

**Texas BBQ with a side of glucagon:
The Ins and Outs of
Eosinophilic Esophagitis**

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Sravanya Gavini, MD, MPH

Division of Digestive and Liver Diseases University of
Texas Southwestern Medical Center

This is to acknowledge that Dr. Sravanya Gavini has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Gavini will be discussing off-label uses in her presentation and will specify them when doing so.

Dr. Sravanya Gavini is an Assistant Professor of Medicine in the Division of Digestive and Liver Diseases at UTSW. She received her medical degree from the Johns Hopkins University School of Medicine and completed her Internal Medicine Residency at Johns Hopkins Hospital. She trained in Gastroenterology at The Brigham and Women's Hospital and also received a Masters in Public Health from Harvard T.H Chan School of Public Health. Upon completion of her training, Dr. Gavini moved to Dallas in 2015 to join the faculty at UT Southwestern. Her research and clinical interests include esophageal disorders such as GERD with extraintestinal manifestations of GERD particularly in patients undergoing lung transplant, Eosinophilic esophagitis, and esophageal motility disorders.

Purpose & Overview:

Eosinophilic esophagitis (EoE) is a chronic condition with increasing prevalence worldwide that requires timely detection and treatment to avoid stenosis in the esophagus. Appropriate management of this disease requires awareness and coordination among primary care providers, gastroenterologists, allergists, pathologists and nutritionists. This presentation reviews the pathophysiology, clinical presentation, diagnostic criteria, and management of eosinophilic esophagitis.

Educational Objectives:

1. To understand the definition, and epidemiology of EoE
2. To recognize pathophysiology, clinical presentation, endoscopic and histologic features of EoE
3. To outline treatment options in adult patients with EoE including medications, dietary therapy and endoscopic

Introduction

Eosinophilic esophagitis is a chronic disorder which occurs in children and adults, and is characterized by infiltration of the esophageal epithelium by eosinophils. EoE causes swallowing dysfunction¹ and is the most common cause of food impaction². Eosinophilic esophagitis was described as a distinct entity in the 1990s before which it was thought to be related to reflux esophagitis.

Epidemiology

The incidence of EoE is about 1/10000 cases per year². The overall prevalence is around 0.5 to 1 in 1000 cases³. EoE is more prevalent in males (OR 2, 1.92-2.10) and in Caucasians compared to African Americans and Asians. It most frequently affects patients younger than age 50. An increasingly prevalent condition, EoE poses a heavy disease burden estimated around \$1 billion per year in the US.

An increase in prevalence and incidence has been reported even after accounting for improved recognition of the disease and earlier diagnosis^{1, 4}. While the reasons for this is not known, it is hypothesized that early environmental risk factors such as antibiotic use in infancy, cesarean delivery, preterm birth, and lack of breast feeding might predispose to development of EoE^{5, 6}. Other environmental factors such as *Helicobacter pylori* infection is inversely related to presence of esophageal eosinophilia².

