Examining Unmet Needs in the Management of Eosinophilic Esophagitis

HIGHLIGHTS

- Epidemiology, Pathophysiology, and Diagnosis of Eosinophilic Esophagitis
- Currently Available Treatments and Treatment Considerations
- Clinical, Economic, and Humanistic Burden of Disease
Examining Unmet Needs in the Management of Eosinophilic Esophagitis

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OVERVIEW

This supplement to The American Journal of Managed Care® describes the epidemiology and pathophysiology of eosinophilic esophagitis (EoE), currently available treatments and treatment considerations, and the clinical, economic, and humanistic impact of the disease.

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Examining Unmet Needs in the Management of Eosinophilic Esophagitis

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Introduction

Eosinophilic esophagitis (EoE) is a progressive, chronic inflammatory disease that is associated with a substantial disease burden and long-term complications. Early and accurate diagnosis of EoE is critical for preventing worsening, potentially irreversible damage to the esophagus. Esophageal remodeling, narrowing, and fibrosis can occur when EoE is inadequately controlled; the duration of untreated disease is the strongest predictor of esophageal stricture. Despite the availability of treatment options, the clinical needs of patients with EoE remain largely unmet.

Symptoms of undiagnosed and untreated EoE differ by age and include difficulty swallowing (dysphagia), food getting stuck in the esophagus (impaction), regurgitation, chest and/or abdominal pain, and vomiting. Additionally, most patients with EoE have comorbid allergic conditions, such as allergic rhinitis, asthma, atopic dermatitis, or food allergies, suggesting a related pathophysiology among these conditions. Infiltration of the esophagus by eosinophils represents a defining characteristic of EoE, and this persistent inflammation is associated with the formation of esophageal abnormalities such as rings, furrows, strictures, edema, and exudates. The chronic, progressive nature of EoE contributes to significant patient burden.

Epidemiology

EoE can develop at any age, and is more common in males and in Whites, and is strongly associated with atopic diseases. A 2019 systematic review of 24 studies conducted in various locations (United States, Canada, Europe, Australia, South America) found that the overall prevalence of EoE was 34.2 cases per 100,000 inhabitants (95% CI, 23.1-47.5; \( P = 99.9\% \)), and that disease prevalence has been increasing over time. In the United States and Canada, EoE was estimated to occur in 41 (95% CI, 25.7-59.9; \( P = 99.7\% \)) per 100,000 individuals. Although the overall prevalence was found to be higher in adults than children (42.2 [95% CI, 31.1-55; \( P = 99.9\% \)] vs 34.4 [95% CI, 22.3-49.2; \( P = 99.8\% \)], in the United States and Canada, specifically, the disease was found to impact both groups similarly (31.9 [95% CI, 21.5-44.3; \( P = 100\% \)] vs 38.3 [95% CI, 23.7-56.4; \( P = 99.9\% \)].
Pathophysiology

First classified as a unique clinicopathologic syndrome in 1993, much has been learned about EoE over the last approximately 30 years.12 Evidence suggests that EoE is largely driven by a type 2 immune response, characterized by immune dysregulation (elevation of cytokines IL-4, IL-13, and IL-5; eosinophils, basophils, and mast cells; immunoglobulin G4; and epithelial barrier dysfunction).7,13,14 Pathologic processes primarily arise from chronic, uncontrolled type 2 inflammation. In EoE, the Th2-derived cytokines IL-4, IL-13, and IL-5 are responsible for recruiting eosinophils to the esophagus and promoting their maturation and activation (Figure 1).1,7,15,16,17 This culminates in epithelial barrier dysfunction, tissue remodeling, and smooth muscle hyperplasia.17 As depicted in Figure 2, the type 2 inflammation underlying EoE pathophysiology has the potential to significantly remodel the esophagus as the disease progresses.3,14

Diagnosis of EoE

The following 3 criteria must be met to diagnose EoE: (1) presence of clinical signs and symptoms suggestive of EoE; (2) esophageal eosinophilia, and (3) exclusion of other disorders that may cause elevated eosinophil level in the esophagus.7,14

