

Eosinophilic disease of the esophago-gastro-intestinal tract

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Abstract

Eosinophilic gastrointestinal disorders (EGIDs) are a set of conditions with an increased number of eosinophils in any segment of the gastrointestinal tract without a known etiology. Clinical manifestations are based on the location and depth of the tissue eosinophilia. Eosinophilic Esophagitis is the most common one, although all EGIDs have an increasing prevalence. General Pediatricians should keep a high index of suspicion of these disorders and it is important to control symptoms and avoid complications. Diagnosis includes histologic criteria, so endoscopies and biopsies are always needed. Variable and individualized treatment is used.

Resumen

Los trastornos gastrointestinales eosinofílicos primarios son un conjunto de patologías crónicas que se caracterizan por un aumento del infiltrado eosinofílico, excluida una causa secundaria. Ocasionan síntomas variables según la localización del infiltrado. El más frecuente es la esofagitis eosinofílica, aunque la prevalencia de todos ellos está en aumento. Para el control de los síntomas y evitar sus posibles complicaciones es importante que el pediatra de Atención Primaria los conozca e incluya en el diagnóstico diferencial de patología digestiva. Dado que el diagnóstico incluye criterios histológicos, siempre va a ser necesaria la realización de una endoscopia con toma de biopsias. El tratamiento es variable e individualizado.

Key words: Eosinophilic esophagitis; Eosinophilic gastritis; Eosinophilic enteritis; Eosinophilic colitis; Eosinophilic gastrointestinal disorders.

Palabras clave: Esfagitis eosinofílica; Gastritis eosinofílica; Enteritis eosinofílica; Colitis eosinofílica; Trastornos gastrointestinales eosinofílicos.

OBJECTIVES

- To update the understanding of the etiopathogenesis of primary eosinophilic gastrointestinal disorders.
- To identify the clinical symptoms of these disorders so as to make an early diagnosis.
- To learn the diagnostic criteria of these diseases and their differential diagnosis.
- To be aware of the different treatment options available in these pathologies.

Introduction

Eosinophilic gastrointestinal disorders (EGIDs) are characterized by eosinophilic infiltration in the esophagus, stomach, small intestine, or colon, in the absence of other causes of tissue eosinophilia.

The infiltration of eosinophils in the digestive mucosa is common, except in the esophagus, and its increase has been associated with different inflammatory pathologies of the digestive tract that cause dysfunction and digestive symptoms. These entities include: eosinophilic esophagitis (EoE), eosinophilic gastritis (EoG), eosinophilic enteritis (EoN), and eosinophilic colitis (EoC)⁽¹⁾.

In the first part of this review we will focus on EoE, the most prevalent entity of all EGIDs. In the second part we will focus on the other primary eosinophilic diseases of the digestive tract: EoG, EoN and EoC.

EGIDs are part of the group of gastrointestinal allergies (GIA). Other types of GIA have been addressed in

other issues of this journal: No. 3 of 2020. Likewise, other types of esophagitis, beyond EoE, have been described in No. 8 of 2019 of this journal.

Eosinophilic esophagitis (EoE)

EoE is a chronic, immune-mediated disease characterized by a predominantly eosinophil inflammation exclusively at the esophageal level and by symptoms of esophageal dysfunction.

Epidemiology

It is an emerging disease and, currently, it is the most frequent cause of esophagitis after gastroesophageal reflux disease and the most frequent cause of dysphagia and impaction in children and young people.

Table I. Symptoms of eosinophilic esophagitis according to age

Infants and young children	- Reflux	- Food intake refusal
	- Vomiting	- Cough with food
	- Nausea	- Weight stagnation
	- Abdominal pain	
Older children and adolescents	- Dysphagia	- Cough with ingestion
	- Food impaction	- Pyrosis
	- Retrosternal pain	- Abdominal pain
	- Hoarseness	

between the esophageal microbiota of patients with EoE compared to healthy patients⁽¹⁰⁾. More studies on the microbiota are necessary to understand the implications and its potential practical applications.

Clinical manifestations

The clinical manifestations are a consequence of the esophageal dysfunction and vary according to the age of the patient (Table I).

These patients develop compensatory behaviors for dysphagia, such as carefully chopping food before eating it, eating slowly, drinking water after each swallow, and avoiding foods with certain textures⁽¹¹⁾.

Diagnosis

The presence of compatible clinical symptoms (Table I) should raise suspicion of this entity. The confirmatory diagnosis is histological. Atopic comorbidity and family history support the suspicion.

The diagnostic criteria for EoE are:

- Presence of symptoms of esophageal dysfunction.

The first cases were described in the late 1970s and it was defined as an entity in the early 1990s. Since then, numerous studies have been published on it, and its incidence and prevalence have increased exponentially⁽²⁾. The prevalence of pediatric EoE in Spain in 2017 was 111.9 cases per 100,000 inhabitants and an incidence of 10.6 new cases per 100,000 inhabitants per year. It predominates in males, with a ratio of 3:1^(3,4).

