

GI café

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Clinical features of Eosinophilic esophagitis in children and adults

Introduction

Eosinophilic esophagitis (EoE) is an increasingly recognized, chronic and anitgen/immune-driven inflammatory disease of the esophagus. EoE has now evolved to the second most common cause of chronic esophagitis after gastroesophageal reflux disease, and now represents the most frequent cause of dysphagia in young male patients. It is also recognized as the most common manifestation of all eosinophilic gastrointestinal disorders.

EoE is predominantly found in Westernized countries and geographical areas with a higher socioeconomic development and may affect individuals of every race, gender and age. Several epidemiological studies have reported an increasing incidence and prevalence of EoE, however it is still unclear whether this rise is a real phenomenon or caused by increased awareness.

The current knowledge of the etiology and the underlying mechanisms of eosinophilic esophagitis is rapidly evolving. Although there appear to be distinct differences between eosinophilic esophagitis in pediatric patients and adults, it becomes generally accepted as the same disease entity. By definition, the diagnosis of EoE mainly relies on clinical symptoms, endoscopic evaluation including histology, and the clinical exclusion of differential cause for esophageal eosinophilia.

Clinical symptoms in EoE

EoE can affect individuals of any age. It is predominantly a male disorder both in children and adults, being at least 3-times more prevalent in males than in females. The clinical presentation of EoE is strongly depending on the patient's age and ability to communicate symptoms. In fact, more than any other aspect of the disease, the symptoms leading to endoscopy and diagnosis vary considerably between children and adults (Table 1). In children suffering from EoE, the symptom pattern can be rather unspecific including dyspepsia, heartburn or abdominal pain as the most common symptoms. However, pediatric patients may also complain about nausea, regurgitation, chest pain or sialorrhea. Finally, decreased appetite, food avoidance, failure to thrive, sleep disturbances or respiratory complaints may be associated with pediatric EoE.

In contrast, adolescent and adult EoE patients are typically in a good general condition with normal body weight. They usually present with dysphagia for solid foods and/or bolus impaction. EoE was significantly associated with dysphagia, food impaction, male gender, age <50 years and asthma. Food impaction has been the symptom that most often led to the diagnosis. Food impaction is often associated with acute severe retrosternal or chest pain and potentially leads to immediate hospitalization and emergency endoscopy which is in turn associated with a higher risk of complications. With increasing

awareness for EoE in the future, it is likely that dysphagia itself will become the most prominent symptom leading to a rapid diagnosis of EoE in adults.

In clinical practice it is important to realize that EoE patients often adapt long-term coping strategies to guarantee feeding and to avoid bothering symptoms. Adult EoE patients usually do not show any clinical signs of malnutrition at diagnosis or during the evolution of the disease. In the evaluation of patients with suspected EoE, it is therefore recommended to use more sophisticated questions in tools to identify the presence and the burden of dysphagia. Questions such as "Do you wash food down with liquids?", "Do you chew your food for a long time?", "Do you avoid foods such as meat or breads?" or "Are you usually the last one to leave the table?" may be helpful in this matter.

Reflux symptoms are quite common in pediatric and adult EoE patients, however the prevalence rates differ among studies and range from 9% to 94%. Given the variability of the symptom patterns in EoE patients, the measurement of disease activity based on clinical symptoms remains a challenging task. Moreover, there has been discrepancies between histological and symptomatic responses in several clinical trials. Several symptom assessment scores are currently under evaluation to address these challenges.

Endoscopic features of EoE

Upper endoscopy is usually the first part in the diagnostic workup of patients with symptoms of esophageal dysfunction and therefore an important step in the diagnosis of EoE. However, endoscopic features in EoE are variable, unspecific, and may appear in random combinations. Most common endoscopic findings in EoE are white exudates, longitudinal furrow, rings or strictures and mucosal edema (Fig. 1). Overall, at least one endoscopic feature was found in 83% of cases, while the prevalence of endoscopically "normal" patients was significantly lower in prospective studies (7%) compared to retrospective studies (20%) indicating a learning effect of endoscopists. In order to further improve and standardize the endoscopic evaluation of EoE, a novel classification and grading system (EREFS) has been proposed by and validated international expert group. This system includes four major endoscopic findings which are graded semiquantitatively in a simple and practical fashion (Table 2).

