

ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE)

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Abstract

Esophageal eosinophilia and eosinophilic esophagitis (EoE) are increasingly recognized and prevalent conditions, which now represent common clinical problems encountered by gastroenterologists, pathologists, and allergists. The study of EoE has become a dynamic field with an evolving understanding of the pathogenesis, diagnosis, and treatment. Although there are limited data supporting management decisions, clinical parameters are needed to guide the care of patients with eosinophilic–esophageal disorders. In this evidence-based review, recommendations developed by adult and pediatric gastroenterologists are provided for the evaluation and management of these patients. New terminology is emphasized, particularly the concepts of esophageal eosinophilia and proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE) as entities distinct from EoE.

Introduction

As expected with the discovery of a new disease entity, initial enthusiasm is followed by controversy and a plethora of fundamental questions. In no other recent gastrointestinal disease has this been truer than in eosinophilic esophagitis (EoE). Initial series described young, predominantly men with atopy, characteristic endoscopic features, and response to topical steroids or elimination diets (1,2,3,4). Definitions of EoE have been confounded by heterogeneity in symptom presentations and specificity concerns of eosinophil quantification. Nowhere has this controversy been more apparent than in the distinction of EoE from gastroesophageal reflux disease (GERD). Furthermore, both clinicians and investigators have struggled with agreement on the most pertinent clinical endpoints to define therapeutic response in EoE.

On the other hand, there has been remarkable progress in the understanding of EoE since the time of its recognition two decades ago. Genetic studies have identified specific profiles that support an allergic pathogenesis to the condition (5,6). Prospective and randomized trials have demonstrated the effectiveness and efficacy of topical steroids (7,8,9,10) and of withdrawal of food antigens that trigger the epithelial response (11,12). In addition, endoscopic dilation has provided a generally safe and durable means of ameliorating strictures that complicate the disease (13,14,15,16).

This guideline puts forth recommendations regarding fundamental clinical questions pertaining to the management of EoE. Esophageal eosinophilia is emphasized as a conceptual term describing the pathologic finding of increased esophageal epithelial infiltration by eosinophils (eos). This term is highlighted to avoid the etiologic and therefore treatment implications of EoE, and thus places the

emphasis on defining the cause of this pathologic finding in individual patients before implementing a specific therapy. This approach is consistent with that of other recent guidelines in the field (17).

DIAGNOSIS

Definition and Causes of Esophageal Eosinophilia

Recommendation

1. Esophageal eosinophilia, the finding of eosinophils in the squamous epithelium of the esophagus, is abnormal and the underlying cause should be identified. (Recommendation strong, evidence moderate)

Definition of EoE and Diagnostic Criteria

Recommendations

2. EoE is clinicopathologic disorder diagnosed by clinicians taking into consideration both clinical and pathologic information without either of these parameters interpreted in isolation, and defined by the following criteria:
 - Symptoms related to esophageal dysfunction
 - Eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of ≥ 15 eos per high-power field (eos/hpf)
 - Mucosal eosinophilia is isolated to the esophagus and persists after a PPI trial
 - Secondary causes of esophageal eosinophilia excluded (Table 2)
 - A response to treatment (dietary elimination; topical corticosteroids) supports, but is not required for diagnosis. (Strong recommendation, low evidence)

Table 2. Diseases associated with esophageal eosinophilia
Eosinophilic gastrointestinal diseases
PPI-responsive esophageal eosinophilia
Celiac disease
Crohn's disease
Infection
Hypereosinophilic syndrome
Achalasia
Drug hypersensitivity
Vasculitis
Pemphigus
Connective tissue diseases
Graft vs. host disease

3. Esophageal biopsies are required to diagnose EoE; 2–4 biopsies should be obtained from both the proximal and distal esophagus to maximize the likelihood of detecting esophageal eosinophilia in all patients in whom EoE is being considered. (Recommendation strong, evidence low)

4. At the time of initial diagnosis, biopsies should be obtained from the antrum and/or duodenum to rule out other causes of esophageal eosinophilia in all children and in adults with gastric or small intestinal symptoms or endoscopic abnormalities. (Recommendation strong, evidence low)

Utilization of a newly validated classification and grading system for endoscopic findings of EoE may improve diagnostic utility (44). This system allows for more uniform characterization of endoscopic findings, facilitates comparisons of severity among clinicians, and provides information regarding fibrostenotic complications of EoE (Table 3).