Clinical signs and symptoms of EoE vary by age and duration of disease,2 with infants and young children presenting differently than adolescents and adults (Table).1 When EoE is suspected, an esophagogastroduodenoscopy (EGD) is carried out to assess the esophagus for signs of rings, furrows, exudates, edemas, and/or strictures.29 After diagnosis, this procedure is commonly used for monitoring of disease progression.5

Symptoms of EoE may not correlate with the degree of eosinophilia.28 A histological assessment of an esophageal biopsy must reveal at least 15 eosinophils per high-power field (HPF) for an EoE diagnosis, and eosinophilic infiltration must be isolated to the esophagus.1 Other disorders known to cause esophageal eosinophilia must be ruled out to confirm an EoE diagnosis. These non-EoE diseases include gastroesophageal reflux disease, eosinophilic gastrointestinal disorders, Crohn disease, infection, hypereosinophilic syndrome, achalasia, drug hypersensitivity, vasculitis, pemphigus, hypermobility syndromes, and graft-versus-host disease.19 In light of the shared pathophysiologic processes and frequent co-occurrence, suspicion of EoE is elevated in patients with other type 2 inflammatory diseases, such as allergic rhinitis, asthma, food allergies, and/or atopic dermatitis.7,19

Because of the heterogenous symptomology and gradual progression of disease severity, diagnostic delays in EoE are common.6,6,21 Investigators on a 2018 study analyzed the clinical, endoscopic, and histopathologic features of over 700 children and adults with EoE across the United States from a multisite registry developed by the Consortium for Food Allergy Research.4 EoE was diagnosed in these patients based on histology (≥15 eosinophils/HPF) and symptoms of esophageal dysfunction. A total of 705 patients were analyzed in the study; they were predominantly male (68.2%) and White (87.9%), with a median age of 11.2 years (interquartile range [IQR]: 6.7–17.7 years). The median patient age at the time of EoE diagnosis was 8 years. The median diagnostic delay was 1.5 years in the patient population overall; however, longer delays were reported in older patients. The median time from symptom onset to diagnosis was 4.0 years in adults, 2.0 years in 11- to 17-year-old patients, and 1.0 year in children less than 11 years of age. Study results also indicated that a history of food allergy or atopic dermatitis was associated with a significantly shorter delay in the diagnosis of EoE, with the median time from symptom onset to diagnosis being 1.1 years (IQR: 0.5–3.5; P < .05) and 1 year (IQR: 0.5–3.0; P < .05), respectively.6

The results of another study found that patients with longer diagnostic delays were more likely to have both fibrotic (strictures) and inflammatory features of EoE. This retrospective analysis of the Swiss EoE database, which included 783 EoE patients in total, found that 200 had complete clinical, endoscopic, histologic, and laboratory data. Among these 200 patients, the prevalence of strictures at EoE diagnosis was significantly correlated with the duration of diagnostic delay. Strictures occurred in a total of 17.2% of patients (n = 58) with a 0- to 2-year diagnostic delay compared with 70.8% of patients (n = 24) with a more than 20-year diagnostic delay (P < .001). Age at onset of EoE was not associated with the presence of strictures at EoE diagnosis.6

Currently Available Treatments

The current standard of care for patients with EoE consists of dietary therapies, esophageal dilation, and medication. Dietary therapies for EoE include an allergy testing–based elimination, empiric elimination, and an elemental diet. With the goal of mechanically widening the esophagus, esophageal dilation is an endoscopic treatment for EoE that involves bougies or balloons. Standard of care drugs include proton pump inhibitors (PPIs) and topical swallowed corticosteroids.3,12

Diet

There are 3 general diet-modification approaches used to manage patients with EoE: an elemental diet, an elimination diet guided by food allergy testing, and an empiric elimination diet.1 All of these are contingent upon the role dietary antigens appear to play in EoE pathophysiology. Two of the 3 dietary therapies (the food allergy-based elimination diet and the empiric elimination diet) include the elimination of foods that may be exacerbating EoE. The allergy-based elimination diet utilizes allergy-based skin prick and patch testing to determine which foods a patient may be allergic to, whereas the empiric elimination diet removes foods that are most commonly
FIGURE 1. Pathophysiology of Eosinophilic Esophagitis\textsuperscript{7,15,16,17}