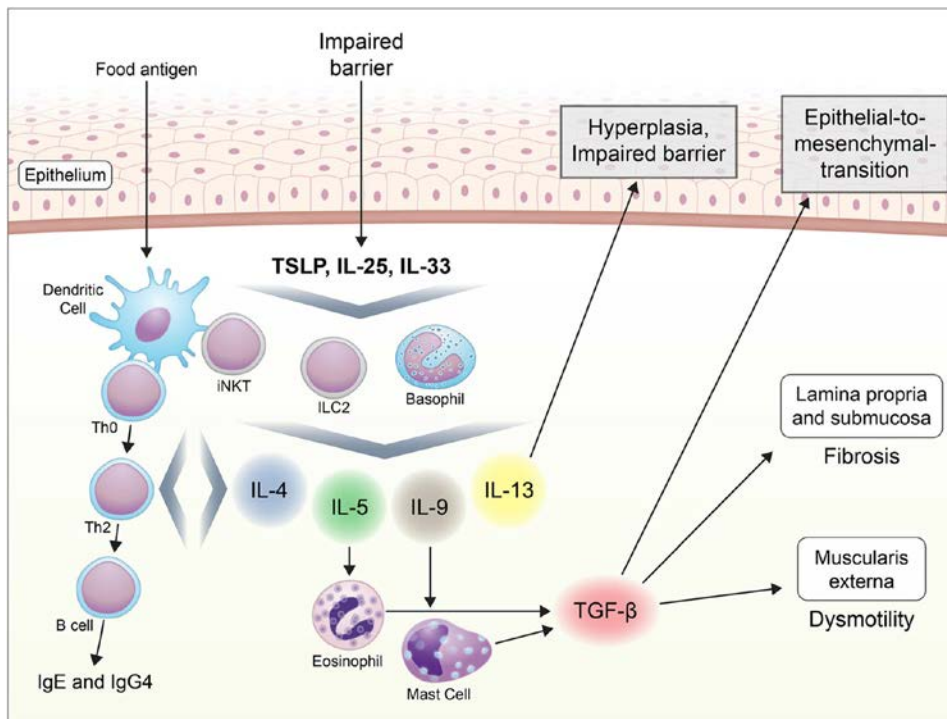
EoE has a strong association with atopic diseases such as asthma, allergic rhinitis, and eczema. EoE has been linked to geographic risks and aeroallergen exposures have been implicated as EoE is more prevalent in arid, cold weather climates and rural areas³. It is also diagnosed more frequently in the summer and spring compared to fall and winter. As with atopic disorders, there is a genetic predisposition in EoE. Monozygotic twins have 58% concordance and 40% of 1st generation offspring of patients with EoE will develop the disease³. Genome-wide association studies have identified defects in EoE susceptibility loci that contribute to pathogenesis of EoE⁷ by affecting eosinophil chemotaxis, regulation of the cytokine response, preferential stimulation of the Th2 pathway, epithelial cell repair, barrier function etc.

Pathophysiology of EoE

Food antigen sensitization and impaired mucosal barrier play important roles in pathogenesis of EoE. Food antigen processed through the antigen presenting cells is thought to trigger an activation of the Th2 pathway and iNKT cells which produce inflammatory cytokines such as IL-4, IL-5, IL-9, and IL-13. Impaired mucosal barrier can also initiate production of an inflammatory response via release of cytokines such as TSLP, IL-15, IL-33. The downstream effect of this inflammatory milieu includes production of eotaxin-3 which attracts eosinophils to the esophagus, stimulates mast cells and eosinophils to produce TGF- β which

promotes remodeling and fibrosis (Fig 1)⁷.

Figure 1: Mechanistic model of EoE ⁷



Clinical presentation

Symptomatology

The most common presenting symptom of EoE in adults is esophageal dysphagia. It is important to elicit altered food behaviors related to difficulty with swallowing such as avoiding “difficult” foods like meat/bread, drinking water with every bite (“fluid chaser”), compensating by eating high calorie foods in small amounts. Food impaction can also be seen in patients up to 25% of the time which is treated with urgent upper endoscopy to remove impacted food. Heartburn and non-cardiac chest pain can also be reported in patients. About 1-8% of patients with reflux type symptoms refractory to PPIs have EoE. Children present differently than adults with symptoms of nausea, vomiting, feeding intolerance, or refusal to eat¹. Patients with EoE frequently have other atopic conditions such as asthma, eczema, allergic rhinitis⁸ and a family history of atopy.

Endoscopic findings

Upper endoscopy with esophageal biopsies is the appropriate diagnostic step in evaluating for EoE as the diagnosis is made by histology. The endoscopic appearance (Figure 1) can be varied and can range from appearing normal, to having inflammatory findings or fibrostenotic findings. Inflammatory findings include white plaques/exudates, longitudinal furrows, edema, decreased vascularity. Fibrostenotic features include rings, strictures, and a diffusely narrow caliber

esophagus. It is important to note that endoscopic features described above are not specific for eosinophilic esophagitis and can be present in other conditions¹.

An endoscopic reference score has been developed to uniformly report and describe these findings and is helpful in tracking treatment response⁹.