Table 3. Proposed classification and grading system for the endoscopic assessment of the esophageal features of eosinophilic esophagitis (44)
<i>Major features</i>
<i>Edema (also referred to as decreased vascular markings, mucosal pallor)</i>
Grade 0: Absent. Distinct vascularity present
Grade 1: Loss of clarity or absence of vascular markings
<i>Fixed rings (also referred to as concentric rings, corrugated esophagus, corrugated rings, ringed esophagus, trachealization)</i>
Grade 0: None
Grade 1: Mild-subtle circumferential ridges
Grade 2: Moderate-distinct rings that do not impair passage of a standard diagnostic adult endoscope (outer diameter 8–9.5 mm)
Grade 3: Severe-distinct rings that do not permit passage of a diagnostic endoscope
<i>Exudates (also referred to as white spots, plaques)</i>
Grade 0: None
Grade 1: Mild-lesions involving less than 10% of the esophageal surface area
Grade 2: Severe-lesions involving greater than 10% of the esophageal surface area
<i>Furrows (also referred to as vertical lines, longitudinal furrows)</i>
Grade 0: Absent
Grade 1: Vertical lines present
<i>Stricture</i>
Grade 0: Absent
Grade 1: Present (specify estimated luminal diameter)
<i>Minor features</i>
<i>Crepe paper esophagus (mucosal fragility or laceration upon passage of diagnostic endoscope but not after esophageal dilation)</i>
Grade 0: Absent
Grade 1: Present
<i>Narrow-caliber esophagus (reduced luminal diameter of the majority of the tubular esophagus)</i>
Grade 0: Absent
Grade 1: Present

Diagnostic Challenges: PPI-Responsive Esophageal Eosinophilia and GERD

Recommendations

5. Proton-pump inhibitor esophageal eosinophilia (PPI-REE) should be diagnosed when patients have esophageal symptoms and have histologic findings of esophageal eosinophilia, but demonstrate symptomatic and histologic response to proton-pump inhibition. At this time, the entity is considered distinct from EoE, but not necessarily a manifestation of GERD. (Recommendation conditional, evidence low)
6. To exclude PPI-REE, patients with suspected EoE should be given a two-month course of PPIs followed by endoscopy with biopsies. (Recommendation strong, evidence low)
7. A clinical, endoscopic, and/or histologic response to a PPI does not establish gastroesophageal reflux as the cause of esophageal eosinophilia. To determine whether reflux is contributing to esophageal eosinophilia, additional evaluation for GERD, as per standard clinical practice, is recommended. This may include ambulatory pH testing in selected cases. (Recommendation conditional, evidence low)

A proposed algorithm of initial treatment and evaluation of esophageal eosinophilia is given in Figure 1, and a PPI trial is central to this.

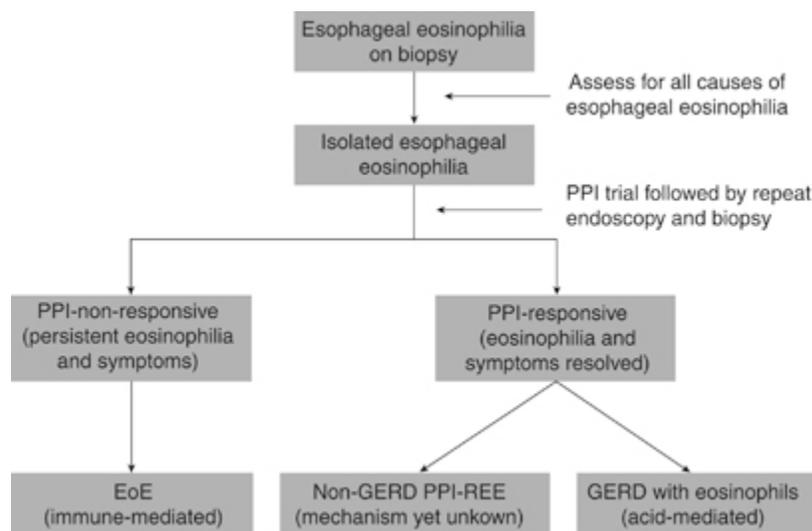


Figure 1. Algorithm for approach to esophageal eosinophilia (EoE) and diagnosis of EoE. After finding EoE on biopsy in a patient undergoing upper endoscopy for symptoms of EoE, the differential diagnosis for this histologic finding should be considered (Table 2). If eosinophilia is isolated to the esophagus, then EoE, gastroesophageal reflux disease (GERD), and proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE) are the most common clinical possibilities. At this point, an 8-week trial of 20–40 mg of any of the available PPIs used twice daily is prescribed. On repeat endoscopy and biopsy, if there is persistent eosinophilia and symptoms, then EoE can be formally diagnosed. However, if symptoms and eosinophilia resolve, then PPI-REE is diagnosed rather than EoE. Some patients with PPI-REE have GERD with an acid-mediated esophageal eosinophilia. Others likely have non-acid mediated PPI-REE, but the mechanism of eosinophilia in these patients is not yet known.

