in children they do not appear to be well tolerated by adults because of taste, volume or high expense. However, patients treated with specific and nutritionally acceptable diets have not been examined. Moreover there are conflicting reports as to the efficacy of treating patients with elemental diets. It is possible as mentioned with previous treatments that the partial or lack of response to these relatively short dietary treatments may depend on the degree of the sub-epithelial fibrosis. In one clinical trial treatment an elemental diet reduced the number of eosinophils in the biopsies from adult patients with EoE. However, symptoms did not significantly improve and the eosinophilic infiltration recurred after the elemental diet was discontinued suggesting that persistent dietary treatment may be necessary.

Another study, however, showed that treatment with an elemental diet for 6 wk significantly improve the esophageal symptoms and markedly reduced the number of eosinophils in the esophageal biopsies. These studies showed that four foods were the most likely to trigger the eosinophilic reaction. Twenty-eight of 52 patients achieved clinical-pathological remission. Milk induced remission in 11 patients (50%), eggs in 8 patients (36%), wheat in 7 (31%) and legumes in 4 (18%) . These conclusions were supported by a meta-analysis. The reasons for the therapeutic responses to different foods are not known. An elimination diet also significantly improved symptoms and reduced endoscopic and pathologic features of EoE in adults. The systematic reintroduction food allergens in these patients lead to the recurrence of clinical and histological features of EoE supporting their role in its pathogenesis. It is conceivable that in some patients, as it occurs with other forms of therapy, the lack of correlation between reductions in the eosinophilic infiltration in the esophagus and symptomatic improvement after an elemental diet may be due to presence of esophageal remodeling and sub-epithelial fibrosis that may not respond to the treatment during the relatively short period of these clinical trials.

A more practical and acceptable treatment was
conducted in a prospective trial comparing swallowed fluticasone and elimination of cow’s milk [98]. After 6-8 wk, esophageal eosinophil counts decreased in 64% of patients treated with cow’s milk elimination and 80% of patients treated with fluticasone. Cow’s milk elimination also significantly improved the Mean pediatric quality of life (PedsQL) EoE Module total scores and total symptoms scores. Cow’s milk elimination may be more acceptable and desirable for EoE patients who do not want to take chronic, long-term steroid medications [99]. The benefits of dietary restrictions is further supported by the reduction in the number of mast cells and its proteases since these cells seem to play a role in the pathophysiology and symptoms of EoE [99].

In conclusion, from the data available to date it is reasonable to conclude that in most patients EoE is primarily caused by food hypersensitivity in subjects with a genetic predisposition induced by an early exposure to allergens that may abnormally stimulate T-helper type cytokines. However, the partial and selective response to specific treatments carried out in the above mentioned clinical trials do not provide conclusive evidence regarding the mechanisms involved in its pathogenesis. It is conceivable that more than one allergen or immune mechanism may contribute to this disease and therefore therapies may not only have to be individualized but also be acceptable to patients since long-term therapy may be necessary in order to avoid sub-epithelial fibrosis and remodeling of the esophagus.