Biopsy sampling and histology

The presence of at least 15 eosinophils per high-power field found in at least one esophageal mucosal biopsy (peak value) is required for the histological definition of the disease. Due to the patchy distribution of esophageal eosinophilia, multiple biopsies should be obtained from different parts of esophagus to achieve a high diagnostic yield. Studies have shown that at least three esophageal biopsies appear necessary to confirm the EoE diagnosis in 97% of patients. In general, several potential pitfalls in the histological EoE diagnosis should be considered. First, eosinophils are recruited from the deeper layers of the esophageal wall and areas with lower eosinophil density may exist in the upper layers which may be missed by superficial mucosal biopsies. Second, esophageal eosinophilia is not an exclusive feature of EoE. Other diseases such as GERD, Crohn's disease, connective tissue disease, infectious esophagitis, celiac disease, graft-versus-host disease, eosinophilic gastroenteritis, and hypereosinophilic syndrome may also be associated with esophageal eosinophilia. Finally, not all high power fields (hpf) are equal, because different microscopes may have different high power fields which could result in significantly different eosinophil counts per hpf. This factor should be taken into consideration when comparisons are made between different histological studies within an individual patient over time or between different clinical trials. In the future, other standardized measurements should be preferred, such as mm²hpf, in order to eliminate this technical factor and to facilitate histological comparisons.

Table 1: Clinical symptoms of EoE in children and adults.

Children

Abdominal pain
Chest pain
Heartburn
Coughing
Decreased appetite
Dysphagia
Food refusal
Failure to thrive
Choking
Nausea
Regurgitation
Sleep disturbance
Throat pain

Adults

Dysphagia
Bolus obstruction
Retrosternal pain
Chest pain
Heartburn
Regurgitation

Natural course of disease

Only little is known about the natural course and the long-term outcome of EoE. In analogy to other inflammatory bowel diseases it can be assumed that EoE may be a progressive disease which, if untreated, may lead to irreversible long-term structural damage of the esophagus. Diagnostic delay turned out to be the only risk factor for strictures at the time of EoE diagnosis. These data clearly indicate that it is very important to minimize the diagnostic delay in EoE in order to avoid potentially irreversible structural damage of the esophagus. So far, it seems that EoE itself is not associated with a decreased life expectancy nor with an increased risk of developing malignant or premalignant lesions.

Differential diagnoses

Due to a potential symptom overlap, gastroesophageal reflux disease (GERD) represents the clinical most common and most relevant differential diagnosis to EoE. Gastroesophageal reflux may by itself cause esophageal eosinophilia, and patients with GERD may also suffer from dysphagia in addition to their reflux symptoms. On the other hand, EoE may lead to an impaired function of the lower esophageal sphincter which in turn may promote increased gastroesophageal reflux.

Finally, a subgroup of EoE patients does substantially respond to proton pump inhibitor (PPI) therapy, both clinically and histologically. This observation had led to the term "PPI-responsive esophageal eosinophilia" (PPI-REE) and to an ongoing discussion whether PPI-REE might be a subtype of GERD.

Allergy testing in EoE

EoE is associated with allergies. Allergic comorbidities including allergic rhinitis, conjunctivitis, asthma or atopic eczema were found in 65% of adult patients. Peripheral eosinophilia and elevated serum IgE levels are usually found in 50% and 75% of patients, respectively. Food-specific IgE or skin prick test (SPT) results may be positive in over 80% of adult EoE patients, however elimination of foods that gave positive results failed to achieve disease remission, and response to food elimination diet has been observed in patients who had exhibited negative allergy test results. Furthermore, in adult EoE patients who responded to 6-food-elimination diet and relapsed after step-wise food reintroduction, prick test was predictive for the responsible food allergen in only a minority of cases. These findings suggest a dissociation between IgE based food allergy test results and true EoE trigger foods. Therefore, allergy testing can be used to help identify food sensitizations associated with EoE, however none of the currently available techniques has been proven useful and reliable for the management of EoE in clinical practice.