EOSINOPHILIC INFLAMMATION
- Eosinophil trafficking to tissues
- Eosinophil differentiation in the bone marrow

REMODELING AND FIBROSIS
- Remodeling and fibrosis, such as strictures, rings, or furrows
- Increased smooth muscle contraction

EPITHELIAL BARRIER DYSFUNCTION
- Decreased levels of epithelial junction proteins
- Increased access to allergens and pathogens across the epithelial barrier
- Increased epithelial permeability and barrier disruption

MAST CELL AND BASOPHIL INFLAMMATION
- IL-4 and IL-13 contribute to the activation of mast cells and basophils
- Leads to cellular activation and the degranulation of several inflammatory mediators

EOS, eosinophil; IgE, Immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; Th, T helper; TSLP, thymic stromal lymphopoietin.
associated with allergic responses. The 2020 guidelines from the American Gastroenterological Association (AGA) and Joint Task Force on Allergy-Immunology Practice Parameters (JTF) recommend all 3 dietary therapies over no treatment, but note that the evidence for these recommendations is of low to moderate quality, and that the inherent challenges of the different diets may not be preferred by all patients.

**Dilation**

Esophageal remodeling as a result of persistent inflammation may lead to fibrosis, and esophageal narrowing and strictures, resulting in dysphagia and impaction. Results from a systematic review and meta-analysis of 27 studies determined that 95% (95% CI, 90%-98%) of patients with EoE who undergo esophageal dilation (n = 845) report symptom improvement, however, the procedure is associated with risks and multiple dilations may be necessary for symptom control. The potential complications of the dilation procedure include small mucosal tears, chest pain, deep mucosal tears, and esophageal perforation. The AGA/JTF 2020 guidelines recommend dilation over no dilation in adults with stricture-induced dysphagia, and AGA/JTF note that the evidence supporting this intervention is of very low quality and comment that the procedure does not address the esophageal inflammation associated with EoE.

**Medications**

PPIs and corticosteroids to manage EoE are recommended over no treatment at all in the AGA/JTF 2020 guidelines, with topical swallowed corticosteroids recommended over oral corticosteroids.

**PPIs**

No FDA-approved dosage guidelines exist for PPI therapy in EoE, thus treatment is primarily guided by symptomatic and histological responses in patients. Following a trial period, those who do not respond can discontinue PPI therapy, whereas those who achieve a partial response can add a topical swallowed corticosteroid or dietary modification to PPI therapy. Patients who achieve complete endoscopic normalization may try a lower PPI dose to establish a minimum maintenance dose, as long-term treatment with PPIs might rarely be associated with increased risk of gastrointestinal infections, pneumonia, kidney impairment, fracture risk, and gastric tumors.

Overall response to therapy with PPIs is mixed. The results of a 2016 systematic review and meta-analysis of 33 studies reported clinical remission of EoE in 60.8% (95% CI, 48.4%-72.2%; P = 80.2%) of patients treated with PPIs, and histological remission in 50.5%
Topical Swallowed Corticosteroids

Topical formulations of corticosteroids are used to coat the esophagus and provide broad anti-inflammatory effects. Although there are no FDA-approved medications for EoE, the topical corticosteroids budesonide and fluticasone are commonly used off-label in the United States in patients with EoE who fail to respond to PPIs. Budesonide is aqueous and patients are instructed to mix the liquid with a sugar substitute and swallow it. Fluticasone is aerosolized and packaged in a multidose inhaler; patients are instructed to puff the medication into their mouths and swallow it.

The use of topical swallowed corticosteroids is strongly recommended by the AGA/JTF over no treatment, and in patients who achieve histologic remission following short-term use of topical swallowed corticosteroids, continuation of treatment is recommended over cessation. The guidelines do note that longer-term safety data in children are needed, particularly in relation to adrenal function and growth suppression.