Patients with EoE have a high incidence of atopic diseases, such as: asthma, rhinoconjunctivitis, atopic dermatitis or food allergies.

Pathophysiology

EoE is a non-IgE-mediated gastrointestinal allergy. Predisposing genetic variants have been identified that, together with environmental interactions, can trigger the disease.

EoE is highly hereditary, with 64 times higher risk of developing it among siblings⁽⁵⁾. The association between monozygotic twins is 58%, which implies a genetic determinant⁽⁶⁾. Some studies have identified certain genes that contribute to the development of EoE (*TSLP*, *CAPN14*, *EMSY*, *LRRC32*, *STAT6* and *ANKRD27*); however, it is important to highlight that dizygotic twins have a 36% association, while that of non-twin brothers is 2.4%. This significant difference would imply that environmental factors and epigenetic mechanisms influence its etiopathogenesis⁽⁶⁾.

EoE is caused primarily, but not exclusively, by a non-IgE-mediated immune response to food antigens. In some patients, seasonal environmental allergy may play an important role⁽⁷⁾. An abnormality of the epithelial barrier occurs with an increase in permeability,

which facilitates the penetration of food antigens or pneumoallergens. Th2 lymphocytes, together with the proinflammatory cytokines, interleukin 5 (IL-5) and 13 (IL-13), induce eosinophilic infiltration in the esophageal mucosa⁽⁸⁾.

A recent meta-analysis indicates that 3% of patients undergoing oral tolerance induction (OTI) to a specific food have esophageal biopsies compatible with EoE⁽⁹⁾. These patients could have undiagnosed or subclinical disease, and it could have been exacerbated by immunotherapy.

In the same way as in other atopic diseases, digestive dysbiosis may play a role in the pathogenesis of EoE. Several studies have indicated differences

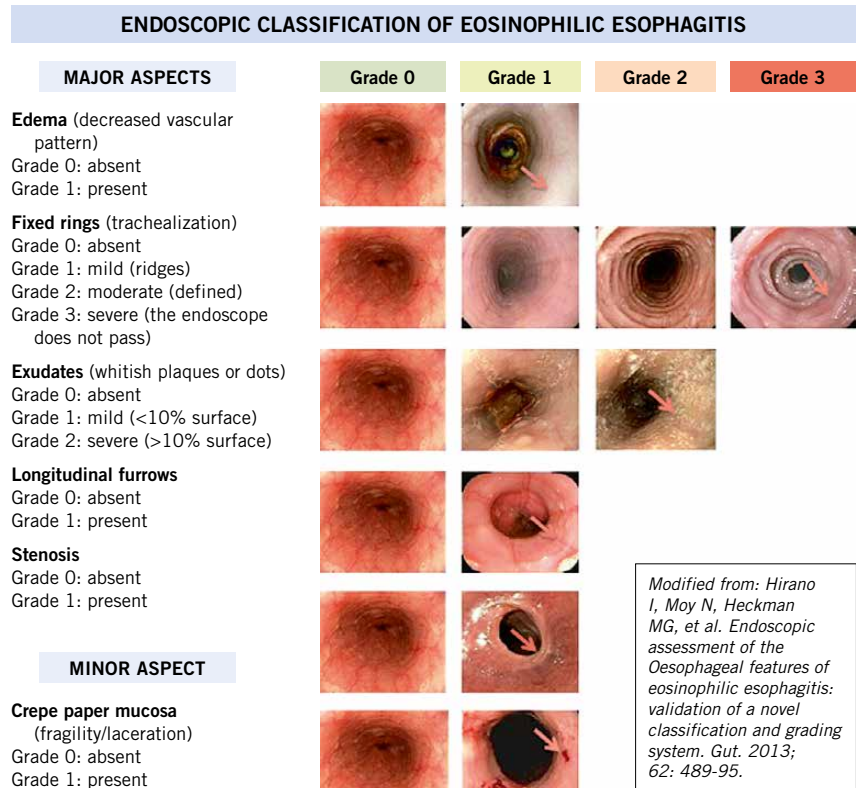


Figure 1. Eosinophilic esophagitis scoring system: EoE Endoscopic Reference Score (EREFS).

Table II. Causes of tissue eosinophilia⁽¹⁵⁾

- Inflammatory bowel disease	- Infections (herpes, candida, parasitosis)
- Hypereosinophilic syndrome	- Certain neoplasms
- Celiac disease	- Vasculitis
- Drug reactions	- Food protein-induced enterocolitis
- Gastroesophageal reflux*	

*Gastroesophageal reflux disease can induce eosinophilic infiltration, but generally below 5 eos/high-power field (HPF).

- Eosinophilic esophageal inflammation, with ≥ 15 eos/high-power field (HPF) (or ≥ 15 eosinophils/0.3 mm² or ≥ 60 eosinophils/mm²).
- Exclusion of other causes of esophageal eosinophilia.

