

Archives of The Medicine and Case Reports

Journal Homepage: <https://hmpublisher.com/index.php/AMCR/index>
eISSN: 2747-2051



Eosinophilic Esophagitis: Atopy Conditions of the Esophagus

Puspa Zuleika¹

¹Department of Ear, Nose, Throat, Head and Neck Surgery, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

ARTICLE INFO

Keywords:

Eosinophilic Esophagitis
Dysphagia
Atopy

Corresponding author:

E-mail address:

puspazuleika@yahoo.com

The author has reviewed and approved the final version of the manuscript.

<https://doi.org/10.37275/AMCR.v2i3.25>

ABSTRACT

Eosinophilic esophagitis is an immune-allergic pathology of multifactorial etiology (genetic and environmental) characterized by major symptoms of esophageal dysphagia and eosinophil-predominant inflammation of the esophageal mucosa that affects both pediatric and adult patients. EoE is an immune-mediated disease by which environmental and food antigens stimulate the Th2 inflammatory cascade. It is correlated with food allergy and atopy condition such as asthma, atopy dermatitis, rhinitis allergic and often in conjunction with Gastroesophageal Reflux Disease (GERD). Eosinophilic esophagitis (EoE) was first described in the 1990s, showing an increasing incidence and prevalence since then, in the United States is estimated to be approximately 57 per 100,000 persons being the leading cause of food impaction and the major cause of dysphagia. Its symptoms, which include heartburn, regurgitation, and esophageal stenosis. This symptoms similar to those of gastroesophageal reflux disease, causing delays in diagnosis and treatment. The endoscopic findings such as furrows, esophageal mucosa trachealization, and whitish exudates, this diagnosis should be confirmed histologically confirmed by biopsy on the presence of more than 15 eosinophils per high-power field and the exclusion of other causes of eosinophilia. Management includes medications, diet, and surgical dilatation.

1. Introduction

Eosinophilic esophagitis is a chronic inflammatory process characterized by esophageal symptoms, in which the eosinophil epithelium infiltrates the esophageal mucosa (> 15 eosinophils / TBSA). EoE is an immune disease in which environmental and dietary antigens stimulate the inflammatory cascade of Th2. There is a close interaction between specific diseases of this organ and the trigger antigens for EoE and other atopic conditions. EoE patients are sensitized to aeroallergens, food-allergens and concomitant atopic diseases, including asthma, allergic rhinitis, and eczema.^{1,2,3,4}

There are variations in the prevalence of eosinophilic esophagitis, with most cases reported in Caucasian men. Cases were also found in Asia and the Middle East. India and Sub-Saharan Africa by exception as there are no case documents in this

area. EoE is more common in temperate and dry areas, and in rural areas, and frequently in people under 50 years of age, men, and ethnic Caucasians. A recent Canadian study by Teoh T et al. Found a lower prevalence in East Asia (including Japan and China) compared with whites and patients in South Asia in the EoE cohort study. So that the prevalence of cases in European and North American countries, as well as the low prevalence in Eastern countries, indicates that this disease is related to environment and immune factors, as well as based on climate and season zones, which is more common in summer.^{4,11}

Patients are usually male with a background of allergies such as increased IgE, peripheral eosinophils, allergic diseases. In children, this disorder usually presents with symptoms of GERD and failure to thrive, while symptoms in adolescents include dysphagia, food impaction, stricture and a



history of untreated disease. There are three approaches that can be used, namely: drugs, diet therapy, and dilation.^{1,7}

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic inflammatory process, involving local immunity or antigens accompanied by symptoms of esophageal dysphagia, which is characterized by eosinophilic infiltration in the esophageal mucosa (> 15 eosinophils / LPB). In adults it is usually characterized by solid food dysphagia, reflux symptoms and repeated food impactions. Eosinophilic esophagitis was initially diagnosed as a common population of children with eating disorders. Diagnosis of EoE in children is often found when evaluating patients with complaints of nausea, vomiting, regurgitation, patients tend to refuse food, and the presence of failure to thrive due to lack of intake. This diagnosis is becoming increasingly common in adults with evaluation of dysphagia and the incidence of food impaction in adults.^{1,2,7,8}

