Oesophageal eosinophilia and oesophageal diseases in children: are the limits clear?

Sarah Esther Diaz-Oliva ¹, Idalmis Aguilera-Matos ¹,
Oscar Manuel Villa Jiménez ², Angel A Escobedo ^{1,3}

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ABSTRACT

Gastro-oesophageal reflux disease, eosinophilic oesophagitis and oesophageal motility disorders are among the most common diseases accompanying oesophageal eosinophilia. They have similarities and their limits are frequently not well defined. This article reviews the main characteristics relating to their similarities and differences, highlighting existing controversies among these diseases, in addition to current knowledge. In the case of a patient with symptoms of oesophageal dysfunction, it is suggested to carry out an integral analysis of the clinical features and diagnostic test results, including histology, while individualising each case before confirming a definitive diagnosis. Future investigation in paediatric patients is necessary to assess eosinophilic infiltration in the various layers of the oesophageal tissue, along with its clinical and pathophysiological implications.

INTRODUCTION

Under normal physiological conditions, eosinophils are present throughout the gastrointestinal tract distal to the squamous oesophagus, so the oesophagus normally lacks these.¹ Several conditions are associated with the infiltration of eosinophils within the oesophagus, or oesophageal eosinophilia (box 1), many of which are uncommon or may present distinctive clinical characteristics.² However, in the clinical setting, there are some frequent oesophageal diseases with the evidence of eosinophils presented on oesophageal histology, such as gastro-oesophageal reflux disease (GERD), eosinophilic oesophagitis (EoE), and even oesophageal motility disorders.

EoE is the most distinctive as it relates to the presence of significant mucosal oesophageal eosinophilia, but other disorders must be considered in the differential diagnosis. Eosinophilic gastroenteritis with oesophageal involvement should be evaluated with the study of gastric and duodenal biopsy samples. Hypereosinophilic syndrome should be considered when the peripheral blood eosinophil count is $>1500 \times 10^9$ cells/L. Children

who have inflammatory bowel disorders, including coeliac disease or Crohn's disease, can have eosinophil-predominant oesophageal inflammation. A diagnosis of EoE is not appropriate when another condition could account for the histological changes. Treatment should be initiated for the presumed primary aetiology, with monitoring of the oesophageal inflammation. If oesophageal eosinophilia persists after the primary disease is controlled, EoE could be diagnosed as an overlapping condition. EoE has also been associated with connective tissue diseases, perhaps due to a shared pathogenic mechanism. It can also present with other unrelated medical conditions. Many other causes of oesophageal eosinophilia are relatively rare and can be excluded with a comprehensive medical history and laboratory tests; however, in the case of GERD, it can be more complex. Also, there are various reports of association of oesophageal eosinophilic infiltration and oesophageal motility disorders, with recent studies based on its pathophysiology.^{2 3} It is to these three disorders (EoE, GERD and oesophageal motility disorders) that we will make reference to in this article, since they are common diseases in clinical practice, which can overlap and sometimes their limits are not well defined. There have been some consensus and multiple investigations in regards on these diseases separately, but many aspects may still need to be clarified. The intention of this review is to offer a joint approach to these three conditions, with many similarities and sometimes their limits are not so well defined, emphasising their main characteristics that make they may be similar and be different.

DEFINITIONS

EoE is a chronic, inflammatory, local disease of immunological origin and mediated by antigens, usually food. Eosinophilic

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¹Pediatric Gastroenterology, Institute of Gastroenterology, Havana, Cuba