The British consensus guidelines on EoE, published in 2022, propose expressing eosinophilic infiltration as the number of eosinophils per 0.3 mm², thus adapting to the current use of digital optical microscopy, which is replacing the analogue one⁽¹²⁾.

Diagnosis requires gastroscopy with biopsy. Gastroscopy allows visualizing the state of the esophageal mucosa and the presence of characteristics suggestive of EoE, such as: exudates, furrows, edema, strictures, rings, or the *crêpe* paper sign on the mucosa. The EoE Endoscopic Reference Score (EREFS) scoring system assesses these endoscopic characteristics (Fig. 1)⁽¹³⁾.

Although the esophageal mucosa appears normal, biopsies must be performed. The involvement can be patchy, so it is recommended to take 6 biopsies from at least 2 locations in the esophagus, generally distal and mid-proximal. The consensus guidelines establish a threshold value of equal to or more than 15 eosinophils per high-power field (eos/HPF) in at least one of the esophageal biopsies to confirm the diagnosis⁽²⁾.

In addition to the eosinophil peak count, there are other histological markers suggestive of this entity. The EoE Histology Scoring System has 8 histological characteristics that allow a more extensive evaluation of the esophageal mucosa⁽¹⁴⁾: number of eosinophils, eosinophil abscesses, basal zone hyperplasia, dilated intercellular spaces, eosinophils in the superficial layer, dyskeratosis, abnormality of the superficial epithelium and fibrosis of the lamina propria.

Currently, there are no non-invasive biomarkers validated for the diagnosis and/or monitoring of EoE, although it is a field continuously developing⁽²⁾.

Differential diagnosis

For the diagnosis of EoE, it is mandatory to rule out other pathologies that may present with tissue eosinophilia (Table II).

Treatment

There are 3 treatment alternatives, all of them currently considered first-line: proton pump inhibitors (PPIs), swallowed topical corticosteroids (STCs), and empirical diet.

EoE is a chronic disease. Its natural history, without treatment, is associated with persistent symptoms. In addition, persistent esophageal inflammation causes esophageal remodeling that can lead to a fibrostenotic pattern. It is

essential to establish early treatment to control symptoms, esophageal inflammation and prevent progression.

Current consensus guidelines establish three treatment alternatives: PPIs, swallowed corticosteroids, and an empirical diet, all of which are considered first choice⁽²⁾. The option chosen must be individualized and agreed with the patient.

8-12 weeks after the start of treatment, a new gastroscopy should be performed with biopsies. This will allow evaluating the efficacy of the treatment and adjusting it in each patient. Clinical symptoms are not enough to assess the histological response; since, sometimes, there is not a good correlation between the symptoms and the histology.

Proton Pump Inhibitors (PPIs)

PPIs have an anti-inflammatory action at the esophageal level and a histological remission of 50% has been observed after treatment in children and adults⁽¹⁶⁾. No differences have been seen between the different types of PPI (Table III). If they are effective, the dose will be gradually reduced until the minimum effective dose is found to maintain histological remission.

Swallowed topical corticosteroids

The histological remission rate is higher than the other treatment alternatives. Studies indicate remission rates of up to 85% at 12 weeks of treatment⁽¹⁷⁾. Treatment with systemic corticosteroids should only be used in severe stenosis or dysphagia, due to increased side effects compared to topical treatments.

No drug specifically designed for EoE in children is yet on the market in Spain. Currently, the most commonly used corticosteroids are viscous oral budesonide in magistral compounded formula and liquid fluticasone, marketed for rhinitis (Flixonase® nasal solution) (Table IV).

Dietary treatment

Dietary treatment is the only one that addresses the cause of the disease. It eliminates the triggering food or foods from the diet so that long-term clinical and histological remission is achieved. It avoids the use of pharmacological treatments. Dietary treatment requires motivation on the patients' part

Table III. Proton pump inhibitors most commonly used in the treatment of eosinophilic esophagitis

Drug	Induction dose	Maintenance dose
Omeprazole/ esomeprazole	1 mg/kg/12 h (maximum 40 mg/12 h)	1 mg/kg/day (maximum 40 mg/day)
Lansoprazole	0.75 mg/kg/12 h (maximum 30 mg/12 h)	0.75 mg/kg/day (maximum 30 mg/day)

Table IV. Swallowed topical corticosteroids used in the treatment of eosinophilic esophagitis

Drug	Induction dose	Maintenance dose
Viscous Oral Budesonide (VOB)*	<10 years: 0.5 mg/12 h	<10 years: 0.5 mg/24 h
	≥10 years: 1 mg/12 h	≥10 years: 1 mg/24 h
Liquid fluticasone	<10 years: 400 µg/12h	<10 years: 400 µg/24 h
	≥10 years: 800 µg/12 h	≥10 years: 800 µg/24 h

*VOB in magistral compounded formulation prepared in pharmacy at a concentration 0.2 mg/ml or 0.5 mg/ml or preparation by the patient himself using budesonide 0.25 mg/mL suspension for nebulizer inhalation, mixed with 4-5 g of maltodextrin⁽¹¹⁾.