Etiology

The etiology of eosinophil esophagitis is not fully understood. There remains the question of whether eosinophilic esophagitis is based on allergic disorders, due to abnormal immunological responses or secondary to severe reflux disease. There are several factors that are believed to have a role in the occurrence of EoE, including genetic factors, allergies, seasonal variations, and GERD. Many other studies have supported EoE as an allergic condition caused by an antigen (antigen-driven allergic). Studies have shown that there is a unique transcriptome expression in EoE and differentiate it from GERD, with eotaxin-3 being overexpressed in patients with EoE. IL-13 has been found to be specifically upregulated in the esophagus in patients with EoE and may serve as a major regulator of the

EoE transcriptome. Rothenberg et al have performed the first genome identification with a locus at 5q22. Sherrill et al. Reported that polymorphisms in the Thymic Stromal Lymphopoietin (TSLP) gene were risk factors for EoE independent of underlying allergy phenotypes. Antibiotic exposure in early life in infants, cesarean delivery, preterm birth, lack of breastfeeding, food allergy factors, and environmental and population factors are risk factors for EoE. This suggests that aberrant stimulation of the immune system at an early age predisposes to this disease. In addition, a decrease in the prevalence of *Helicobacter pylori*, an increase in the use of proton pump inhibitors, changes in food sources, and food packaging, can also have an impact on the epidemiological changes of EoE.^{2,4,6,12}

Pathogenesis

The causes and pathogenesis of eosinophilic esophagitis are not completely clear, but atopic hypersensitivity response conditions are strongly suspected. In addition, genetic factors, immune system, and environment also influence mucosal damage and the incidence of esophageal mucosal fibrosis.^{2,6,11,13}

Environmental Factor

The increasing prevalence of eosinophilic esophagitis greatly affects environmental exposure. Risk factors at an early age, such as cesarean delivery or prematurity, administration of antibiotics at the age of five, lack of breastfeeding or food allergies, can change the immune system at an early age which predisposes to this disease. Studies have also shown that EoE has also been linked to other atopic diseases such as asthma and atopic dermatitis, most patients are sensitive to one or more foods and have hypersensitivity to aeroallergens or respiratory allergies.^{2,4}



Immunogenetic Factors

The predominance of EoE in men and studies on the genetic history of genomic relationships, are thought to be a genetic component of EoE. In almost every study, male sex has a higher number of comparisons than women, which is 3: 1. Studies of genetic linkages have reported that three genes with functional sequelae, namely genes encoding thymic stromal lymphopoietin, eotaxin-3 (also known as chemokine C-C ligand motif 26), and calpain-14 are aberrant in EoE. Evidence also suggests that this disease is associated with the presence of T helper 2 (Th-2) lymphocytes, a type of immune response that often occurs in atopic conditions, accompanied by changes in the function of the esophageal barrier. Furthermore, there was an increase in the value of Th2 cytokines interleukin (IL) IL-4, IL-5, and IL-13, as well as mast cells found on the results of esophageal biopsy in EoE patients. These cytokines play an important role in the activation and recruitment of eosinophils into the esophagus.^{2,3,11}

Assessment of the esophageal tissue of patients with eosinophilic esophagitis shows characteristic features of a dilated interepithelial space pattern, altered epithelial barrier function, and down-regulation of proteins associated with barrier function (filaggrin and zonulin-1) and adhesive molecules (desmoglein-1). Interleukin-13 has been shown to decrease desmoglein-1 and filaggrin in vitro. Altered epithelial permeability can lead to a permissive environment that increases antigen presentation, which in turn leads to eosinophil recruitment. Eosinophils then affect the remodeling of esophageal tissue, and histologically it appears as subepithelial fibrosis through degranulation and secretion of granule cationic proteins, especially Major Basic Protein, and the elaboration of fibrogenic growth factors such as TGF- β . The formation of the esophageal ring is associated with histamine which activates acetylcholine causing muscular contraction of the esophageal mucosa. This ring may be