Table 2: Endoscopic classification and grading system

Major features	Grading		
	Mild	Moderate	Severe
Fixed rings	Subtle circumferential ridges	Distinct rings, no occlusion	Distinct rings, endoscopic passage impossible
Exudate	Mild Covering <10% of surface area	Severe Covering <10% of surface area	
Furrows	Mild Vertical lines without visible depth	Severe Vertical lines with clear depth (indentation)	
Edema	Mild Decreased clarity of mucosal vessels	Severe Mucosal vessels completely invisible	

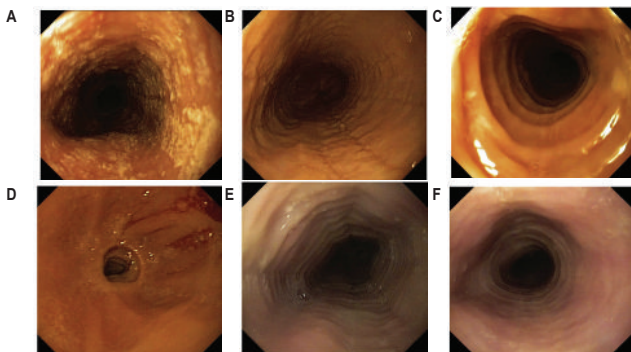


Fig. 2. Endoscopic features in EoE: a) white exudates; b) longitudinal furrows and edema; c) fixed rings; d) stricture e) fixed rings and edema; f) edema.

Reference: Clinical features of Eosinophilic esophagitis in children and adults. Stephan Mielke. Best Practice & Research Clinical Gastroenterology 29 (2015) 739-748



Medical therapy in eosinophilic oesophagitis

Indications for treatment of eosinophilic oesophagitis

When scientific community is confronted with a new disease, the understanding of its natural course is crucial before any treatment modality can be considered. The first natural history study has demonstrated that EoE is a chronic disease, and that symptoms as well as inflammation persist over the years. As such, the quality of life of EoE patients is substantially impaired as long as EoE is not properly treated. Improvement of quality of life is therefore a first indication for treatment.

In addition, basic science research and clinical studies have accordingly confirmed that an ongoing active eosinophilic oesophageal inflammation leads to deposition of subepithelial fibrous tissue in the oesophageal wall. This so-called "remodelling" induces alterations that finally result in a rigid and fragile oesophagus with impaired function. It is well documented, that this process can be prevented or even reversed by an efficient anti-eosinophil treatment. Organ preservation can therefore be regarded as a second, important indication for treatment.

Finally, EoE patients frequently experience long-lasting food-impactions requiring endoscopic interventions. This complication harbours a risk for oesophageal injury, either caused by retching or by improperly performed endoscopic intervention. Food impactions are mostly observed in nonadequately treated patients. Prevention of this unforeseeable EoE complication is therefore a further indication for treatment.

In summary, clinically and histologically active EoE should be treated with anti-eosinophil medication because this measure has potential: first, to diminish symptoms and to improve therefore the quality of life of EoE patients; second, to prevent oesophageal damage caused by tissue remodelling due to unbridled eosinophilic inflammation; and third, to reduce the risk of severe oesophageal injury by preventing long-lasting food impactions.

Treatment goals in eosinophilic oesophagitis

At present, the target of EoE treatment is still a subject of intensive debate. Should the treatment result in the improvement of symptoms or in the normalisation of altered biologic measures or even in both? In the absence of agreement on meaningful therapeutic endpoints, a uniform treatment algorithm for EoE patients is still lacking. The ideal therapeutic intervention in EoE has to improve symptoms and to reduce inflammation.

General principles of pharmacological EoE-treatment

Eosinophilic oesophagitis is a new disease. However, it shares many similarities with gastroesophageal reflux disease, atopic diseases, such as asthma and atopic dermatitis, and even inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis. Therefore, evaluation of drugs with proven efficacy in these disorders merits careful consideration. Those pharmacologic therapies that have already been evaluated for the purposes of EoE management will now be discussed.