– 0.5 mg dose: 1 ampoule (2 ml) of budesonide 0.25 mg/mL.

– 1 mg dose: 1 ampoule (2 ml) of budesonide 0.5 mg/mL.

and their families, and in general there is worse adherence to the diet in adolescents.

- **Elemental diet** based on the exclusive administration of free amino acid formulas induces histological remission in 90% of patients. In many cases, administration through a nasogastric tube is necessary. Given the deterioration in the patient's quality of life, it should only be recommended in severe cases and temporarily after lack of response to appropriate drug treatment or an empirical elimination diet. Targeted **diets based on allergy testing** are not recommended in EoE. The utility of food allergy tests to identify foods that trigger EoE is low⁽²⁾.
- **Empirical diet** eliminates foods that have most often been linked to EoE, regardless of allergic testing. It always requires the performance of upper digestive endoscopies with biopsies after each dietary intervention, to evaluate the effect at the histological level. Initially, a 6-food elimination diet (cow's milk, gluten, egg, soy, nuts, fish, and shellfish) was tested, with progressive sequential reintroduction. Given the difficulty in following these diets and the large number of endoscopies required, elimination diets of 4 foods (milk-gluten-egg-legumes) and then 2 foods (cow's milk and gluten) were tested. More recently, a staggered approach has been proposed, starting with 2 foods, if there is no response, ascending to 4 and, finally, to 6. Currently, in Pediatrics, the empirical single food (milk) elimi-

nation diet is the recommended modality as the initial treatment, as it is much easier to implement. It achieves histological remission rates of up to 50% in pediatric patients, in addition to clinical and endoscopic improvement. In the absence of a response, the traditional pattern of empirical food elimination (2-4-6)⁽¹⁸⁾ could be continued.

Endoscopic dilation

It is used in cases of severe esophageal stricture. In pediatric EoE, this procedure is exceptional, since in most cases it can be reversed with conventional treatment.

Dupilumab

Many biologic drugs have been studied; however, the only one approved by the FDA (United States Food and Drug Administration) in the US for EoE is Dupilumab. It is a monoclonal antibody directed against the interleukin 4 receptor α subunit (IL-4R α) that blocks both IL-4 and IL-13 signaling and is not immunosuppressive. It is a drug previously approved for other pathologies such as atopic dermatitis and asthma, and since 2022 for pediatric EoE in children over 12 years of age weighing 40 kg or more. It is expected to be approved soon by the European Medicines Agency.

Other eosinophilic gastrointestinal disorders (EGIDs) besides EoE

EGIDs, beyond EoE, are also chronic immune-mediated disorders, clinically characterized by gastrointes-

tinal (GI) symptoms and histologically by a pathologic increase in eosinophils in specific regions of the GI tract, in the absence of secondary causes of eosinophilia. They are named according to the location of the eosinophilic infiltrate. A recent consensus has established the proper nomenclature to refer to these disorders: eosinophilic gastritis (EoG), eosinophilic enteritis (EoN), and eosinophilic colitis (EoC). The term "eosinophilic gastroenteritis" (EGE), which generally involves the stomach and small intestine, has been widely used in the literature, although its use is currently recommended to be avoided⁽¹⁾.

Epidemiology

The prevalence of EGIDs other than EoE is low and predominates in females.

The prevalence of EoG in children is 4.4, EGE 10.7, and EoC 4.3/100,000. The prevalence of EoG increases with age, while the prevalence of EGE is higher in children under 5 years of age. The prevalence of EoC does not differ according to age⁽¹⁹⁾.

In general, EGIDs other than EoE, are more frequent in women than in men, unlike EoE, with a prevalence of EoG in women of 7.9/100,000 *vs.* 5.4/100,000 cases in men⁽²⁰⁾. It can coexist with other atopic comorbidities and with EoE. The association with EoE is 10.6% in EoG, 12% in EGE and 10.9% in EoC⁽²⁰⁾.

Pathophysiology

The pathophysiology of EGIDs is only partially known. The combination of a genetic predisposition, the existence of dysbiosis and other environmental triggers (ingested or inhaled allergens) can lead to eosinophilic inflammation in patients with EGID.

Eosinophils induce bioactive inflammatory mediators that can trigger mast cell degranulation and release cytokines, lipid mediators, and neuromediators. These produce a Th2 immune response and intestinal inflammation. Recent studies seem to implicate Th2 cytokines (IL-4, IL-5 and IL-13) and eotaxin-3 in the pathogenesis of most of these diseases⁽²¹⁾, although EoC seems to have a different transcriptome from the rest of EGIDs.