temporary and reversible, although the continuous contraction of the muscle fibers, hypertrophy and thickening of the muscle layer of the mucosa can contribute to permanent scar formation. IL-5 and eotaxin-3 activate eosinophils to release Major Basic Protein (MBP) and Eosinophil-derived Neurotoxin (EDN), which respectively activate mast cells and dendritic cells, mast cell activation contributes to fibrosis. Eosinophils also produce TGF- β , activate epithelial cells and cause hyperplasia, fibrosis, and dysmotility. There are differences in eosinophil subpopulations by comparing the expression of proinflammatory protein and tissue eosinophils in various parts of the gastrointestinal tract. Eosinophils and interleukins were measured in the esophageal and intestinal tissue as well as blood eosinophils from eosinophilic esophagitis sufferers and controls. Patients with eosinophilic esophagitis show strong evidence of eosinophil activation with increased CD-25, IL-5 and IL-13.^{2,6,11}

Clinical Manifestations

Clinical manifestations and the onset of EoE, although more common in children, can also be found at various ages. Symptoms can appear long before the diagnosis of EoE in children and adults, especially when the disease or symptoms appear gradually. However, diagnosis is not infrequently made after the initial event or even after an acute episode, especially patients who present with complaints of food impaction.^{3,11,12}

Patients can have asymptomatic symptoms for several periods. Symptoms can appear 3-5 years before being diagnosed. Symptoms are sometimes underestimated as a condition that lasts a long time and is not too annoying or noteworthy, such as a child who tends to eat slowly, chew carefully, cut food into small pieces, sauce food to make food softer or slippery, drinking fluids to help thin foods, avoiding tablets or pills and foods that are likely to cause dysphagia, such as meat and bread.²



Complaints in patients may vary depending on age, progression and the findings of nonspecific symptoms. Clinical manifestations in infants and toddlers have various nonspecific symptoms, generally in the form of nausea, vomiting, heartburn, refusal of food, choking on food, which can result in failure to thrive. Children who present with abdominal pain, vomiting, heartburn, heartburn with impacted food, can then be associated with a stricture or narrowing of the esophagus. In contrast, the main symptoms in school-age children and

adolescents, about 30-80% include dysphagia (difficulty swallowing) and food impaction, as well as other accompanying symptoms, namely heartburn, heartburn, nausea, and choking when eating, especially when eating food. which is rough textured. The degree of dysphagia is associated with other factors such as concomitant esophageal dysmotility, degree of mucosal inflammation, and fibrostenosis.^{1,3,11,12}

Table 1. Symptoms of Eosinophilic Esophagitis^{5,3,11}

	Baby	Child	Adult
Symptoms	<ul style="list-style-type: none"> • Intolerance • Refusal to eat • Gag • Choking while eating • Failure to thrive • Sleep disturbances 	<ul style="list-style-type: none"> • Dysphagia • Choking with rough texture • Food impaction • Abdominal or chest pain • Sore throat • Nausea-Vomiting / regurgitation • Sleep disturbances • Decreased appetite 	<ul style="list-style-type: none"> • Dysphagia on solid food (predominant) • Food bolus impaction • Chest pain • Discomfort in the throat • Diarrhea • Chapter bleeding • Anxiety at eating

Diagnosis

Eosinophilic esophagitis is important to recognize that some patients are asymptomatic, and suspicion of this disease is sometimes based on incidental findings on endoscopic examination performed on indications or examinations of other diseases or evidence of food impaction. T.K. Desai et al., In their study that approximately 9-32% of patients with symptoms of eosinophilic esophagitis had normal endoscopic findings and in the study also showed patients whose histological findings supported an eosinophilic esophagitis, but could have normal macroscopic findings on endoscopic examination. Patients found to have signs of EoE on endoscopy should undergo an 8-week empirical trial of high-dose PPI therapy (twice daily) before repeated endoscopy, to rule out a GERD or PPI-REE. The response to PPI therapy was significantly higher in

patients with pathologic pH monitoring. It is unclear about the PPI trials (length of treatment, type of PPI, dosage, and frequency of dosing), differences between children and adults or the clinical accuracy of phenotypes that can predict response to PPI therapy. This raises the question of whether PPI-REE is a clinical disorder in isolation or is a subdivision of EoE or GERD. According to the latest guidelines, Lucendo AJ, et al stated that GERD and PPI-REE are no longer considered a differential diagnosis, where EoE and GERD can occur together and side by side in the same patient, therefore the pathological abnormalities are not independent. In addition, PPI-REE and EoE have similar phenotypic, molecular, and pathophysiological characteristics and response to treatment. Based on this, the researchers then did not classify them as distinct pathologies. The



response to PPIs is no longer used as a differential diagnosis, but as management of EoE.^{3,11,12,15}