Proton-pump inhibitors

Currently, PPI are used in EoE patients with co-existing gastro-oesophageal reflux disease (GORD). Given the high prevalence of GORD in a general population, it is likely that both diseases can cooccur. However, it is also possible that impairment of the lower oesophageal sphincter may lead to gastro-oesophageal reflux as sequela of EoE. Moreover, it is also known that acid exposure in EoE subjects is more painful than in control patients. As such, use of PPI may improve symptoms, such as pain, but may in general not have an effect on the underlying inflammatory process.

Based on the initial assumption that EoE does not respond to treatment with proton-pump inhibitors (PPI), in contrast to reflux oesophagitis, a 2-month trial with double dose PPI was recommended to distinguish patients with EoE from those with GORD. Unexpectedly, the use of this so-called diagnostic PPI-trial has shown that a subset of patients with EoE responds to treatment with PPI. This so called "PPI-responsive oesophageal eosinophilia" is observed in both adult and paediatric EoE and is characterised by symptoms, endoscopic, histologic and even transcriptional abnormalities comparable with "classic" EoE, but responding to monotherapy with PPI.

Corticosteroids

A number of controlled clinical trials performed in adult and paediatric EoE patients has demonstrated that swallowed corticosteroids (budesonide, fluticasone and ciclesonide) deposited on the oesophageal surface are highly effective in resolving symptoms, endoscopic and histologic alteration of EoE. The results of these studies are difficult to compare, because different

compounds, different formulations, different dosages and different treatment periods were used. Overall, the response rates to treatment with swallowed topical corticosteroids were between 50% and 87%. The main drawback of systemic and topical corticosteroid treatment is that almost all patients relapse rapidly after cessation of therapy. Therefore, corticosteroids are able to control, but not to cure EoE. The main side effect of swallowed topical corticosteroids is infection of the oro-pharyngeal cavity or the oesophagus with *Candida albicans*. This occurs in 10-15% of the patients. This infection is often asymptomatic and can be treated with topically administered anti-fungal drugs in the majority of patients.

Since EoE is a chronic disease, a long-term therapeutic management strategy is required. However, the optimal maintenance regimen has not yet been determined, and further studies are necessary to evaluate the optimal dose of swallowed topical corticosteroids for maintenance therapy in adult and paediatric EoE patients.

Immunosuppressants

As mentioned above, in up to 70% of patients symptom resolution can be achieved with properly performed treatment with swallowed topical corticosteroids. However, approximately 30% of patients remain symptomatic and suffer therefore from steroid-refractory EoE. In analogy to steroid-refractory inflammatory bowel disease, immunosuppressants have been evaluated in these patients. Indeed, purin-analogues have shown to be effective in a small series of adult patients with refractory EoE. Surprisingly, this promising treatment modality has not been further evaluated and is currently almost neglected.

Prostaglandin D2 receptor antagonists

OC000459 is a first generation selective prostaglandin D2 receptor 2 antagonist that blocks the ability of prostaglandin D2 to recruit and activate eosinophils and TH2 cells. Patients with EoE respond to treatment with OC000459. The drug had an excellent safety profile. However, the overall effect was only moderate.

Biologic agents

Among the already evaluated biologic agents, anti-IL-13 monoclonal antibody holds most promise as a novel therapeutic approach for management of EoE.

Pharmacological EoE treatment in clinical practice

Following a discussion of currently available options for the pharmacological treatment of EoE, we would like to discuss the way these therapies can be used in a routine clinical practice.

Once clinician is confronted with a patient with clinically and histologically active EoE, it is prudent to evaluate whether this patient should be treated with an anti-eosinophil drug or with food elimination diet. Since no studies directly comparing the efficacy of these two completely different modalities have been carried out to date, the treatment decision taken is not an evidence-based one and should be based on the individual preference of the patient. Physicians in EoE centers should therefore be adept in treating patients choosing either pharmacological or dietary therapy. Given the fact that not a single pharmacological therapy for management of EoE has been approved by regulatory authorities in USA and Europe, patients should be carefully instructed on how to administer these drugs, originally designed for the delivery into the airway and not into the oesophagus. Indeed, the improper administration of these drugs is believed to be one of the main causes of refractory EoE. The dietary treatment has the drawback that more than one staple food is removed from the diet. As such, the patients should be encouraged to seek the professional advice of both allergists and dieticians familiar with the particularities of EoE. Lastly, the recommendations that follow pertain to management of adult EoE, and pediatricians may have to adapt some of these recommendations.