Table V. Clinical symptoms of eosinophilic gastrointestinal disorders (ESIDs), excluding eosinophilic esophagitis (EoE), according to location⁽²⁰⁾ and according to the depth of eosinophilic infiltration^(21,22)

<i>According to location</i>	<i>Symptoms</i>
Eosinophilic gastritis (EoG)	Epigastric pain, vomiting, or weight loss
Eosinophilic enteritis (EoN)	Abdominal pain, vomiting, hematemesis, or diarrhea
Eosinophilic colitis (EoC)	Abdominal pain, diarrhea or constipation, and rectal bleeding
<i>According to depth of infiltration</i>	
Mucosal	Abdominal pain, nausea, vomiting, diarrhea, rectal bleeding, anemia, malabsorption, weight loss, protein-losing enteropathy, and hypoalbuminemia
Muscular	Dysmotility and obstruction
Serosal	Bloating and ascites

Clinical manifestations

EGIDs other than EoE, present a great diversity of symptoms that depend on the location in the gastrointestinal tract and the layer affected by tissue eosinophilia (Table V).

Diagnosis

Diagnostic criteria are based on a compatible clinical picture, an increased eosinophil count in biopsies, and the exclusion of secondary causes of gastrointestinal eosinophilia.

Diagnosis can be challenging, given the variability of the symptoms, the sometimes patchy involvement, the difficult access through endoscopic procedures on some occasions, or the possibility that the eosinophilic infiltrate only affects the deep layers, where biopsies cannot reach⁽²³⁾.

20-50% of patients with EGID have normal levels of eosinophils in peripheral blood, so a normal count is not enough to exclude the diagnosis. Recently, an endoscopic scoring system has been published to assess involvement in EoG with a strong correlation with histological results. The endoscopic findings evaluated are: erosions/ulcerations, nodularity, granularity, erythema, friability, fold thickening, and pyloric stenosis⁽²⁴⁾.

The presence of eosinophils is common in the digestive system except in

the esophagus. The number of eosinophils in the rest of the sections of the gastrointestinal tract increases from proximal to distal, except in the colon, where it is higher in the ascending than in the descending⁽²³⁾. The diagnostic criteria for EGID include the finding of a higher than usual tissue eosinophilic infiltration for each region of the gastrointestinal tract according to recently established criteria (Table VI)⁽²⁵⁾.

A recent study established a high level of agreement between the histological and endoscopic findings of patients with EoG and a transcriptome-based panel of gastric biopsies and blood markers (eotaxin-3, IL-5, and thymic stromal lymphopoietin, among others). They do not replace the histological study of the samples, but the blood markers could serve as an initial non-invasive marker, and the study of the transcriptome can be used to confirm

the diagnosis⁽²⁶⁾. At the moment, these markers are not available in routine clinical practice.

Differential diagnosis

Other causes of tissue eosinophilia must be ruled out (Table II), mainly inflammatory bowel disease (IBD).

In both EoC and IBD, eosinophilia can be found in the colonic lamina propria; however, IBD presents other acute and chronic histological changes that differentiate it from EoC. The clinical and endoscopic and histological findings must be considered to make the differential diagnosis.

Treatment

The low prevalence of EGIDs besides EoE, and their little-understood pathogenesis make it difficult to reach a consensus on its treatment.

No randomized controlled study on the treatment of EGIDs has been published, so there is not enough evidence available for the establishment of effective protocols.

More than a third of patients achieve spontaneous remission, but the majority will require dietary treatment and/or pharmacological intervention. Most patients treated with diets are pediatric, either using elemental or extensively hydrolyzed formulas or empirical diets eliminating a single food (milk or wheat) or combinations of foods considered to have a high risk of triggering an allergic response, as in the EoE, excluding also red meat in some studies⁽²⁷⁾.

The most commonly used pharmacological treatment is systemic glucocorticoids. Several corticosteroid

Table VI. Diagnostic criteria for eosinophilic infiltration in eosinophilic gastrointestinal disorders (EGIDs), excluding eosinophilic esophagitis (EoE)⁽²⁵⁾

<i>Location</i>	<i>Eosinophilic infiltrate</i>
Eosinophilic gastritis (EoG)	≥30 eos/high power field (HPF)
Eosinophilic enteritis (EoN)	≥52 eos/HPF in duodenum ≥56 eos/HPF in ileum
Eosinophilic colitis (EoC)	≥100/HPF in the cecum and right colon ≥84 eos/HPF in the transverse and descending colon ≥64 eos/HPF in the rectosigma

treatment strategies have been described: oral prednisone and topical budesonide. Treatment with oral prednisone is started at an induction dose of 0.5-1 mg/kg/day until clinical remission is achieved. Subsequently, the dose is gradually decreased until it is discontinued or until a minimum maintenance dose that maintains clinical remission is achieved. Regarding treatment with topical budesonide, the induction dose is 9 mg/day with a subsequent decrease in dose⁽²¹⁾. Rates of up to 42% of resistance or relapse have been published in a cohort of patients with EGE⁽²⁸⁾. Topical treatment is less effective than in EoE and systemic treatment has long-term side effects.