Based on clinical symptoms and diagnostic tests, eosinophilic esophagitis was enforced based on criteria including: (1) symptoms of esophageal dysphagia; (2) eosinophilic esophageal inflammation, with a histological finding, ≥ 15 eosinophils per field of view, affecting only the esophagus; (3) by excluding or excluding other causes of esophageal eosinophilia. There are other causes of esophageal eosinophilia, such as eosinophilic gastroenteritis, Celiac disease, Crohn's disease, infection, hypereosinophilic syndrome, achalasia, hypersensitivity to drugs, vasculitis, pemphigus, and connective tissue diseases.^{2,3}

Laboratory Examination

There is no clear laboratory picture that shows an eosinophilic esophagitis, due to the unknown sensitivity and specificity of laboratory tests. Overall, 10-50% of adults and 20-100% of children have an increased number of peripheral eosinophils, but usually only slightly.⁶

Radiology

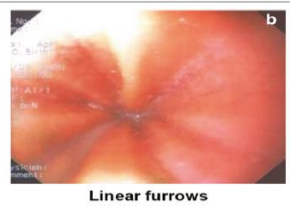
Radiological examination is not recommended except in certain cases to find abnormalities or anatomical variations. In children with EoE, radiological examination usually shows normal results. The most common diagnostic test currently

recommended for detecting eosinophilic esophagitis is the use of barium which is considered in a symptomatic patient, prior to endoscopy, to exclude a very narrow esophagus (severe small-caliber esophagus). Esophageal narrowing is sometimes found in conjunction with thickening of the esophageal wall.^{6,11,12}





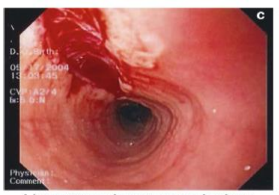
Endoscopy

Endoscopic examination of the upper gastrointestinal tract is the first diagnostic examination performed when an EoE condition is suspected, which includes examination of the esophagus, stomach, duodenum, followed by biopsy at several sites and excludes other pathological abnormalities. Endoscopic findings on EoE are divided into signs of inflammation and fibrostenosis. Based on the endoscopic phenotype, fibrostenotics are characterized by ring formation, narrowing, and strictures of the esophageal panda, whereas inflammation is characterized by the formation of grooves, white patches / plaques. The inflammatory phenotype is more representative of the Pediatric EoE population, ie, mean age 13 years, may experience abdominal pain, vomiting and failure to thrive. The phenotype of fibrostenotics, in contrast, was more typical in adult EoE patients, with a mean age of 39 years, who had symptoms of dysphagia and food impaction.^{1,3}

Table 2. Endoscopic overview of eosinophilic esophagitis^{3,11}

Endoscopic Picture	Description
<p><i>Linear furrowing</i></p>  <p>Linear furrows</p>	<p>Vertical lines or vertical waves in the esophageal wall</p>



<p><i>Concentric rings</i></p> 	<p>Multiple fine ring features, which can resemble a net or thickened, are also called "<i>corrugated</i>" or "<i>ringed esophagus</i>"</p>
<p><i>White speckled exudates</i></p>  <p>White exudates</p>	<p>The appearance of whitish papules (1-2 mm in diameter), resembling esophageal candidiasis</p>
<p><i>Schatzki ring</i></p> 	<p>Narrowing of the esophageal tissue just above the junction of the esophagus and stomach</p>
<p><i>Small-calibre esophagus</i></p> 	<p>Narrowing of the esophagus, with a fixed diameter, unfavorable esophageal expansion on air insufflation, and proximal and / or distal stenosis</p>
<p><i>Linear superficial mucosal tears</i></p>  <p>Linear tear plus concentric rings</p>	<p>Tear or rub on the mucosa that occurs during a simple endoscope procedure</p>