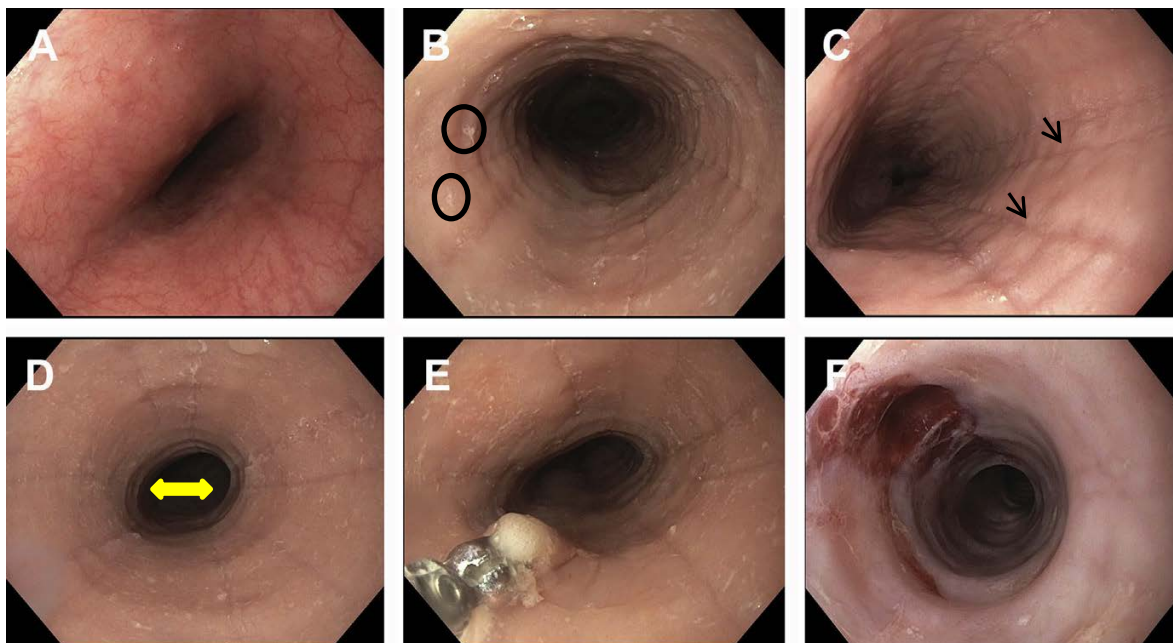


Fig. 2. Endoscopic features of EoE.

(A) The endoscopic appearance of the normal esophagus. Note the uniform and smooth appearance of the esophageal mucosa, with the fine vascular pattern clearly visible.

(B) A patient with EoE with evidence of esophageal rings, furrows, edema, and exudates (circles).

(C) A patient with EoE with esophageal edema, deep furrows (black arrows), and mild exudates.

(D) A patient with EoE with a focal stricture, in addition to mild rings, furrows, edema, and exudates.

(E) Esophageal biopsy under way.

(F) A patient with EoE with a very narrow caliber esophagus and tight rings, as well as edema, after esophageal dilation. Good dilation effect (mucosal rent) is seen in the 11 o'clock position¹