²Institute of Gastroenterology, Havana, Cuba

³Research department, Epidemiology, Institute of Gastroenterology, Havana, Cuba

Correspondence to

Dr Sarah Esther Diaz-Oliva; sarahediaz@gmail.com

Box 1 Conditions associated with oesophageal eosinophilia.²

- ▶ Eosinophilic oesophagitis
- ▶ Eosinophilic gastritis, gastroenteritis or colitis with oesophageal involvement
- ▶ Gastro-oesophageal reflux disease
- ▶ Achalasia and other disorders of oesophageal involvement
- ▶ Hypereosinophilic syndrome
- ▶ Crohn's disease with oesophageal involvement
- ▶ Infections (fungal, viral)
- ▶ Connective tissue disorders
- ▶ Hypermobility syndromes
- ▶ Autoimmune disorders and vasculitides
- ▶ Dermatological conditions with oesophageal involvement
- ▶ Drug hypersensitivity reactions
- ▶ Pill oesophagitis
- ▶ Graft-versus-host disease
- ▶ Mendelian disorders (Marfan syndrome type II, hyper-IgE syndrome, *PTEN* hamartoma tumor syndrome, Netherton syndrome, severe atopy metabolic wasting syndrome)

infiltration of the oesophagus was initially described in 1978 in biopsies of a patient that was diagnosed with achalasia.⁴ Eosinophilic infiltration was initially considered a consequence of GERD. It has been recognised as a clinicopathological entity from a report made in 1993.⁵ Subsequently, the response to dietary therapy was identified.⁶ The general recognition of this new disorder was in the current millennium, when it has been reported in adults and children.^{7,8} It is predominantly inflammatory during childhood (inflammatory phenotype) and with progression to fibrosis in adulthood (fibrostenosing phenotype), characterised by signs and symptoms of oesophageal dysfunction related to eosinophilic inflammation limited to the oesophagus.⁹ According to the latest international consensus update on the diagnostic criteria for EoE, *suspicion of EoE* was defined as symptoms of oesophageal dysfunction (concomitant atopic conditions can increase suspicion of EoE) and at least 15 eosinophils/high-power field (hpf) or approximately 60 eosinophils/mm² in oesophageal biopsy. *Confirmed EoE* was defined as symptoms of oesophageal dysfunction and at least 15 eosinophils/hpf or approximately 60

eosinophils/mm² on oesophageal biopsy (eosinophilic infiltration should be limited to the oesophagus), after evaluation for other causes of oesophageal eosinophilia.² In this consensus, there is recognition that it is the same disease in children and adults. The need to evaluate for conditions that might contribute to oesophageal eosinophilia has been recognised. This allows the diagnosis of EoE to coexist with that of GERD and other conditions.

The North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Pediatric Gastroesophageal Reflux (GER) Clinical Practice Guidelines defines GER as the passage of gastric contents into the oesophagus with or without regurgitation and vomiting. GERD is when GER leads to troublesome symptoms and/or complications.¹⁰ However, GERD shares symptoms and complications with EoE, making it difficult to distinguish these conditions. It also shares symptoms with some motility disorders and both entities may be present in the same patient. Therefore, a definition based on symptoms that can be shared with other conditions may not be completely clear (table 1).

The diagnosis of oesophageal motility disorders is based on alterations present in oesophageal manometry. Conventional manometry has been gradually replaced by high-resolution manometry (HRM), which is currently the 'gold standard' for diagnosis. The Chicago Classification (CC), which defines oesophageal motility disorders, was first published in 2008, and its last update was in 2015 (V.3.0).^{11,12} The CC provides uniformity in diagnoses, consisting of a hierarchical analysis; it initially focuses on disorders within oesophagogastric junction (OGJ) outflow obstruction (achalasia, OGJ outflow obstruction), later on major disorders of peristalsis (diffuse oesophageal spasm, Jackhammer oesophagus (JO), absent contractility) and finally minor disorders of peristalsis (ineffective motility, fragmented peristalsis).^{13,14} The CC was based on manometric studies carried out in a healthy adult population; therefore, it may have limitations in the paediatric population. The limitation for obtaining similar studies in a healthy paediatric population is an ethical consideration.¹⁵ Studies have been carried out to

Table 1 Main similarities and differences between eosinophilic oesophagitis (EoE), gastro-oesophageal reflux disease (GERD) and oesophageal motility disorders in terms of concept and clinical aspects