Endoscopic signs are helpful but are not pathognomonic of EoE and are not sufficient to make a diagnostic decision for EoE without confirmation of a biopsy. Sometimes the appearance of white exudate in the esophagus can be mistaken for candidiasis esophagitis so that a fungal culture sample can be considered, especially in patients receiving topical corticosteroid treatment. Biopsy is always done, because as many as 10% of adult patients and 32% of children with symptoms of eosinophilic esophagitis

have normal endoscopic features. From these findings, all patients with endoscopic features consistent with eosinophilic esophagitis should undergo biopsy. Histologically, EoE has an irregular esophageal eosinophilia and varies between the distal and proximal esophagus, so it is recommended that a biopsy be taken at least six points from two different locations, namely in the proximal and distal esophageal tissue to strengthen the diagnosis. Endoscopic assessment has a role in the assessment



of treatment response to EoE, which supports endoscopy as an important and objective treatment outcome. In addition, the image of the esophagus identified endoscopically may be an important determinant of disease severity in EoE.^{3,6,14}

A scoring system for the severity of endoscopic findings was then developed to evaluate the level of disease activity. The system for grading the severity of endoscopic findings is based on a consensus developed by the opinion of three gastroenterologists (Nirmala Gonsalves, Sami R Achem, Ikuo Hirano) to evaluate based on the severity of disease based on major characteristics and minor characteristics.^{3,14}

Endoscopy has an important role to play in excluding esophageal disorders associated with secondary eosinophilic esophagitis including achalasia, infectious esophagitis and gastroesophageal reflux disease. An endoscope is then used to diagnose EoE. Biopsy using endoscopy is required in determining the histopathological criteria of the dominant esophagus. Endoscopic assessment has a potential role in assessing treatment response to EoE. Studies have shown a significant improvement in the esophageal appearance after topical steroid use. The study report supports the use of EoE endoscopic images as an important and objective assessment of treatment outcome. The uniform nomenclature of safeguards facilitates communication between clinicians and comparison of findings between clinical studies conducted at different medical centers. In addition, the esophageal features identified endoscopically may be a determinant of disease severity in EoE. Thus, the utility of this classification system is to incorporate the main

features of EoE and to determine specific values for the severity of changes which have the potential for comparisons of patients between clinicians and investigators and as an assessment of response to medical or treatment diets in EoE.¹⁴

Histopathology

The diagnosis of eosinophilic esophagitis depends on the infiltration of the eosinophils into the squamous epithelium of the esophagus. The mucosa in the esophagus is usually in the absence of eosinophils, so that an increase in the number of eosinophils in the esophageal epithelium is a histological feature of eosinophilic esophagitis, where in clinical practice evaluation of histological examination is enough to do haematoxylin-eosin staining. The finding of at least 15 eosinophils per field was close to 100% sensitivity and 96% specificity for establishing a histological diagnosis of eosinophilic esophagitis. In GERD, the eosinophil infiltration may increase in the distal esophagus but with a lower density <10 eosinophils / LPB, therefore the increase in eosinophils on mid or proximal esophageal biopsy is more specific for eosinophilic esophagitis. Other features that may be helpful but not essential or pathognomonic for diagnosis include basal hyperplasia, increased number of inflammatory cells, including lymphocytes, mast cells, and basophils in the affected epithelial space, increased papillary size, with accumulated eosinophils on the superficial layer or microabscess. along the lumen surface.^{2,3,6,12}

Table 3. Major and minor characteristics of eosinophilic esophagitis^{3,14}

Major Criteria	Minor Criteria
Rings (<i>fixed rings, trachealization</i>) Grade 0: none Grade 1: light (appears fine ring image) Grade 2: moderate (formed a ring, but does not interfere with the endoscopic course,	Fragile mucosa " <i>crepe paper</i> " • Grade 0: none • Grade 1: available



