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Case Report

New Guidelines for the Management of Eosinophilic Oesophagitis

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ABSTRACT

Objective: Eosinophilic oesophagitis is an immunologically mediated chronic disease of the oesophagus, characterized clinically by symptoms related to oesophageal dysfunction, and histologically by predominantly eosinophilic inflammation. The role of allergens is very important in triggering this condition. The oesophagus is an immunologically active organ, capable of recruiting eosinophils in response to various stimuli.

Methods: Eosinophilic oesophagitis has been reported in several countries outsideAfrica, with an increased incidence in men between 20 and 30 years old and people living in urban areas. This disorder is associated with other conditions, the most important being gastroesophageal reflux disease (GERD).

Results: From a paraclinical point of view, patients have a peripheral eosinophilia, and diagnostic certainty is realized by performing upper endoscopy with biopsy. The recommended treatment has 3 stages, namely diet, drug therapy (such as fluticasone propionate, budesonide and proton-pump inhibitors) and investigations such as upper endoscopy.

Conclusion: The article aims to highlight recent recommendations in international guidelines for the management of eosinophilic oesophagitis, as well as to review its clinical manifestations, genetics, immunopathogenesis diagnosis and treatment.

Keywords: Eosinophilic oesophagitis; Gastroesophageal reflux disease (GERD); Peripheral eosinophilia; Upper endoscopy with biopsy; International guidelines

INTRODUCTION

Eosinophilic oesophagitis is a chronic, immunologically mediated disease of the oesophagus, characterised clinically by symptoms related to oesophageal dysfunction, and histologically by predominantly eosinophilic inflammation. When gastrointestinal eosinophilia is limited to the oesophagus, and accompanied by characteristic symptoms, other causes of eosinophilia are excluded. In that case, the term used is eosinophilic oesophagitis [1]. Seasonal exacerbations of the described charges have suggested a possible role of aeroallergens [2].

Epidemiologically, eosinophilic esophagitis has been reported in the USA, Europe, Asia and Australia. This disease is not present in Africa [3]. Increased incidence has been observed in urban areas [4], with the majority of affected adults being men aged between 20 and 30 [5]. The first cases of eosinophilic oesophagitis were reported between 1960 and 1970 [6].

Recent studies have shown that smoking, long-term administration of NSAIDs [7] and the presence of Helicobacter Pylori [8] do not present statistically significant risk factors, but antibiotic therapy and antacid medication have a high potential risk to lead to the development of this condition [9,10].

The pathogenic mechanism of eosinophilic oesophagitis has not been studied, but the implications of genetic, environmental and immune factors are recognised. The oesophagus of patients with this condition have an imbalance between epithelial cells and the 'barrier' function, thus leading to the appearance of oesophageal epithelial dysfunction. The mechanism of the immune system also shows an imbalance due to the mismatch between Ig E mediated response and the delayed response of helper T cells type2 (Th2). The pathogenesis of eosinophilic oesophagitis involves a number of allergens, cytokines, microRNAs [11] and chemokines (IL4, IL-5, IL-13, eotaxin -3). At the same time, several genetic defects have been identified that predispose patients to the onset of eosinophilic oesophagitis, namely the deletion of chromosome 2p23 and calpain-14 (calcium-dependent cystein protease) [12].

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Table 1: Treatment in eosinophilic oesophagitis.

Proton pump inhibitors (PPIs)	Topical glucocorticoids			
	Fluticasone propionate	**Budesonide**	**Ciclesonide**	**Mometasone furoate**
• first-line treatment options • control the symptoms • once daily/ twice daily for eight weeks [38] • reduce acid production in patients with coexistent GERD	• decrease eosinophilic counts • dose inhaler without a spacer – 220 mcg/ spray , 4 sprays daily in divided doses for 4-8 weeks [39] • symptoms improvement • oesophageal eosinophilia is not improve • side effects: oesophageal candidiasis, herpes esophagitis, cataracts (at higher doses) [40], adrenal suppression • higher rates in sustained remission	• decrease eosinophilic counts • approved by European Medicine Agency and Health Canada • orodispersible tablet for adults or oral viscous slurry – 2mg daily for adults [41] for 12 weeks • symptomatic improvement • it is effective for treating eosinophilic esophagitis • higher rates in sustained remission [42]	• 80 or 160 mcg, 2 sprays twice daily for 2 months [43] • symptomatic improvement • eosinophilic esophagitis improvement • further studies are needed	• treating children and adolescents with eosinophilic esophagitis [44] • further studies are needed

Oesophageal dilatation is effective in relieving symptoms like dysphagia patients with high-grade strictures or rings who have not responded to pharmacological therapy (45).

Table 2: Experimental versus ineffective treatments in eosinophilic oesophagitis.