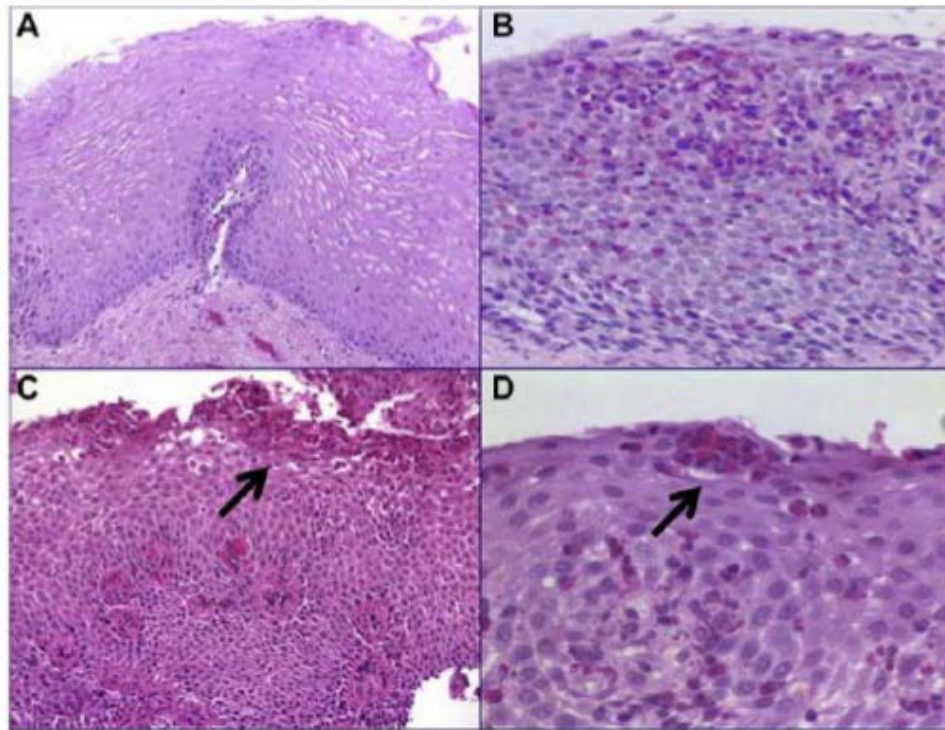
Histologic features

While the prominent histologic features of EoE are as follows, these findings are not specific to EoE:

- Increased eosinophils in the esophagus (>15 per high power field) which are frequently found in the superficial layers
- Eosinophilic microabscesses
- Basal layer hyperplasia
- Dilated intracellular spaces

- Lamina propria fibrosis (Fig 3,4)¹.

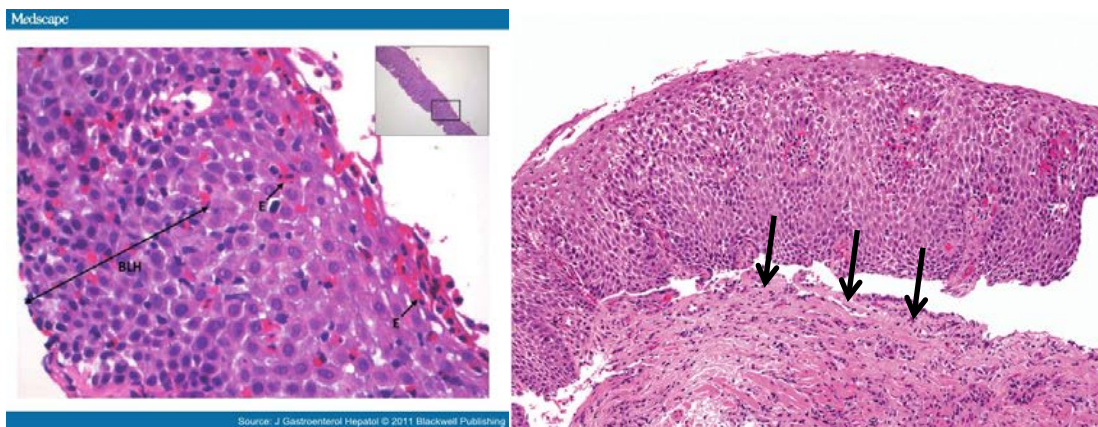
Figure 3: Histologic features of EoE



A : normal, B&C : superficial layering of surface eosinophils, D : Eosinophilic microabscess

Eosinophilic esophagitis: Updated consensus recommendations for children and adults, J Allergy Clin Immunol 2011;128:3-20

Figure 4: Histologic features of basal layer hyperplasia(BLH), spongiosis (dilated intracellular spaces) and lamina propria fibrosis (black arrows)



Diagnostic Criteria

Clinical criteria and histologic features required to make the diagnosis of EoE are

as follows:

- a) Clinical symptoms of esophageal dysfunction which include dysphagia, food impaction, heartburn, chest discomfort. It's important to note children present differently
- b) Presence of eosinophilic infiltration of esophageal mucosa with at least 15 eosinophils per high power field. This threshold has 100% sensitivity and 96% specificity for establishing the diagnosis of EoE¹⁰.
- c) Exclusion of alternate explanations for esophageal eosinophilia¹¹

The differential diagnosis for esophageal eosinophilia includes Achalasia, infections, connective tissue diseases, Crohn's disease, pill esophagitis, drug hypersensitivity, hypereosinophilic syndrome. The contribution of Gastroesophageal reflux disease (GERD) to esophageal eosinophilia remains controversial and GERD can overlap with EoE. Prior guidelines required a nonresponse to proton pump inhibitors (PPIs) to differentiate EoE from GERD and to establish diagnosis of EoE¹¹. However, PPIs are no longer part of the diagnostic algorithm and are instead considered part of the management according to the most current guidelines^{11, 12}.