with an outer diameter of 9.5 mm) Grade 3: severe (does not allow endoscope entry)	
Exudates (<i>white spots, plaques</i>): Grade 0: none Grade 1: mild (<10% esophageal surface) Grade 2: heavy (> 10% of the esophageal surface)	<i>Feline esophagus</i> (concentric mucosal rings observed spontaneously or during belching, vomiting, or swallowing which resolves with air insufflation) • Grade 0: none • Grade 1: available
Wrinkles (Vertical lines, longitudinal Furrow) Grade 0: none Grade 1: light (<i>vertical lines with no visible depth</i>) Grade 2: heavy (vertical line with deep mucosal indentation)	<i>Esophageal narrow caliber</i> (reduced lumen diameter of most of the tubular esophagus) • Grade 0: none • Grade 1: available
Edema (decreased vascularity) Grade 0: none Grade 1: mild (faint signs of vascularity) Grade 2: heavy (no sign of vascularity)	
Stricture Grade 0: none Grade 1: Yes	

Governance

EoE patient management remains controversial. Eosinophilic esophagitis is a chronic disease and its activity can peak unexpectedly from any intervention, is therapeutic, and can interfere with quality of life. It is not associated with malignant or premalignant conditions and several treatment modalities have been tested to control EoE.¹²

Patients with eosinophilic esophagitis sometimes have a mismatch between symptoms and histopathology, requiring some assessment of the disease. Based on the American College of Gastroenterology guidelines in 2013 published that the ultimate goal of therapy is the improvement of clinical symptoms and eosinophilic esophagistic inflammation. There are three approaches that can be used, namely: drugs, diet therapy, and dilation. Drug management and diet function to treat inflammation and dilation acts on fibrosis of the esophagus. Where possible, therapy should be provided with a multidisciplinary approach and the

collaboration of several experts including gastroenterologists, allergists, pathologists and nutritionists, as a strategy in patient care with EoE.^{2,3,16}

EoE treatment can be started from two initial options, namely drugs and diet elimination. Treatment begins with first-line PPIs, because these drugs are quite safe and effective. In patients who fail to respond to PPIs, the second step that can be taken could be dietary elimination or steroid therapy, where treatment also takes into account the lifestyle of each patient or family. Ultimately PPIs, topical steroids, or an elimination diet may be offered as first-line therapy in EoE patients. Regarding which therapy is given first to a patient, individual and family considerations must be taken into account, and perhaps this choice may change over time based on the disease and patient preferences.^{3,15}



Medical

Proton-pump inhibitors

Administration of a Proton-Pump Inhibitor (PPI) is the initial pharmacological option for EoE. PPIs play a role in evaluating the diagnostics of patients with eosinophilic esophagitis. The patient is initial a PPI to confirm the absence of esophageal Patients who experience a poor response to PPI administration are the only criteria to rule out GERD as a cause of eosinophilic esophagitis. Lucendo, Alfredo J, et al in their systemic review and meta-analysis stated that PPIs showed improvement in clinical response by 60.8% and histological remission by 50.5% in patients with eosinophilia esophagitis. Thus the investigators support the evidence that PPIs are the first-line therapy used in children and adults in these cases, followed by diet therapy and topical steroid therapy as effective second-line alternatives to EoE. After experiencing remission or improvement, the patient is continued with the PPI at the lowest dose as a maintenance dose.^{2,4,6,15}

Topical Corticosteroids

Several studies have shown the effectiveness of topical corticosteroid administration in improving symptoms and reducing inflammation in cases of eosinophilic esophagitis. There is a difference in the percentage of response depending on the drug, dose or formulation used. Tan, Nian Di, et al., In a meta-analysis study showed that topical administration of steroids resulted in a significant reduction in the number of esophageal eosinophils compared to non-steroidal individuals and also showed a reduction in symptoms and improvement in endoscopy.^{3,17}

It is known that short-term topical use of corticosteroids in EoE is relatively safe, but several studies have also discussed the safety of long-term use, in which cavities can occur in the oropharyngeal area and esophageal candidiasis in 10% of patients, and usually with asymptomatic symptoms. Other studies suggest possible suppression of the adrenals.