Aspects	EoE	GERD	Oesophageal motility disorders
Definition ^{2,10,11}	<p>Symptoms are mentioned in both definitions and may be common. Some complications of GERD are also common to EoE</p> <p>Histology is important in EoE definition; in both diseases, there is eosinophilia mucosa</p> <p>Generally higher number of eosinophils on biopsy</p>	<p>Some complications are typical of GERD (Barrett's oesophagus)</p>	Based mainly on manometric parameters, so it does not exclude other aspects
Clinical aspects	<p>Symptomatology compatible (symptoms of oesophageal dysfunction)</p> <p>More frequent history of atopy</p>	There may also be atopy and respiratory manifestations	

evaluate manometric parameters in symptomatic children depending on factors such as oesophageal length and age, but still without definitive conclusions.¹⁶ Being a diagnosis based only on manometric alterations, it leaves an open gap for other pathologies that could coexist.

CLINICAL ASPECTS

In paediatric patients, diagnostic guidance based on symptoms is difficult, especially at younger ages, when symptoms are more non-specific, and generally reported by caregivers, and therefore depend on their interpretation.

EoE is suspected clinically when there are symptoms of oesophageal dysfunction, which could manifest in various ways, including dysphagia, food impaction, food refusal, failure to progress with food introduction, heartburn, regurgitation, vomiting, chest pain, odynophagia, abdominal pain and malnutrition. Atopic comorbidities such as asthma, atopic dermatitis, or immediate food allergies should increase the clinical index of suspicion. In younger children, the most common symptoms are those similar to GER, in addition to vomiting, abdominal pain, food refusal and failure to thrive. In older children, adolescents and adults, dysphagia to solids, food impaction and chest pain not associated with swallowing are more frequently reported.¹⁷ Because these symptoms are non-specific, patients should be treated as clinically indicated. The diagnostic algorithm cannot anticipate all clinical possibilities, and provides scope for appropriate evaluation.²

Among the most frequent symptoms that may be associated with GERD in infants and children are general manifestations (irritability, food refusal, failure to thrive), gastrointestinal manifestations (heartburn, regurgitation/vomiting, retrosternal chest pain, dysphagia, epigastric pain) and manifestations of the airway (cough, wheezing, stridor, apnoea episodes, asthma, pneumonia).^{10 18 19} Given that the symptoms of GERD are not specific, 'red flags' or warning signs have been defined to guide the need for research studies to rule out complications of GERD and underlying disorders with similar symptoms. It should be noted that GER in infants is very common, and is usually self-limiting. In the presence of an infant with recurrent regurgitation, a thorough history and physical examination with attention to warning signals suggesting other diagnoses is generally sufficient to establish a clinical diagnosis of uncomplicated infant GER. In the absence of warning signs, diagnostic testing and/or therapies including acid suppression are not needed if there is no impact of the symptoms on feeding, growth or acquisition of developmental milestones. Referral to the paediatric gastroenterologist is recommended when in infants or children there are warning signs or symptoms suggesting an underlying gastrointestinal disease.¹⁰

Oesophageal motility disorders also show a spectrum of symptoms similar to EoE and GERD, including weight

loss (non-specific symptom predictive of abnormal HRM), feeding difficulties, dysphagia, vomiting, manifestations of GERD, respiratory symptoms, chest pain, failure to thrive, among others.²⁰ More non-specific symptoms are described in younger children, such as vomiting, anorexia, chronic cough, which often delays diagnosis.^{21 22} In oesophageal motility disorders, allergic disorders have also been reported among the most frequent comorbidities.¹⁵

Many of the clinical manifestations are similar in the three entities (table 1), which makes clinical-based differential diagnosis difficult, and diagnostic procedures should be performed when indicated.