Treatment

The goals of treatment of Eosinophilic esophagitis are to

- 1) Halt esophageal inflammation to avoid remodeling and fibrosis in the esophagus
- 2) Treat the fibrostenotic pathology to alleviate dysphagia.

A combination of medications or diet and endoscopic therapy might be necessary in achieving these goals (Figure 5).

Medications

There are no Food and Drug Administration approved medications currently available for treatment of EoE. However proton pump inhibitors (PPI) and topical steroids are used widely as they have been shown to target and stop active inflammation.

While the acid reduction by PPIs is widely known fact and this can heal mucosal barrier breakdown, some anti-inflammatory effects of PPIs have been proposed¹³. While the exact mechanism is unknown, some in-vitro studies have shown that expression of Eotaxin-3 (potent chemoattractant of eosinophils to esophagus) is decreased in epithelial cells of EoE patients when treated with omeprazole in the absence of gastric acid¹⁴. One meta-analysis noted histologic remission in 50.5% although long term data for over 1 year of follow-up is not available^{15, 16}.

Glucocorticoids cause an anti-inflammatory effect by targeting epithelial cells as well as innate and adaptive immune response pathways that drive eosinophilic esophagitis¹⁷. Topical steroids with poor intestinal absorption such as fluticasone propionate and budesonide have been shown to induce remission and reduce esophageal remodeling. Fluticasone inhaler (2-4 puffs of 220mcg inhaler twice

daily) is administered into the mouth during a breath hold after which patient is instructed to fast for 30-60 minutes¹⁸. Oral viscous budesonide (1-2mg daily), which is prepared by mixing budesonide respules with 5mg of sucralose or thickener, has been shown to achieve high remission rate compared to the nebulized formulation¹⁹. Topical therapy is equally efficacious compared to systemic steroids in achieving histologic and clinical improvement. Therefore, systemic steroids are not commonly used to treat EoE due to side effects such as Cushing's syndrome, weight gain etc. except in cases where urgent symptom relief is necessary. Side effects of topical therapy include esophageal candidiasis, and rarely herpes esophagitis. Tapering off steroid therapy is associated with recurrent eosinophilic inflammation²⁰

Diet

Dietary therapy has been studied for treatment of EoE owing to the food antigen sensitization that is a part of the pathogenesis of EoE. Exclusive elemental diet which is amino-acid based is the most effective although is not a very practical long term treatment given high cost, poor tolerability due to taste, significant effect on quality of life for patients. Targeted elimination diets have also been studied although low predictive value of skin prick and Atopy patch tests limit their efficacy and use especially in adult patients. Empiric elimination diets are the most popular due to higher efficacy in inducing remission (up to 72%)²¹ although they require multiple upper endoscopies to assess response to elimination of food groups. In six food elimination diet, patients are instructed to eliminate milk products, wheat, peanuts and tree nuts, eggs, soy, fish and shellfish. Due to significant food restriction and need for multiple endoscopies, less restrictive regimens such as the four food (milk, wheat, egg, legumes restricted) and two food (milk, wheat) elimination diets are gaining popularity^{22, 23}. Milk and wheat are the most common food triggers in most studies.

Endoscopic therapy

If patient has developed fibrostenotic disease, medication and diet therapy is not sufficient, then esophageal dilation of esophageal stricture either by wire guided bougie (Savary) or through-the-scope balloon dilation is undertaken to alleviate dysphagia. Typically longer duration of symptoms prior to diagnosis of EoE is associated with presence of esophageal stricture requiring dilation. Dilation is performed to reach a goal diameter of 16-18 mm and is tolerated well safe with no major bleeding, perforation or deaths²⁴. The procedure is >85% effective and most common complication is post procedure pain (~5%).