Given the data on efficacy of swallowed topical corticosteroids in bringing active EoE into remission, we recommend that EoE patients should be put on

an induction treatment with 1 mg bid fluticasone or budesonide for a period of two-four weeks. Of note, it has been demonstrated by Dellon and co-workers that the effect of the compound strongly depends on contact time of the compound with the oesophageal surface. Therefore, viscous syrup, melting tablet or powder are preferable formulations for swallowed topical corticosteroids. Patients should be instructed to avoid eating and drinking for at least half an hour after administration of the drug. The best time for application of the drug is at bedtime and after breakfast. A 2-week induction treatment is able to bring approximately 70% of EoE patients into clinical and histological remission.

After achieving a remission, a patient should be put on a maintenance treatment, because if EoE is left untreated, the flare-up episodes occur after approximately three months on average. The long-term regimens are still not well defined. A daily 0.5 mg dose of budesonide might be likely too low for some patients, as approximately one third of the patients had experienced a flare-up episode when being treated with this dose in a one-year trial. Using doses higher than 2 mg daily has the drawback of lacking safety data regarding systemic side effects. Therefore, the optimal dose might lay somewhere in-between 0.5 and 2.0 mg. So long that many uncertainties regarding the evolution of the disease and the long-term side effects of pharmacologic treatment still exist, we strongly recommend that EoE patients are seen by gastroenterologist on an annual basis for clinical, endoscopic and histologic work-up.

Patients that do not achieving a remission after an induction-treatment with swallowed topical corticosteroids need to be re-evaluated in order to distinguish between those patients, in whom both symptoms and inflammation persist and those, in whom only symptoms remain. If inflammation is under control, symptoms might be caused by fibro-stenosis and a gently performed dilation might be appropriate. In contrast, if inflammation is not under control, either a repeated induction treatment with swallowed topical corticosteroids, a combination of swallowed topical corticosteroids with a single-food elimination diet or a treatment with immunosuppressants should be considered. However, it is generally recommended to refer patients with refractory EoE to specialized centers. The proposed treatment algorithm is shown in Fig. 1.

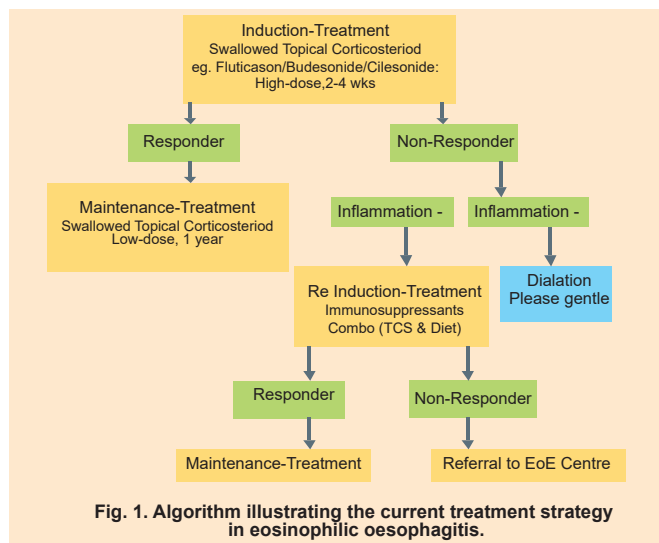


Fig. 1. Algorithm illustrating the current treatment strategy in eosinophilic oesophagitis.

Reference: Medical therapy in eosinophilic oesophagitis. Alex Straumann. Best Practice & Research Clinical Gastroenterology 29 (2015) 805e814

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Editorial Note:

Dear Doctor, It's our immense pleasure to inform you that we have published the second issue, Vol: 8, of GI Café. In this newsletter, we have highlighted the "Eosinophilic Oesophagitis"- a new disease unknown to the medical community. The articles help you to manage some of your difficult patients.

Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.

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