Among the biological drugs, cen dakimab (anti-IL-13) and dupilumab (anti IL-4R α) have been studied, showing that both decrease the eosinophil count and improve symptoms. Vedolizumab (binds to α 4 β 7 integrin) has also been used successfully in some patients. Mepolizumab (anti-IL-5) and reslizumab (anti-IL-5) have shown a reduction in the number of eosinophils, but without clinical improvement. For EoG and EGE, both benralizumab (anti-IL-5) and liletrinemab or AK002 (anti-Siglec 8) have produced clinical and histological improvement⁽²⁹⁾.

EGID Prevention

There is not enough evidence to recommend any effective prevention measure for EGIDs.

Role of the primary care pediatrician

The role of the Primary Care pediatrician is essential in recognizing the symptoms of EGIDs, especially in atopic patients. EoE is the most common entity and should be suspected in a patient with compatible symptoms. Referral to the pediatric gastroenterologist should always be done, since a gastroscopy is necessary for diagnosis. In the case of EGIDs besides EoE, a diagnostic delay is common given the non-specific nature of the symptoms; however, in the event of alarm symptoms, referral to a pediatric gastroenterologist should be made to expedite the diagnostic and therapeutic process.

Conflict of interests

There is no conflict of interest in the preparation of the manuscript. Declaration of interests: none.

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The asterisks reflect the interest of the article in the opinion of the authors.

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- Updated guide for the management of EoE in Spain, prepared by the SEGHN Working Group on Eosinophilic Gastrointestinal Disorders.
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- Review article on EGIDs excluding EoE, which addresses everything from pathophysiology to clinical symptoms and diagnostic and therapeutic management. It promotes the creation and promotion of platforms for patients and professionals, such as CEGIR in the US.
- Licari A, Votto M, D'Auria E, Castagnoli R, Caimmi SME, Marseglia GL. Eosinophilic Gastrointestinal Diseases in Children: A Practical Review. *Current Pediatric Reviews*. 2020; 16: 106-14.
- Updated article that summarizes the knowledge and management of EGIDs in Pediatrics. It describes the clinical features and diagnostic criteria, and addresses the differential diagnosis.

Recommended bibliography

- Lucendo A, Molina-Infante J, Arias A, von Arnim U, Bredenoord AJ, Bussmann Ch, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterology Journal*. 2017; 5:335-58.
- Consensus article between the main European Digestive and Allergology societies and working groups on the management of EoE.
- Gutiérrez Junquera C, Fernández Fernández S, Domínguez-Ortega G,

Clinical case

A 12-year-old boy consulted for symptoms of intermittent dysphagia in the last 2 years, after the initiation of oral tolerance induction (OTI) to milk by the Allergology service. The patient refers that the episodes of dysphagia have been very occasional in recent years and generally feels "very well" in himself. He denies impactions.

Personal history

Atopic dermatitis, IgE mediated allergy to cow's milk protein (CMP) and egg. The allergy to CMP commenced in the first months of life, with symptoms of perioral erythema after ingesting an adapted CMP formula. Prick test and CAP positive for CMP. CMP elimination diet was started, with favorable outcome, except for an episode of anaphylaxis 2 years later after accidentally ingesting it. From the age of 10, oral immunotherapy began under surveillance by Allergology with a good response, currently drinking 200 ml of milk per day.

Physical examination

Normal examination and appropriate anthropometry.