REFERENCES

1. Dobbins JW, Sheahan D, Behar J. Eosinophilic gastroenteritis with eosinophilic involvement. Gastroenterology 1977; 72: 1312-1316.
2. Attwood SE, Smyrk TC, Demeester TR, Jones IB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993; 38: 109-116.
3. Straumann A, Spichtig HP, Bernoully R, Loosli J, Vöglin I. Idiopathic esophageal eosinophilia: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. Schweiz Med Wochenschr 1994; 124: 1419-1429.
4. Pellicano R, De Angelis C, Ribaldone DG, Fagnoone S, Astegiano M. 2013 update on celiac disease and eosinophilic esophagitis. Nutrients 2013; 5: 3329-3336 [DOI: 10.3390/nu5093329].
5. Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? J Allergy Clin Immunol 2005; 115: 418-419 [PMID: 15696105].
6. Hruz P, Straumann A, Bussmann C, Heer P, Simon HU, Zwahlen M, Beglinger C, Schoepfer AM; Swiss EoE study group. Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. J Allergy Clin Immunol 2011; 128: 1349-1350.e5 [PMID: 22019091 DOI: 10.1016/j.jaci.2011.09.013].
7. Hurrell JM, Genta RM, Dellon ES. Prevalence of esophageal eosinophilia varies by climate in the United States. Am J Gastroenterol 2012; 107: 698-706 [PMID: 22310220 DOI: 10.1038/ajg.2012.6].
8. Franciosi JP, Tam V, Liacouras CA, Spergel JM. A case-control study of sociodemographic and geographic characteristics of 335 children with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2009; 7: 415-419 [PMID: 19118642 DOI: 10.1016/j.cgh.2008.10.006].
9. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic esophagitis in Western Australia. Arch Dis Child 2006; 91: 1000-1004 [PMID: 16877474].
10. Spergel JM, Book WM, Mays E, Song L, Shah SS, Talley NJ, Bonis PA. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. J Pediatr Gastroenterol Nutr 2011; 52: 300-306 [PMID: 21057327 DOI: 10.1097/MPG.0b013e3181e59a0].
11. Prasad GA, Alexander JA, Schleck CD, Zinsmeister AR, Smyrk TC, Elias RM, Locke GR, Talley NJ. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. Clin Gastroenterol Hepatol 2009; 7: 1055-1061 [PMID: 19570711 DOI: 10.1016/j.cgh.2009.06.023].
12. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, Franciosi JP, Hurrell JM, Walsh JS, Book WM, Mays E, Song L, Shah SS, Talley NJ, Bonis PA. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. J Pediatr Gastroenterol Nutr 2011; 52: 300-306 [PMID: 21057327 DOI: 10.1097/MPG.0b013e3181e59a0].
13. Zink DA, Amin M, Gehara S, Desai TK. Familial dysphagia and eosinophilia. Gastrointest Endosc 2007; 65: 330-334 [PMID: 17258999].
14. Lefinert B, Sunyecz J, Garcia-Esteban R, Svanes C, Jarvis D, Cerveri I, Dratva J, Risiglson T, Heinrich J, Janson C, Kuenzli N, de Marco R, Omenaas E, Raherison C, Gómez Real F, Wjst M, Zemp E, Zureik M, Burney PG, Anto JM, Neukirch F. Gender differences in prevalence, diagnosis and incidence of allergic and non-allergic asthma: a population-based cohort. Thorax 2012; 67: 625-631 [PMID: 22334535 DOI: 10.1136/thoraxjnl-2011-201249].
15. Blatman KH, Ditto AM. Chapter 26: Eosinophilic esophagitis. Allergy Asthma Proc 2012; 33 Suppl 1: S88-S90 [PMID: 22794699 DOI: 10.2500/aap.2012.33.3559].
16. Furuta GT, Katzka DA. Eosinophilic Esophagitis. N Engl J Med 2015; 373: 1640-1648 [PMID: 26488694 DOI: 10.1056/NEJMra1502863].
17. Dellon ES, Speck O, Woodward K, Covey S, Rusin S, Shaheen NJ, Wooley JT. Distribution and variability of esophageal eosinophilia in patients undergoing upper endoscopy. Mod Pathol 2015; 28: 383-390 [DOI: 10.1038/modpathol.2014.110].
18. Pentik S, Putnum PE, Collins MH, Rothenberg ME. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2009; 48: 152-160 [PMID: 19179876 DOI: 10.1097/MPG.0b013e318179f107].
19. Hirano I. Editorial: Should patients with suspected eosinophilic esophagitis undergo a therapeutic trial of proton pump inhibition? Am J Gastroenterol 2013; 108: 373-375 [PMID: 23459046 DOI: 10.1038/ajg.2012.459].
20. Dellon ES, Speck O, Woodward K, Gebhart JH, Madanick RD, Levinson S, Fritchie KJ, Wooley JT, Shaheen NJ. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. Am J Gastroenterol 2013; 108: 1854-1860 [PMID: 24145677 DOI: 10.1038/ajg.2013.363].
21. Bhattacharya R, Carlsten J, Sabo E, Kethu S, Meitner P, Tavares R, Jakate S, Mangray S, Aswad B, Resnick MB. Increased expression of eotaxin-3 distinguishes between eosinophilic esophagitis and gastroesophageal reflux disease. Hum Pathol 2007; 38: 1744-1753 [PMID: 17900656 DOI: 10.1016/j.humpath.2007.05.008].
22. Matos A, Allen D, Herzlinger M, Ferreira J, Chen S, Lu S, Fabre V, Monahan R, Yang D, Noble L, Mangray S, Resnick MB. Correlation of ALOX15 expression with eosinophil or reflux esophagitis in a cohort of pediatric patients with esophageal eosinophilia. Hum Pathol 2014; 45: 1205-1212 [PMID: 24742828 DOI: 10.1016/j.humpath.2014.01.021].
23. van Rhijn BD, Weijenborg PW, Verheij J, van den Bergh Weerman A, de Vries K, van den Wijngaard RM, de Jonge WJ, Smout AJ, Bredenoord AJ. Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. Clin Gastroenterol Hepatol 2014; 12: 1815-1823.e2 [PMID: 24657840 DOI: 10.1016/j.cgh.2014.02.037].
24. Croese J, Fairley SK, Masson J, Chong AK, Whitaker DA,
manometric findings in eosinophilic esophagitis before and after steroid therapy: a case series. *Endoscopy* 2007; **39**: 765-771 [PMID: 17703383]