After a patient is found to have PPI-REE, a clinician may choose to continue the evaluation to determine whether GERD is the cause, given that a PPI response may not be specific for reflux (67). Recent guidelines on the evaluation of GERD have been published and can direct this evaluation, and ambulatory pH monitoring may be used in selected patients (68). It is important to note, however, that two studies have found that pH monitoring at baseline reliably whether a patient with esophageal eosinophil responds to a PPI trial (60,69).

TREATMENT

Endpoints of Treatment in EoE

Recommendations

8. The endpoints of therapy of EoE include improvements in clinical symptoms and esophageal eosinophilic inflammation. While complete resolution of symptoms and pathology is an ideal endpoint, acceptance of a range of reductions in symptoms and histology is a more realistic and practical goal in clinical practice. (Recommendation conditional, evidence low)
9. Symptoms are an important parameter of response in EoE, but cannot be used alone as a reliable determinant of disease activity and response to therapy, given that compensatory dietary and lifestyle factors can mask symptoms, and that esophageal strictures may not respond to medical therapy. (Recommendation conditional, evidence moderate)

Pharmacologic Treatments

Recommendations

10. Topical steroids (i.e., fluticasone or budesonide, swallowed rather than inhaled, for an initial duration of 8 weeks) are a first-line pharmacologic therapy for treatment of EoE. (Recommendation strong, evidence high)
11. Prednisone may be useful to treat EoE if topical steroids are not effective or in patients who require rapid improvement in symptoms. (Recommendation conditional, evidence low)
12. Patients without symptomatic and histologic improvement after topical steroids might benefit from a longer course of topical steroids, higher doses of topical steroids, systemic steroids, elimination diet, or esophageal dilation (Recommendation conditional, evidence low). There are few data to support the use of mast cell stabilizers or leukotriene inhibitors, and biologic therapies remain experimental at this time.

Topical corticosteroids have been proven to be an effective therapy for EoE, and are a first-line therapy. The medications, available as multi-dose inhalers or aqueous nebulizer solutions for use in asthma, are swallowed rather than inhaled to coat the esophagus and provide topical medication delivery. Dose ranges are presented in Table 4.

Table 4. Topical steroid initial dosing for treatment of EoE		
Medication	Age Group	Dosing
Fluticasone ^a	Children ^b	88–440 mcg/day in a divided dose
	Adults	880–1760 mcg/day in a divided dose
Budesonide ^c	Children ^b	1 mg/day
	Adults	2 mg day, typically in a divided dose

EoE, eosinophilic esophagitis.
^a Use a multi-dose inhaler preparation. The patient should be instructed to puff the medication into their mouth during a breath hold, and then swallow it, to minimize pulmonary deposition.
^b Specific doses in children will be determined by age, height, or weight.
^c Use the aqueous solution in a ratio of 1 mg/2 ml budesonide mixed with 5 gm of sucralose for the oral viscous budesonide preparation.

Dietary Treatments

Recommendations

13. Dietary elimination can be considered as an initial therapy in the treatment of pediatric and adult EoE. (Strong recommendation, evidence moderate)
14. The decision to use a specific dietary approach (elemental, empiric, or targeted elimination diet) should be tailored to individual patient needs and available resources. (Recommendation conditional, evidence moderate)
15. Clinical improvement and endoscopy with esophageal biopsy should be used to assess the response to dietary treatment when food antigens are either being withdrawn from or reintroduced to the patient. (Recommendation conditional, evidence low)
16. Gastroenterologists should consider consultation with an allergist to identify and treat extraesophageal atopic conditions, assist with treatment of EoE, and to help guide elemental and elimination diets. (Recommendation conditional, evidence low)

Endoscopic Treatment

Recommendations

17. Esophageal dilation, approached conservatively, may be used as an effective therapy in symptomatic patients with strictures that persist in spite of medical or dietary therapy and initially in patients with severely symptomatic esophageal stenosis. (Recommendation conditional, evidence moderate)
18. Patients should be well informed of the risks of esophageal dilation in EoE including post-dilation chest pain, which occurs in up to 75% of patients, bleeding, and esophageal perforation. (Recommendation conditional, evidence moderate)

OUTCOMES

Natural History of EoE

Recommendation

19. While knowledge of the natural history of EoE is limited, patients should be counseled about the high likelihood of symptom recurrence after discontinuing treatment due to the chronic nature of this disease. (Recommendation strong, moderate evidence)

Maintenance Therapy

Recommendations

20. The overall goal of maintenance therapy is to minimize symptoms and prevent complications of EoE, preserve quality of life, with minimal long term adverse effects of treatments. (Recommendation conditional, evidence low)
21. Maintenance therapy with swallowed, topical corticosteroids and/or dietary restriction should be considered for all patients, but particularly in those with severe dysphagia or food impaction, high-grade esophageal stricture, and rapid symptomatic/histologic relapse following initial therapy. (Recommendation conditional, evidence low)