Future directions for therapy

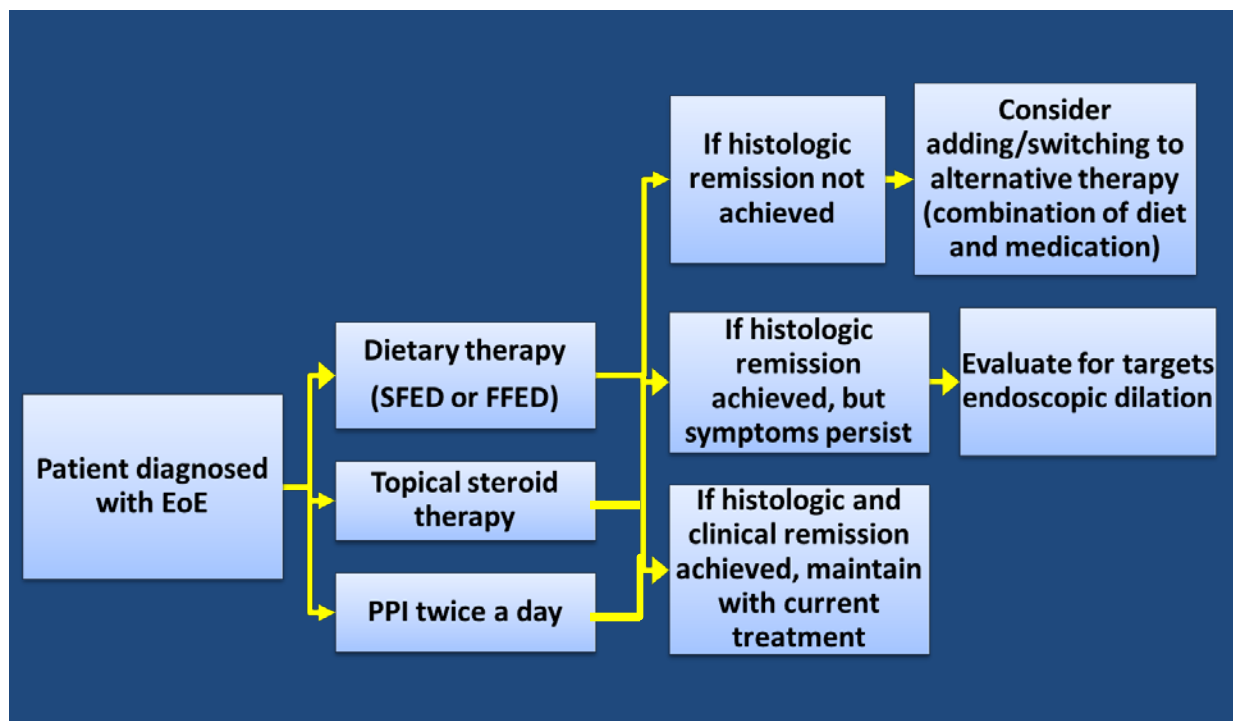
Investigational therapies include monoclonal antibodies against IL-5, IL-4R and IL-13 all of which have pathways to recruit eosinophils to the esophagus²⁵:

- Reslizumab (already approved for severe asthma with eosinophilic phenotype) targets IL-5 which plays an important role in recruitment of eosinophils.
- Dupilumab (currently approved for atopic dermatitis and asthma) IL-4R

alpha monoclonal antibody that blocks both IL-4 and IL-13 which are also instrumental in eosinophilic inflammation.

- Recombinant humanized monoclonal antibody against IL-13 called RPC4046

Figure 5: Treatment approach to EoE



Conclusion

Eosinophilic esophagitis is a chronic immune mediated esophageal disorder that has significant health care costs and imposes significant morbidity in children and adults. The pathophysiology involves the food antigen sensitization that preferentially promotes the Th2 inflammatory pathway and release of cytokines that cause recruitment of eosinophils and mast cells which release inflammatory mediators that cause tissue damage. Timely diagnosis with careful attention to history, referral for endoscopy and histology is paramount to avoid untreated inflammation and fibrostenotic disease.

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