20. *Cheng E*, Zhang X, Huo X, Yu C, Zhang Q, Wang DH, Spechler SJ, Souza RE. Omeprazole blocks otxain-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. *Gut* 2013; **62**: 824-832 [PMID: 22580413 DOI: 10.1136/gutjnl-2012-302250]

21. *Rothenberg ME*. Molecular, genetic, and cellular bases for treating eosinophilic esophagitis. *Gastroenterology* 2015; **147**: 1143-1157 [PMID: 26566678DOI: 10.1053.j.gastro.2015.02.002]

22. *Abonia JP*, Wen T, Stucke EM, Grojtan T, Griffith MS, Kenna RA, Collins MH, Putnam PE, Franciosi JP, von Tiele F, Tinkle BT, Marsolo KA, Martin LJ, Ware SM, Rothenberg ME. High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. *J Allergy Clin Immunol* 2013; **132**: 378-386 [PMID: 23608731DOI: 10.1067/j.jaci.2013.02.030]

23. *Blanchard C*, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, Jameson SC, Kirby C, Konikoff MR, Collins MH, Cohen MB, Aker S, Hogan SP, Assa’ad AH, Putnam PE, Aronow BJ, Rothenberg ME. Eotaxin-3 and a uniquely conserved gene expression profile in eosinophilic esophagitis. *J Clin Invest* 2006; **116**: 536-547 [PMID: 16453027DOI: 10.1172/JCI26679]

24. *Rothenberg ME*, Spiegel JM, Sherrill JD, Annaiah K, Martin LJ, Cianferoni A, Gober L, Kim C, Glessner J, Frackelton E, Thomas K, Blanchard C, Liaouras C, Verma R, Aceves S, Collins MH, Brown-Whithorne T, Putnam PE, Franciosi JP, Chiavacci RM, Grant SF, Abonia JP, Sleiman PM, Hakonarson H. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat Genet* 2010; **42**: 289-291 [PMID: 20208534DOI: 10.1038/ng.547]

25. *Alexander ES*, Martin LJ, Collins MH, Kottyan LC, Sucharew H, He H, Mukkada VA, Succop PA, Abonia JP, Foote H, Eby MD, Grojtan TM, Greeniner AJ, Dellow ES, Demain JG, Furuta GT, Gurian LE, Harley JB, Hopp RJ, Kagalwalla A, Kaul A, Nadeau KC, Noel RJ, Putnam PE, von Tiele KF, Rothenberg ME. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. *J Allergy Clin Immunol* 2014; **134**: 1084-1092.e1 [PMID: 25258143DOI: 10.1016/j.jaci.2014.07.021]

26. *Noel RJ*, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004; **351**: 940-941 [PMID: 15329438DOI: 10.1056/NEJM200408263510924]