ENDOSCOPIC ASPECTS

Upper digestive endoscopy or oesophagogastroduodenoscopy (EGD) may have specific features but may also be normal in EoE and GERD. (table 2)

In the EoE, an endoscopic reference score has been developed: Edema, Rings, Exudates, Furrows, Strictures that gives a score according to the degree of severity of the finding.²³ The findings of mucosa on crepe paper and mucous friability are also described.^{7 24 25}

In the case of GERD, it does not have a gold standard test. EGD is recommended if the complications of GERD need to be assessed and if underlying mucosal disease is suspected before intensification of therapy. The probability of having erosive oesophagitis caused by reflux varies from 15% to 71% between studies, so a normal endoscopy does not necessarily rule out the possibility of GERD.^{10 26} When GERD is erosive, the diagnosis of this is facilitated, the most used classification is Los Angeles classification.²⁷ There are, of course, other complementary tests, such as pH-metry and multichannel intraluminal impedance to support the diagnosis of GERD in necessary cases.

For the diagnosis of oesophageal motility disorders, anatomic causes of the symptoms must have been excluded by means of a contrast study of the oesophagus and/or EGD.^{7 22} Therefore, EGD should be normal, which does not exclude the presence of oesophageal disease. If there is EoE or GERD, and oesophageal manometry is performed, we can find the diagnosis of motor disorders in these entities.

HISTOLOGICAL ASPECTS

Although there are aspects that could help differentiate GERD and EoE from the histological point of view, there are some cases that are histologically indistinguishable and both conditions can overlap (table 2). It is also more complex if samples are only taken from the distal third of the oesophagus, since this is the most affected in GERD, while in EoE the entire oesophagus is affected in patches. In addition, in severe cases of GERD, more proximal areas can be affected.²⁸ A study of EoE performed in paediatric age showed a denser eosinophilic infiltrate in the distal

Table 2 Some aspects of diagnostic test in eosinophilic oesophagitis (EoE), gastro-oesophageal reflux disease (GERD) and oesophageal motility disorders

Diagnostic tests		EoE	GERD	Oesophageal motility disorders
Upper digestive endoscopy		Can be normal Endoscopic reference score (EREFS: Oedema, Rings, Exudates, Furrows and Strictures) Involvement throughout the oesophagus	Los Angeles classification for erosive oesophagitis; stenosis, oesophageal metaplasia, etc. Distal involvement	Organic causes of dysphagia should be excluded
Histology ²⁸	General features	Eosinophilic infiltration, basal cell hyperplasia, dilated intercellular spaces, elongation of the papillae		Findings compatible with GERD, with EoE and eosinophilic infiltration of the submucosa and the muscularis propria have been described
	Eosinophil number	≥15 eos/hpf	Usually less, although in some cases it can reach 15 eos/hpf	
	Location of eosinophil infiltration	Patched along the oesophagus	More intense in distal oesophagus	
	Eosinophilic abscesses	Frequent	Rare	
	Eosinophils degranulated	Frequent	Infrequent	
	Erosion/ulcer	Rare	May be present	
	Damage and loss of superficial squamous cells	Useful if present	Rare	
Oesophageal manometry		It can be pathological		With alterations

EREFS, Edema, Rings, Exudates, Furrows, Strictures; hpf, high-power field.

oesophagus relative to the middle oesophagus.²⁹ Eosinophil levels in EoE are reported to vary widely by patient, in the same patient per biopsy sample and in the same biopsy by hpf analysis.²⁸ Therefore, in all cases where EoE is a clinical possibility, even when visualising the normal mucosa, multiple biopsy samples of two or more oesophageal levels, directed to areas of apparent inflammation, are recommended to increase diagnostic performance.² In the histological study, in addition to the peak of the eosinophil count, a histological score (EoEHSS) has been developed recently. This provides more histological elements to evaluate EoE and has been shown to be superior in the diagnosis of EoE and in therapeutic decision-making.^{30–32}

In GERD, the characteristic histological changes are: polymorphonuclear leucocyte infiltrate, intraepithelial eosinophils, hyperplasia of the basal area and elongation of the papillae.²⁶ These changes are also mentioned in EoE.²⁵ The absence of histological changes does not exclude GERD.¹⁰

MANOMETRIC ASPECTS

No specific manometric pattern for EoE has been identified.³³ Variable motor abnormalities, both hypocontractile and hypercontractile, were described with conventional oesophageal manometry.^{8 34} After the use of HRM with CC, they have continued to report, even with a favourable response to steroid therapy.³⁵