Cortisol monitoring is recommended to prevent adrenal insufficiency in children receiving high doses of topical corticosteroids (either ingested or concomitantly inhaled / nasal) in the long term.^{1,4}

The topical corticosteroids that are commonly used are fluticasone propionate and budesonide. Both can be used by spray using a metered inhaled dose and then swallowed. Administration of budesonide in viscous liquid by mouth (Oral viscous budesonide / OVB) results in higher histological remission than when sprayed and swallowed, because the liquid has longer contact with the esophageal mucosa. Administration of high doses of fluticasone has also shown better response rates in children and adults.^{2,3,18,20}

Both fluticasone propionate and oral administration of viscous budesonide (1000-2000 µg per day) have been shown to be effective in overcoming EoE. Propionate fluticasone is dispensed through a pressurized metered dose inhaler (pMDI) that is given into the mouth and swallowed directly (without inhalation). Budesonide can be given orally by using a nebulizer mixed with a thickening agent to increase the viscosity of the fluid, which, in theory, can slow down the movement of the surface layer of the esophagus. Clinical trials of topical administration of fluticasone propionate have shown histological and symptomatic improvement in 50-80% of children and adult patients with EoE. Oral administration of viscous budesonide is a more comfortable and viable option, with a high clinical response rate and histological improvement in children and adults. Complications of oropharyngeal and esophageal candidiasis should be considered with topical administration of fluticasone, whereas oral budesonide has a lower risk for esophageal candidiasis.^{11,16}

After receiving topical therapy for 6-8 weeks, the patient should undergo repeat endoscopy, to assess and confirm histological response to therapy. Once a therapeutic response has been confirmed, treatment



should be reduced to the lowest effective dose with appropriate follow-up. The optimal topical maintenance dose of corticosteroid for the long-term maintenance dose has not been fully established, however, it is recommended that the minimum effective dose be given to maintain clinical and histological improvement, ie maintenance dose of pediatric fluticasone 0.5 mg twice daily; and adults 1 mg twice a day. It is important to note that the disadvantage of using corticosteroids is that patients tend to relapse quickly after discontinuation of the drug, so that many patients with EoE will require long-term involvement, therefore with maintenance treatment the patient can control the disease but not cure it.^{1,3,11}

Systemic Corticosteroids

The use of systemic corticosteroids is benefitfully similar to topical corticosteroids, but carries a higher risk of side effects. Its use is primarily in emergency situations with severe dysphagia or significant weight loss. Oral prednisone may cause histological improvement, but has many side effects. About 40% of patients experience side effects, such as hyperphagia, weight gain, and / or cushingoid features. Because of its potential side effects, the use of prednisone has only been considered when topical steroid administration has been deemed ineffective or in patients who require rapid symptom improvement.^{2,3,13}

Diet therapy

In 1995, a study from Spergel JM, demonstrated the effectiveness of using a proprietary amino acid-based formula diet in the management of 10 children with eosinophilic esophagitis. The results of the study showed symptom improvement and histological improvement, but the symptoms returned when the patient returned to a normal diet. Diet therapy can be very effective and can directly address the underlying allergic mechanism. It can also serve the purpose of

identifying the various antigens that trigger the inflammatory response. Since endoscopy with biopsy is currently the method of choice for the assessment of histological response, patients may undergo several endoscopic examinations in an attempt to identify the type of food that triggers inflammation in EoE.²

There are three dietary approaches in overcoming EoE, namely: (1) Elemental diet; (2) dietary empiric restriction (empiric elimination of the diet based on allergic foods, without the use of allergy testing); and (3) a targeted diet, namely dietary restrictions based on the results of the *skin prick* and *atopy patch test*.¹¹

Diet Elemental

Elemental diets are carried out by eliminating all food sources containing potential allergenic proteins with a diet based on a nutritional formula that supports amino acids. With the hope of clinical improvement and histological features suggesting a response. Each week, a new type of food will be introduced to the patient, starting with the least allergenic properties, such as fruits and vegetables, then continuing with foods high in allergenic properties, such as dairy products, soy, eggs, wheat, and peanuts. Endoscopic assessments are then re-performed for each introduction of 3-5 foods to ensure inflammation does not recur.¹¹