27. *Vicario M*, Blanchard C, Stringer KF, Collins MH, Mingler MK, Ahrens A, Putnam PE, Abonia JP, Santos J, Rothenberg ME. Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. *Gut* 2010; **59**: 12-20 [PMID: 19528036DOI: 10.1136/gut.2009.178020]

28. *Miehlke S*, Alpan O, Schröder S, Straumann A. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. *Case Rep Gastroenterol* 2013; **7**: 363-368 [PMID: 24163646DOI: 10.1159/000355161]

29. *Mishra A*, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001; **107**: 83-90 [PMID: 11134183DOI: 10.1172/JCI101224]

30. *Bove M*, Tegtmeyer B, Persson S, Bergquist H. The pharyngeal mucosa is not involved in eosinophilic oesophagitis. *Aliment Pharmacol Ther* 2009; **30**: 495-500 [PMID: 19508404DOI: 10.1111/j.1365-2636.2009.04059]

31. *Balatsinou C*, Milano A, Caldarella MP, Laterza F, Pierdomenico SD, Cucurullo F, Neri M. Eosinophilic esophagitis is a component of the antinuclear hypersensitivity syndrome: description of two cases. *Dig Liver Dis* 2008; **40**: 145-148 [PMID: 17395557DOI: 10.1016/j.dld.2007.01.017]

32. *Blanchard C*, Rothenberg ME. Basic pathogenesis of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* 2008; **18**: 133-143; x [PMID: 18061107DOI: 10.1016/j.jaci.2007.09.016]

33. *Foroughi S*, Foster B, Kim N, Bernardino LB, Scott LM, Hamilton RG, Metcalfe DD, Manning PJ, Prussin C. Anti-IgE treatment of eosinophil-associated gastrointestinal disorders. *J Allergy Clin
Guarino MPL et al. Eosinophilic esophagitis