In GERD, it is suggested to use manometric studies when a motility disorder is suspected.¹⁰ The alterations associated with GERD are dysfunction of the OGJ and alterations in the motility of the oesophageal body, mainly ineffective oesophageal motility.^{20 36 37}

The association of motility disorders with oesophageal eosinophilia in the different layers of the oesophagus has been described for decades.⁸ In relation to achalasia, the association with mucosal eosinophilia only (EoE) is uncommon, but there are several publications about the association with eosinophilic infiltration of the different oesophageal tissues, especially muscularis propria.^{4 38–45}

It is not clear when the motility disorder is due to oesophageal eosinophilia or vice versa. In a study, a decrease in oesophageal eosinophilia is described after the therapy of motility disorder,³³ or just clinical improvement.⁴⁶ However, other authors reported a patients with achalasia and EoE with a response to steroid therapy,⁴⁷ mainly vigorous achalasia.^{44 45} Improvement of oesophageal eosinophilia has also been described with the use of steroids in JO.^{48 49}

Sato *et al* described the heterogeneous infiltration of eosinophils in the oesophagus in the mucosa, submucosa and muscularis propria. The presence of eosinophils in the oesophageal muscle tissue is named as eosinophilic oesophageal myositis, and was associated with hypercontractile oesophagus. In the oesophageal epithelium of these patients, no increase in eosinophils or cytokine

overexpression was observed, but in muscle tissue, there was eosinophilia, eotaxin-3 and C-C chemokine receptor type-3 overexpression. The research has limitations as it was a small-size pilot study and the use of patients with achalasia as a control group.⁵⁰

The relationship between oesophageal motility disorders with oesophageal eosinophilia and GERD requires new researches, mainly in paediatric patients because most of the researches were completed within the adult population.

TREATMENT-RELATED ASPECTS

In managing infants with GERD, non-pharmacological treatment such as avoiding overfeeding, thickened feeds and continuous breast feeding in breastfed infant are initially recommended. If there is no improvement, consider 2–4 weeks of a protein hydrolysate or aminoacid-based formula, or in breastfed infant: elimination of cow's milk in maternal diet. In children and adolescents, the initial recommendation is also lifestyle and dietary education. If there is no improvement pharmacological treatment is recommended: acid suppression for 4–8 weeks, preferably with proton pump inhibitors (PPIs). Refer to the paediatric gastroenterologist when patients are refractory to optimal treatment and cannot be permanently weaned from pharmacological treatment within 6–12 months.¹⁰

GERD was previously distinguished from other diseases and from EoE by clinical response to PPI therapy. Then, it was found that there was a group that histologically met the criteria for EoE but also responded to this treatment and was termed PPI-responsive oesophageal eosinophilia (PPI-REE). In the last diagnostic consensus of EoE, PPI-REE was included in EoE because studies had shown that it was the same disease.² To understand this, it is necessary to mention some aspects of the pathophysiology of EoE. The abnormalities found in cases of EoE are increased oesophageal mucosa permeability. It may be responsible for entry of food and environmental allergens into subepithelial tissues and induce allergic reactions following eosinophil infiltration. These allergens then stimulate a Th2-type immune response with increased production of Th2-type cytokines, including interleukin (IL)-13 and IL-4, which increases eosinophil accumulation in the

oesophagus through stimulation of eotaxin-3 production by oesophageal epithelial cells.^{51 52} Cheng *et al*⁵³ showed that in EoE and GERD cell lines, IL-4 and IL-13 activated the eotaxin-3 promoter. Similar levels of eotaxin-3 were observed in both diseases. PPI might have eosinophil-reducing effects independent of effects on acid reflux, and that response to PPI does not distinguish EoE from GERD. A molecular EoE diagnostic panel (EDP) was identified, that is composed of 94 EoE genes and distinguishes patients with EoE from control subjects. Applying EDP, similar expression patterns were demonstrated in EoE and PPI-REE, indicating that PPI-REE is a condition within the same spectrum as EoE.⁵⁴ Due to this, a test with PPI is not required for the diagnosis of EoE in the diagnostic algorithm of the mentioned disease.² And we cannot distinguish GERD and EoE by their response to PPI therapy (table 3).