Ancillary tests

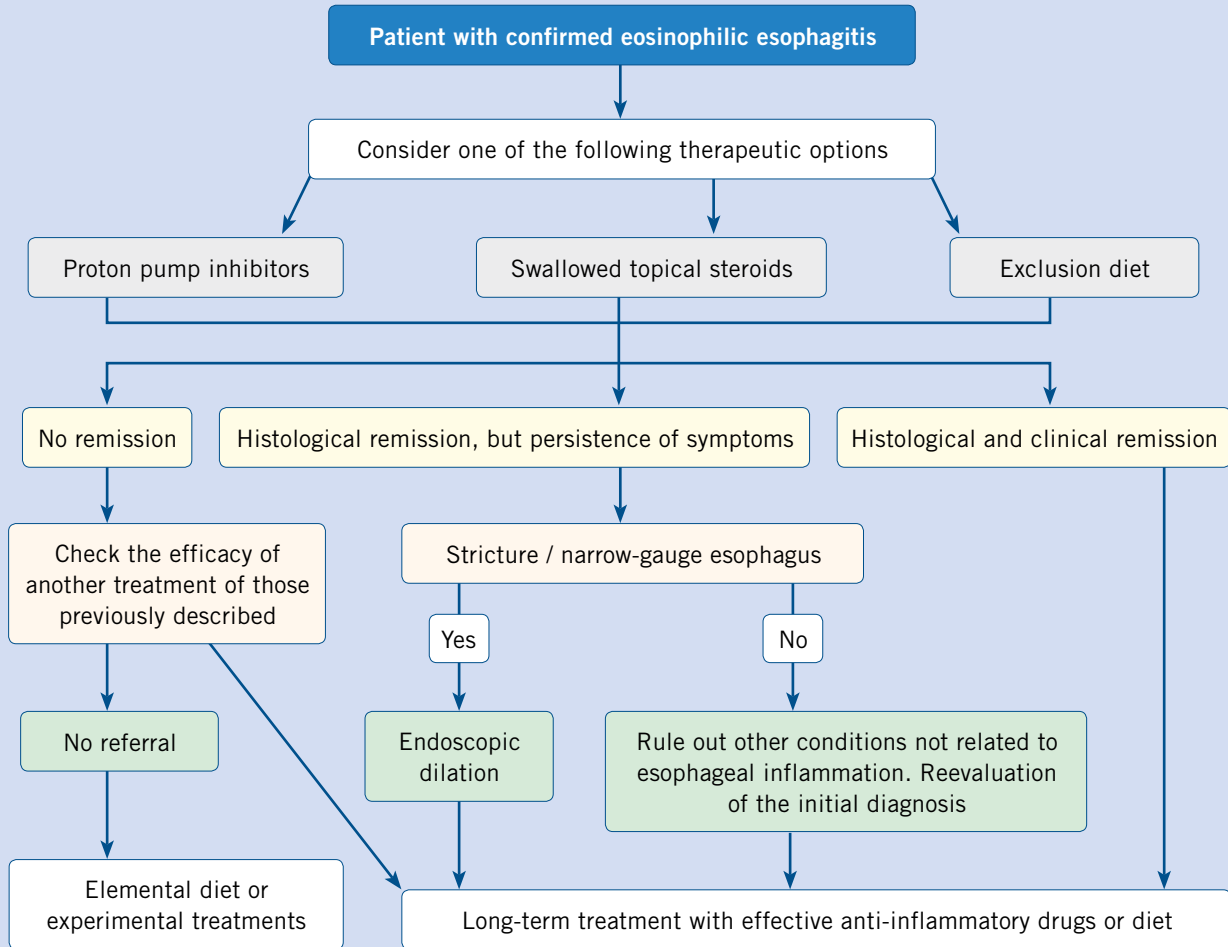
Upper digestive endoscopy: Hirano (EoE Endoscopic Reference Score: EoE-EREFS) 2 points, with exudates <10% and edema in 3 thirds. Microscopically: proximal esophagus: 3 eos/HPF; middle esophagus: 7 eos/HPF; distal esophagus: 10 eos/HPF. Basal cell hyperplasia and mild dyskeratosis in the middle and distal third. Normal gastric and duodenal mucosa.

Progression

Given the compatible symptoms, the allergic comorbidity, and the macroscopic endoscopic findings, the suspicion of eosinophilic esophagitis (EoE) is high; however, it does not meet the histological criterion of finding ≥ 15 eos/HPF in at least one of the esophageal biopsies. Since the involvement of the esophageal mucosa in EoE can be patchy, we may be facing initial stages of the disease. We decided clinical follow-up and scheduled a new gastroscopy in 4 months. However, 3 months later, he attended the emergency room due to esophageal impaction with a piece of beef that required a gastroscopy for resolution. Esophageal biopsies were taken. Macroscopically, the following findings were identified: Hirano 3 points, with exudates <10%, edema and furrows in the 3 thirds of the esophagus. Microscopically: proximal esophagus: 12 eos/HPF; middle esophagus: 45 eos/HPF; distal esophagus: >60 eos/HPF. Eosinophilic abscesses, basal cell hyperplasia and dyskeratosis in 3 thirds. Gastric and duodenal biopsies without pathological findings. With these findings and adequate screening for other causes of tissue eosinophilia, EoE was diagnosed. Omeprazole at 1 mg/kg/12 h for 8-12 weeks was commenced, followed by gastroscopy showing a favorable response, and thus, lowering the omeprazole dose to maintenance (1 mg/kg/day).

In patients where the endoscopic score is abnormal, but the maximum peak of eosinophils is <15, the EoEHSS histological score (Eosinophilic Esophagitis Histology Scoring System) could help detect the existence of eosinophilic inflammatory activity.

Suggested therapeutic algorithm for eosinophilic esophagitis



Modified from: Lucendo A, Molina-Infante J, Arias Á, et al⁽²⁾.



Accreditation quiz

The Accreditation Questionnaires for FC topics can be done at "On line" through the web: www.sepeap.org and www.pediatriaintegral.es. To obtain the single continuous training accreditation from the accreditation system for health professionals for the entire national health system, 85% of the questions must be answered correctly. The accreditation questionnaires on the different issues in the journal may be carried out during the period stated in the online questionnaire.



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Accreditation quiz

Subsequently, the following accreditation quiz of *Pediatría Integral* collects questions on this topic, which must be answered online through the website: www.sepeap.org.

In order to obtain certification by the Spanish "formación continuada" national health system for health professionals, 85% of the questions must be answered correctly. The accreditation quizzes of the different numbers of the journal may be submitted during the period indicated in the "on-line" quiz.