Immuno 2007; 120: 594-601 [PMID: 1765756]  
54 Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA, Lowchick A, Chen X, Emerson L, Cox K, O’Gorman MA, Peterson KA. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology 2014; 147: 602-609 [PMID: 24904794 DOI: 10.1053/j.gastro.2014.05.036]  
55 Gonsalves N, Yang GB, Doerfler B, Ritz S, Ditto AM, Hiranio I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012; 142: 1451-1459.e1; quiz e14-15 [PMID: 22391333 DOI: 10.1053/j.gastro.2012.03.001]  
56 Sugnanam KK, Collins JT, Smith PK, Connor F, Lewindon P, Chung JS, Jung KW, Arora AS, Enders F, Katzka DA, Newbury RO, Dohil R, Bastian JF, Broide DH. 2012; 2464-2469 [PMID: 11859139 DOI: 10.4049/jimmunol.168.5.2464]  
57 Rijn M, Bonventre JV, Oettgen HC, Leder P, Luster AD. Eotaxin 3 triggers eosinophil-selective chemotaxis and calcium flux via a distinct receptor and induces pulmonary eosinophilia in the presence of interleukin 5 in mice. Mol Cell Med 1996; 2: 334-348 [PMID: 8784786]  
58 Hogan SP, Rothenberg ME. Eosinophil Function in Eosinophil-associated Gastrointestinal Disorders. Curr Allergy Asthma Rep 2006; 6: 65-71 [PMID: 16476198 DOI: 10.1007/s11882-006-0013-8]  
59 Dennon ES. Eosinophilic esophagitis. Gastroenterol Clin North Am 2013; 42: 133-153 [PMID: 23452635 DOI: 10.1016/j.gcc.2012.11.008]  
60 Wershil BK. Exploring the role of mast cells in eosinophilic esophagitis. Immuno Allergy Clin North Am 2009; 28: 189-195, xii [PMID: 19143134 DOI: 10.1016/j.iac.2008.09.006]  
61 Lucendo AJ, Bellón T, Lucendo B. The role of mast cells in eosinophilic esophagitis. Pediatr Allergy Immunol 2009; 20: 512-518 [PMID: 18681944 DOI: 10.1111/j.1399-3038.2008.00798]  
62 Niranjani R, Rayapudi M, Mishra A, Dutt P, Dynda S, Mishra A. Pathogenesis of allergen-induced eosinophilic esophagitis is independent of interleukin (IL)-13. Immuno Cell Biol 2013; 91: 408-415 [DOI: 10.1038/icb.2013.21]  
63 Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. J Allergy Clin Immunol 2007; 119: 206-212 [PMID: 17208063 DOI: 10.1016/j.jaci.2006.10.016]  
64 Kim N, Sohn UD, Manganan V, Rich H, Jain MK, Behar J, Bianciani P, Leukotrienes in acetylsalicylic-induced contraction of eosinophilic smooth muscle in experimental esophagus. Gastroenterology 1997; 112: 1548-1558 [PMID: 9136833]  
65 Moawad FJ, Veerappan GR, Dias JA, Baker TP, Maydovonitch CL, Wong RK. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for eosinophilic esophagia. Am J Gastroenterol 2013; 108: 366-372 [PMID: 23399553 DOI: 10.1038/ajg.2012.443]  
66 Molina-Infraste J, Katzka DA, Dennon ES. Proton pump inhibitor-responsive eosinophilic esophagitis: a historical perspective on a novel and evolving entity. Rev Esp Enferm Dig 2015; 107: 29-36 [PMID: 25603329]  
67 Francis DL, Foxx-Orenstein A, Arora AS, Smyrk TC, Jensen K, Nord SL, Alexander JA, Romero Y, Katzka DA. Results of ambulatory pH monitoring do not reliably predict response to therapy in patients with eosinophilic oesophagitis. Aliment Pharmacol Ther 2012; 35: 300-307 [PMID: 22118833 DOI: 10.1111/j.1365-2036.2011.04922.x]  
68 Ally MR, Dias J, Veerappan GR, Maydovonitch CL, Wong RK, Moawad FJ. Safety of dilation in adults with eosinophilic esophagitis. Dis Esophagus 2013; 26: 241-245 [PMID: 22676406 DOI: 10.1111/j.1442-2050.2012.01363.x]  
69 Bohn M, Richter JE, Kelsen S, Thomas R. Esophageal dilation: simple and effective treatment for adults with eosinophilic esophagitis and esophageal rings and narrowing. Dis Esophagus 2010; 23: 377-385 [PMID: 20354444 DOI: 10.1016/j.denis.2010.08.015]  
70 Moawad FJ, Chatham JG, DeZee KJ. Meta-analysis: the safety and efficacy of dilation in eosinophilic oesophagitis. Aliment Pharmacol Ther 2013; 38: 713-720 [PMID: 23915046 DOI: 10.1111/apt.12438]  
71 Konikoff MR, Noel RJ, Blanchard C, Kirby C, Jameson SC, Buckmeier BK, Akers R, Cohen MB, Collins MH, Assa’ad AH, Acetone: a randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterology 2006; 131: 1381-1391 [PMID: 1710314 DOI: 10.1053/j.gastro.2006.08.033]  
72 Dennon ES, Sheikh A, Speck O, Woodward K, Whitlow AB, Hores JM, Ivanovic M, Chau A, Woolsey JT, Madanick RD, Orlando RC, Shaheen NJ. Viscous topical is more effective than nebulized steroid to therapy in patients with eosinophilic esophagitis. Gastroenterology 2012; 143: 321-324.e1 [PMID: 22561055 DOI: 10.1053/j.gastro.2012.04.049]  
73 Alexander JA, Jung K, Neo RA, Anderson EA, Kafa A, Kafa K, Hryzka LA, Romero Y, Smyrk TC, Talley NJ. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2012; 10: 742-749.e1 [PMID: 22475741 DOI: 10.1016/j.cgh.2012.03.018]  
74 Lucendo AJ, Arias A, De Rezende LC, Yague-Compadre JL, Meta-Huertas T, Gonzalez-Castillo S, Cuesta RA, Tenias JM, Bellón T.
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: 1037-1046 [PMID: 21880354 DOI: 10.1067/j.jaci.2011.08.007]

Luceno AJ, De Rezende L, Comas C, Caballero T, Bellón T. Treatment with topical steroids downregulates IL-5, eotaxin-1/ CCL11, and eotaxin-3/CCL26 gene expression in eosinophilic esophagitis. Am J Gastroenterol 2008; 103: 2184-2193 [PMID: 18844613 DOI: 10.1111/j.1572-0241.2008.01937.x]

Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology 2010; 139: 418-429 [PMID: 20457157 DOI: 10.1053/j.gastro.2010.05.001]

Straumann A, Comas S, Degen L, Frei C, Bussmann C, Beglinger C, Schoepfer A, Simon HU. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011; 9: 400-409.e1 [DOI: 10.1016/j.cgh.2011.01.017]

Chuang MY, Chinnaratha MA, Hancock DG, Woodman R, Wong GR, Cock C, Fraser RJ. Topical Steroid Therapy for the Treatment of Eosinophilic Esophagitis (EoE): A Systematic Review and Meta-Analysis. Clin Transl Gastroenterol 2015; 6: e82 [PMID: 25809314 DOI: 10.1038/ctg.2015.9]

Assa’ad AH, Gupta SK, Collins MH, Thomson M, Heath AT, Smith DA, Perschy TL, Jurgensen CH, Ortega HG, Aceves SS. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology 2011; 141: 1593-1604 [PMID: 21835135 DOI: 10.1053/j.gastro.2011.07.044]

Otani IM, Anilkumar AA, Newbury RO, Bhagat M, Beppo LY, Dohil R, Broide DH, Aceves SS. Anti-IL-5 therapy reduces mast cell and IL-9 cell numbers in pediatric patients with eosinophilic esophagitis. J Allergy Clin Immunol 2013; 131: 1576-1582 [PMID: 23625266 DOI: 10.1016/j.jaci.2013.02.042]

Straumann A, Comas S, Grzonka P, Kita H, Kephart G, Bussmann C, Beglinger C, Smith DA, Patel J, Byrne M, Simon HU. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. Gut 2010; 59: 21-30 [PMID: 19828470 DOI: 10.1136/gut.2009.178558]

Spiegel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G, O’Gorman MA, Abonia JP, Young J, Henkel T, Wilkins HJ, Liacouras CA, Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol 2012; 129: 456-463, 463.e1-3 [PMID: 22206777 DOI: 10.1016/j.jaci.2011.11.044]

Lin SK, Sabharwal G, Ghaffari G. A review of the evidence linking eosinophilic esophagitis and food allergy. Allergy Asthma Proc 2015; 36: 26-33 [PMID: 25562553 DOI: 10.2500/aap.2015.36.3804]

Peterson KA, Byrne KR, Vinson LA, Ying J, Boynton KK, Fang JC, Gleich GJ, Adler DG, Clayton F. Elemental diet induces histologic response in adult eosinophilic esophagitis. Am J Gastroenterol 2013; 108: 759-766 [PMID: 23381017 DOI: 10.1088/ajg.2012.468]

Molina-Infante J, Arias A, Barrio J, Rodríguez-Sánchez J, Sanchez-Cazalla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. J Allergy Clin Immunol 2014; 134: 1093-1099.e1 [PMID: 25174868 DOI: 10.1016/j.jaci.2014.07.023]

Arias A, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology 2014; 146: 1639-1649 [PMID: 24534634 DOI: 10.1053/j.gastro.2014.02.006]

Lucendo AJ, Molina-Infante J. Emerging therapeutic strategies for eosinophilic esophagitis. Curr Treat Options Gastroenterol 2014; 12: 1-17 [PMID: 24370990 DOI: 10.1007/s11938-013-0001-8]

Kruszewski PG, Russo JM, Franciosi JP, Varni JW, Platts-Mills TA, Erwin EA, Proctor. Comparative effectiveness trial of cow’s milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis. Dis Esophagus 2015; Epub ahead of print [PMID: 25721813 DOI: 10.1111/dote.12339]

Arias Á, Lucendo AJ, Martínez-Fernández P, González-Castro AM, Fortea M, González-Cervera J, Yagüe-Compadre JL, Mota-Huertas T, Vicario M. Dietary treatment modulates mast cell phenotype, density, and activity in adult eosinophilic esophagitis. Clin Exp Allergy 2016; 46: 78-91 [PMID: 25640519 DOI: 10.1111/cea.12504]

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