EXPERIMENTAL	INEFFECTIVE
Monoclonal antibody against IL-13 • Significant reduction in oesophageal eosinophil count, endoscopic severity and histological grade • No significant improvement in dysphagia symptoms [46]	
Dupilumab • A monoclonal antibody to the α subunit of the IL-4 • Improvement in dysphagia, histologic and endoscopic findings [47]	
Mepolizumab • A humanised monoclonal antibody against IL-5 • Significant role in eosinophil recruitment [48]	• Anti-TNF = Infliximab • Antihistamines and cromolyn • Anti –Ig E monoclonal antibody
Reslizumab • IL-5 neutralising antibody • Significant reduction in eosinophil counts [49]	
Prostaglandin D2 receptor antagonist • Significant reduction in eosinophil counts • Symptom improvement [50]	
Montelukast • Maintenance of remission [51]	
Purine analogues • Clinical and histological improvement [52]	

DISCUSSION

The clinical manifestations of eosinophilic oesophagitis vary with age [13], as follows: adolescents and adults frequently have dysphagia and food impactation, while children more often report symptoms of gastroesophageal reflux disease and abdominal pain.

The most common clinical manifestations in adults are:

- Dysphagia - the most common symptom [14,15]
- food impaction, present in approximately 50% of patients [16,17]
- Chest and retrosternal pain that does not respond to antacid therapy
- Treatment-related heartburn and other symptoms associated with GERD [18]
- Disorders of oesophageal motility suggesting involvement of oesophageal muscle layers [19]

Eosinophilic oesophagitis is associated with other allergic conditions, such as:

- Asthma [20]
- Chronic rhinosinusitis [21]

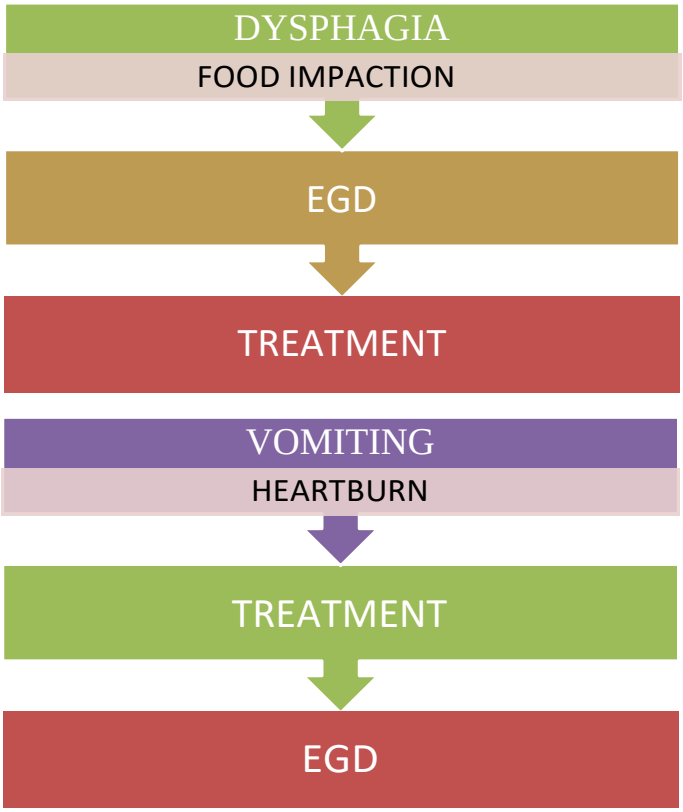

Figure 1: Confirmed Oesophageal Eosinophilia.

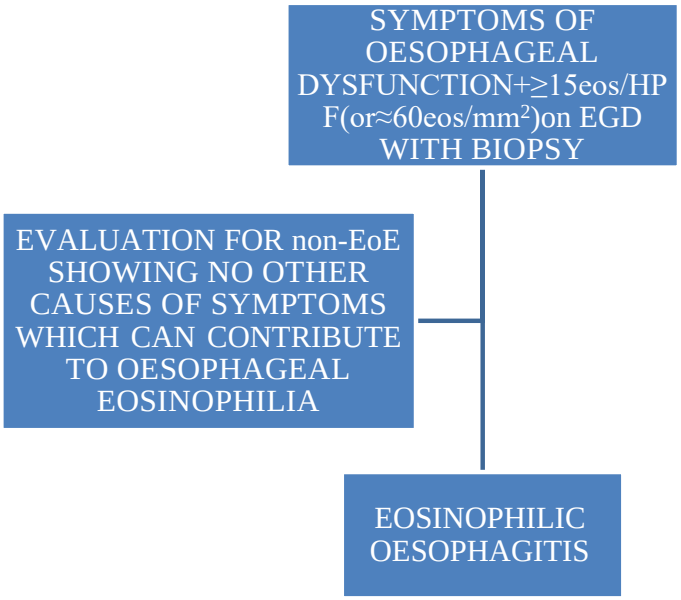

Figure 2: Diagnostic algorithm for patients with eosinophilic oesophagitis [55].

- Atopic dermatitis [22]
- Celiac disease [23,24]
- Inflammatory bowel disease [25]
- Exposure to caustic agents [26]
- The Schatzki ring has been described, but the association has not been sufficiently investigated [27]
- Allergic vasculitis
- Parasitic or fungal infections
- Neoplasms

The definite diagnosis of eosinophilic oesophagitis is based on the association of chronic symptoms of oesophageal dysfunction, personal history of allergic diseases, personal history of pathology (parents who have been suspected of eosinophilic oesophagitis), history of postoperative oesophageal perforation, confirmed by upper endoscopy with biopsies and laboratory tests.