SOME ASPECTS IN RELATION TO THE PATHOPHYSIOLOGY

New hypotheses related to the mechanisms of inflammation and cytokine release have been developed to explain the abnormalities. In the case of GERD, a new concept has been proposed, stating that it is not reflux that directly damages the epithelium, but rather stimulates epithelial cells to release cytokines that induce proliferative changes and attract T lymphocytes and other inflammatory cells that they end up damaging the mucosa.⁵² In EoE, it is known that there is an abnormal immune reaction mediated by Th2 ILs, in which there is a recruitment of eosinophils, inflammatory cytokines are released and the degranulation products released by the eosinophils contribute to epithelial damage.²⁴ By having similar pathophysiological mechanisms, mediated by cytokines, other similarities in GERD and EoE could be justified.⁵²

EoE is defined by the infiltration of eosinophils into the oesophageal mucous layer. Because of this, and for of the invasiveness and difficult access to the rest of the layers of the oesophageal wall, these are generally not studied. Oesophageal biopsies that are limited to the evaluation of the oesophageal epithelium are an inadequate means to assess overall, clinical disease severity in EoE.⁵⁵ However, in a study carried out in patients with EoE, the authors reported activated eosinophils in all oesophageal layers.⁵⁶

Table 3 Aspects related to treatment in eosinophilic oesophagitis (EoE), gastro-oesophageal reflux disease (GERD) and oesophageal motility disorders

Treatment	EoE	GERD	Oesophageal motility disorders
	There may be a good response to PPI		
	Response to other therapies (steroids, diet)	Non-pharmacological treatment is initially indicated Other treatments depending on the evolution and severity	Treatment depending on the type of disorder Steroid response has been described in some cases with oesophageal eosinophilia

PPI, proton pump inhibitor.

Several studies have proposed hypotheses to explain the association of achalasia and other motility disorders with oesophageal eosinophilia. From weak evidence that the oesophageal stasis of achalasia causes eosinophilia mucosa,^{33 42 46} to the oesophageal eosinophilia causes motility abnormalities through the release of cytokines and neurotoxic eosinophil secretory products.^{39 41 56–59}

Spechler has proposed that EoE, similar to what occurs in eosinophilic gastroenteritis, could have forms with a predominance of mucosa and forms with a predominance of muscle; the predominantly muscular form could cause a variety of oesophageal motor disorders, including achalasia. Some eosinophil products can cause oesophageal muscle contraction (thromboxane B₂, leukotriene D₄); others cause muscle relaxation (IL-6, IL-13) and fibrosis (transforming growth factor β , IL-13). They can also secrete neuroactive products, or others that destroy oesophageal intramural neurons.⁶⁰

CONCLUSIONS

The clinical similarity between GERD, EoE and oesophageal motility disorders, along with the possibility that they may overlap, requires great attention from the physician. It should be remembered that other entities may be underdiagnosed in the clinical context of GERD. We recommend, in the presence of symptoms of oesophageal dysfunction, if an EGD is to be performed, always take oesophageal biopsy samples in the distal and middle/upper thirds, even if there are no endoscopic alterations, nor have EoE been initially considered. The results of oesophageal manometry should be evaluated in conjunction with those of EGD and oesophageal histology. Before reaching a definitive diagnosis, carry out a comprehensive analysis of the clinical symptoms and the diagnostic tests performed, including oesophageal histology.

Future research, including paediatric patients, is required to assess eosinophilic infiltration of the different layers of the oesophagus and its pathophysiological implications.

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ORCID iDs

Sarah Esther Diaz-Oliva <http://orcid.org/0000-0002-6611-4823>

Idalmis Aguilera-Matos <http://orcid.org/0000-0002-7364-1533>

Oscar Manuel Villa Jiménez <http://orcid.org/0000-0002-6675-584X>

Angel A Escobedo <http://orcid.org/0000-0002-6241-3340>

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