Restricted Empirical Diet

The restriction empirical diet is the dietary arrangement of foods without the involvement of allergy testing with skin prick tests or previous atopy patch testing on patients, namely by paying attention to foods that often cause allergies. Some sites chose milk as the first trial, based on data showing fast response rates from six-group food eliminations. The elimination of food restrictions empirically based on the top six food groups associated with allergies, namely milk, wheat, soy / nuts, eggs, peanuts, and fish / shellfish, achieved a histological clinical



response in 72% of patients, where milk and wheat were identified as the most common causes. EoE, followed by eggs and soybeans.^{3,11}

Target Diet

This dietary restriction involves elimination based on the results of the skin prick test and atopy patch testing. Research by Warners MJ et al. Demonstrated success rates of 50-70% in trials in children and lower success rates in adults. In patients who are not sufficiently eliminated milk, there are two other approaches from the six food product groups (milk, eggs, wheat, soy, peanuts, and fish) or a four-food elimination diet (milk, eggs, wheat, and nuts). , because there is research showing fish and shellfish are less often involved in EoE. Dairy products were the triggers most frequently involved (74%), followed by wheat (26%), and eggs (17%). In a pediatric cohort study, eliminating meat (beef or chicken) other than milk, eggs, wheat, and nuts, increased the response to improvement to 77%. Combined with the skin prick test and the atopy patch test in children, it has shown a success and effectiveness of about 75% in eliminating the diet based on the positive results of this test. In adults results can be mixed, due to poor adherence levels.^{3,11,12}

Esophageal Dilation Surgery

Surgical intervention is usually performed on complications of EoE, namely esophageal stenosis. Mechanical dilatation of the esophagus is useful when there is subepithelial fibrosis that causes narrowing of the esophagus. The goal is to reduce dysphagia and achieve an esophageal caliber suitable for the food passage. Esophageal dilation, either with savary dilators or using the unsedated transnasal balloon technique, can provide a symptom improvement response of 83% and with a low complication of 5%, both in children and adults. This treatment is effective in 75% of patients, because the

symptoms improve immediately. Esophageal dilation surgery does not improve the underlying inflammatory process, and may need to be repeated, but it is a viable option in healthy to elderly male patients with EoE, who may prefer surgical intervention over medication or diet. . So that this esophageal dilation surgery cannot be used as a first-line treatment or as a single therapy for EoE, because this action does not affect the underlying inflammation of the disease process. This may be considered in patients with esophageal dysphagia or stenosis who do not respond to inflammation treatment. Esophageal dilation is always associated with risk, with several studies showing that the risk of esophageal perforation can occur in less than 1% of cases, whereas the study identified 1 perforation in 671 dilatation measures (risk of 0.1%).^{3,12,13}

Prognosis and Complications

Eosinophilic esophagitis treated with dietary therapy and corticosteroids did not result in mortality and failure to thrive. Relapses may occur 50% one year after oral corticosteroid therapy and no increased risk of malignant and eosinophilic gastroenteritis was found. In monitoring treatment, the response evaluation system during the treatment process includes a complete normal condition, response to treatment, and non-response to treatment, based on histology, symptoms, and endoscopic findings.^{6,13}

2. Conclusion

Eosinophilic esophagitis has been known for more than 20 years, and requires further study to understand the mechanisms of disease, development, tissue disorders, history, and optimal management. Eosinophilic esophagitis is a disorder in which eosinophil infiltration occurs in the superficial mucosa of the esophagus which is thought to be associated with infection, gastroesophageal reflux, food allergies and atopy such as asthma,



allergic rhinitis and atopic dermatitis which stimulate eosinophils and cause an inflammatory response. Although patient awareness of this condition is quite high, the literature shows that EoE is a condition that is often misdiagnosed, especially in the otolaryngology community. The pathogenesis of eosinophilic esophagitis involves environmental and genetic factors, particularly food antigens that induce Th2 cells releasing IL-5 and IL-13. The diagnosis can be made based on endoscopy and histology. Once the diagnosis is established, first-line treatment options include topical steroids, oral steroids, or dietary elimination. Treatment options depend on the patient's circumstances and preferences. Endoscopic dilation is an effective treatment for a stricture or narrow-caliber esophagus, especially when the symptoms of dysphagia are difficult to treat with medical therapy or diet. Relapses may occur 50% one year after oral corticosteroid therapy and there is no increased risk of malignancy and eosinophilic gastroenteritis.

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