The diagnostic criteria for eosinophilic esophagitis are as follows [28]. Symptoms associated with oesophageal dysfunction. Predominantly eosinophilic inflammation highlighted on biopsy (≥ 15 eosinophils per high power field (HPF) or 60 eosinophils per mm^2). Exclusion of other causes that may contribute to the onset of eosinophilic oesophagitis. The characteristics of upper endoscopy highlight the following [29]:

- Fixed (corrugated or trachealised) and transient oesophageal rings (feline folds or felination = stacked circular rings), strictly common in the proximal region
- Attenuation of the subepithelial vascular pattern
- Linear furrows
- Whitish papules (eosinophilic microabcesses)
- small-calibre oesophagus

Biopsies should be taken from both the proximal or middle level (2-4 biopsies) and the distal level (2-4 more biopsies) [30].

The histological aspects of eosinophilic oesophagitis include the following:

- sheets of eosinophils
- eosinophilic microabscesses
- superficial layering of eosinophils
- extracellular eosinophil granules [31]
- basal cell hyperplasia
- enlarged intercellular spaces
- epithelial exfoliation
- subepithelial and lamina propria fibrosis [32]
- large number of mast cells and B cells [33,34]
- papillary lengthening

Barium transit is not a gold standard for eosinophilic oesophagitis, but it can provide information on strictures [35]. Endoscopic ultrasound, oesophageal manometry and impedance planimetry to measure oesophageal pressure and distensibility are not routinely performed in cases of eosinophilic oesophagitis [36].

Paraclinically, patients have eosinophilia in the peripheral blood> 300-350/mmc associated with elevated Ig E levels (> 114000U/L). Allergic tests are used to identify comorbidities such as asthma, allergic rhinitis, etc., skin prick testing (SPT) and atopy patch testing (APT) are methods of testing food allergies [37].

From dietary point of view, the four-food (milk, egg, wheat and soy) empiric elimination diet followed for 8 weeks represents the best approach for most patients. After the avoidance period, an upper endoscopy with oesophageal biopsies is performed, and foods are reintroduced one at a time [53].

The long-term prognosis of eosinophilic oesophagitis is unclear, but some studies revealed that the disease may progress to a fibrostenotic form (no cases of malignancy were observed)in which intermittent dysphagia represents the most important symptom [54]. Patients underwent a follow-up examination consisting of laboratory testing and an upper endoscopy with biopsies.

The first diagnostic guidelines on eosinophilic oesophagitis were published in 2007 and updated in 2011 [55]. This condition was characterised as a distinct clinical entity by Atwood and Straumann in the early 1990s [56].

Many patients with clinical symptoms and oesophageal eosinophilia ≥15eos/HPF who responded to treatment with high-dose PPIs, but did not have manifestations of GERD, were defined as having PPI-responsive oesophageal eosinophilia (PPI-REE) according to guidelines published in 2011, 2013 and 2014 (55). Oesophageal eosinophilia and GERD are distinct conditions, but they can coexist: the first one can lead to reflux due to oesophageal dysmotility and the second can decrease epithelial barrier integrity, leading to eosinophilia [57,58].

Patients with symptoms of oesophageal dysfunction and ≥15 eos/HPF (or ≈60 eos/mm^2) on biopsy are defined as having suspected oesophageal eosinophilia (PPIs can be used when there is a histologic improvement), while those with symptoms of oesophageal dysfunction and ≥15 eos/HPF (or ≈60 eos/mm^2) on biopsy after evaluation for other causes of the condition are characterised as having confirmed oesophageal eosinophilia

AGA Institute and the Joint Task Force process for developing clinical practice guidelines recommend the following for patients with eosinophilic oesophagitis:

1. Topical glucocorticosteroids rather than oral glucocorticosteroids.
2. After short-term use of topical glucocorticosteroids, which leads to remission, the continuation of this treatment over discontinuation of therapeutic scheme
3. IPPs for symptomatic conditions
4. Elemental diet using an empiric six-food/four-food elimination diet
5. Allergy testing-based elimination diet
6. Endoscopic dilatation for all cases of dysphagia from a stricture
7. Using anti IL-5, anti-IL-13, anti – IL-4 receptor-α, anti –Ig E therapy, montelukast, cromolyn sodium, immunomodulators, and anti-TNF only in the context of clinical trials.

The recently published European and International consensus statements have removed the PPI trial from the diagnostic criteria for eosinophilic oesophagitis.

CONCLUSIONS

In the last 20 years, studies and clinical trials have provided an evidence base that highlights the progress which has been made in the understanding of eosinophilic oesophagitis from clinical, treatment and management strategy points of view. On the other hand, there are many unknowns and controversies regarding this condition. A deeper understanding is needed to inform clinical decisions regarding optimal disease follow-up and the use of long-term maintenance therapy.

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CONFLICT OF INTEREST

The Authors declare that they have no conflict of interest

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