Eosinophilic disease of the esophago-gastro-intestinal tract

33. Indicate the **INCORRECT** answer regarding the etiopathogenesis of eosinophilic gastrointestinal disorders (EGIDs):
- Genetic factors and an abnormal immune response are implicated.
 - Currently, many factors involved in it are still unknown.
 - Epigenetic factors may participate in it.
 - Dysbiosis does not seem to be involved in the etiopathogenesis.
 - Current studies suggest the activation of Th2 immunity mechanisms.
34. Mark the **CORRECT** answer regarding eosinophilic gastrointestinal disorders (EGIDs):
- Eosinophilic gastritis, enteritis and colitis are more common in males.
 - Eosinophilic gastritis is more common in children under 5 years of age, and the prevalence of eosinophilic enteritis increases with age.
 - The finding of eosinophilic infiltration in any part of the digestive tract is pathological.
 - EGIDs are more common in patients with atopic comorbidity.
 - To make the diagnosis of eosinophilic esophagitis, it should not coexist in a patient with another EGID diagnosis.
35. Regarding the diagnosis of eosinophilic gastrointestinal disorders (EGIDs), excluding Eosinophilic Esophagitis (EoE), tick the **WRONG** answer:
- The diagnosis can be complicated, since the symptoms are varied, the affectionation can be patchy or the eosinophilic infiltrate may only affect deep layers.
 - The involvement of the serosa is characterized by dysmotility and obstruction.
 - Diagnostic criteria should include clinical and histological data.
 - We must make the differential diagnosis between eosinophilic colitis and inflammatory bowel disease.
 - Other causes of tissue eosinophilia must be ruled out.
36. Regarding treatment in eosinophilic esophagitis (EoE), tick the **CORRECT** answer:
- Proton pump inhibitors (PPIs), swallowed corticosteroids, and an elimination diet are considered first-line treatments.
 - Starting with PPI treatment is recommended and, if there is no histological response, switch to any of the other two options.
 - PPI treatment achieves histological remission rates of up to 80% in children.
 - In the case of choosing the elimination diet as treatment, the latest guidelines recommend following a diet excluding 6 foods.
 - In a 14-year-old teenager with multiple IgE-mediated allergies, who is diagnosed with eosinophilic esophagitis (EoE), we will propose the elimination diet as the first option due to his allergic background.
37. Regarding the diagnosis and monitoring of eosinophilic esophagitis (EoE), select the **CORRECT** answer:
- Allergy tests (prick test or CAP) are useful to identify the foods that trigger this disease.
 - An 8-year-old patient being followed up for EoE, asymptomatic, with a normal gastroscopy 2 years ago, and with good adherence to treatment, does not require further control gastroscopies.
 - Macroscopic findings during gastroscopy are useful to guide whether there is involvement of the esophageal mucosa.
 - Stenosis as a complication of EoE never occurs in children.
 - In the follow-up of EoE non-invasive markers such as blood eosinophilia can be used.

Clinical case

38. Does our patient **MEET CRITERIA** to be currently diagnosed with EoE?
- Yes. He meets clinical and histological criteria. In fact, after the findings in the first gastroscopy he could already have been diagnosed with eosinophilic esophagitis (EoE).
 - Yes. He presents ≥ 15 eos/HPF in esophageal biopsies, which is sufficient criteria for its diagnosis.
 - No. Despite the fact that the clinic manifestations are very suggestive, the biopsy has less

than 15eos/HPF, so the diagnosis of certainty cannot be made at the present time.

- d. No. Before confirming the diagnosis, we must give him a treatment with proton pump inhibitors (PPIs). If there is no histological remission, then we can diagnose it.
- e. Yes. He shows ≥ 15 eos/HPF, has clinical symptoms, and does not present with other disease that would justify eosinophilic infiltration.

39. What would be the most indicated treatment in this patient? Indicate the MOST RECOMMENDED treatment:

- a. Since cow's milk has been the trigger for eosinophilic esophagitis (EoE), the most indicated treatment is an elimination diet without cow's milk protein

(CMP), thus acting against the cause of the disease.

- b. Since it is a patient with a history of anaphylaxis to the CMP, the treatment must be agreed with Allergology. Consideration might be given to lowering the dose of cow's milk to an amount that prevents anaphylaxis, and also, prescribe pharmacological treatment.
- c. Since he is a patient who has suffered impaction, the initial treatment is the use of systemic corticosteroids to reverse the possible stenosis.
- d. Since he is an IgE-mediated allergy patient, food allergy testing should be done to rule out potential food triggers.
- e. Since he is a patient with food allergies, it is best to keep the intake of 200mL of milk per day

and prescribe pharmacological treatment.

40. How should the FOLLOW-UP be continued in this patient?

- e. We will perform a control endoscopy depending on the clinic.
- b. We will perform a control endoscopy in 8-12 weeks' time.
- c. If he clinically responds to treatment, treatment can be discontinued and endoscopy repeated if new symptoms.
- d. If he clinically responds to treatment, that drug can be de-escalated, without fully suspending, and repeat the endoscopy if new symptoms arise.
- e. If he had stopped taking all types of dairy, it would not be necessary to empirically supplement with calcium and vitamin D.



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