Topical swallowed corticosteroids produce clinical and histologic remission, as well as endoscopic normalization; however, cessation of therapy often results in relapse. The results of 1 observational single-center study found that among 351 patients with EoE, 78.8% relapsed following cessation of treatment (median time to relapse following treatment was 22.4 weeks). Accordingly, patients with EoE who achieve histologic remission with topical swallowed corticosteroids may consider maintenance therapy rather than cessation. Some adverse events (AEs) associated with topical swallowed corticosteroid use include esophageal and oral candidiasis, sore throat, chest pain, pneumonia, and food impaction. Additionally, systemic absorption of topical swallowed corticosteroids in children with EoE may be associated with adrenal axis suppression.

The use of systemic corticosteroids is not recommended in EoE. Although their efficacy is generally comparable to that of topical swallowed corticosteroids, their chronic use is known to be associated with a range of AEs (eg, hyperphagia, weight gain, Cushimgoid features, growth suppression in children, and osteoporosis).

Treatment Considerations

Response to EoE treatment is categorized into 3 general groups (nonresponse, response, and complete endoscopic normalization) based on clinical and histological outcomes. Patients classified as having a nonresponse maintain persistent eosinophilia with at least 15 eosinophils per HPF, persistent symptoms with a less than 30% decrease in a symptom metric, and persistent endoscopic findings with a less than 30% decrease in endoscopic reference score. Responders achieve reduced eosinophilia (higher than normal level of eosinophils in the blood) and a decrease in symptoms with a 30% to 90% decrease in a symptom metric, along with improved endoscopic findings. Patients who achieve complete endoscopic normalization have less than 1 eosinophil per HPF, symptom resolution with a greater than 90% decrease in a symptom metric, and normal endoscopic findings with an endoscopic reference score of less than 2.

Despite the current therapies, long-term management of EoE can be challenging and initial treatment failure and/or disease reoccurrence is common. In a retrospective cohort study of 100 patients with confirmed EoE, 67% of those who chose initial dietary therapy (n = 54/81) achieved histologic remission compared with 56% of those who chose initial pharmacological therapy (n = 9/16). Of the 34 patients who failed to achieve a response to initial therapy, 24 elected to undergo rescue therapy with an elimination diet or food allergy-based elimination diet, or topical swallowed corticosteroids. Eleven of these patients still failed rescue therapy.

Patients who responded to initial therapy had significantly more symptoms (heartburn, dysphagia, vomiting [P < .005]; feeding dysfunction, abdominal pain [P < .05]) and endoscopic findings (furrows [P < .005]; edema and rings [P < .05]) than those who did not. Conversely, those who did not respond to initial treatment were shown to have higher peak eosinophil counts per HPF in the proximal and mid esophagus than those who did respond (28 vs 20, P < .005; 30 vs 20, P < .005, respectively). No statistical differences between symptoms, endoscopic findings, and peak eosinophil counts per HPF were found between those patients who responded to rescue treatments and those who did not.

Optimizing treatment for patients with EoE depends on the severity of their disease, and lifestyle and preferences. Therapy can be combined to improve or expedite remission (ie, a patient...
with severe symptomatic esophageal strictures could initiate treatment with the combination of a topical swallowed corticosteroid, food elimination diet, and esophageal dilation, to achieve clinical and histologic remission, and endoscopic normalization. Further investigation into the natural history of EoE in both children and adults is needed to optimize its management.5

**Burden of Disease**

The long-term complications associated with EoE include: (1) persistent inflammation; (2) esophageal tissue remodeling and potential for fibrosis; (3) increased esophageal constriction; and (4) progressive disease severity.1,14,40 Relapse and recurrence of EoE symptoms occur as a result of diminishing efficacy of long-term treatments or discontinuation of therapy.5,16,41 Complications and disease management can negatively impact the quality of life (QOL) of patients with EoE.42 Patients of all ages face challenges related to social isolation due to dining restrictions, the potential need for a gastrostomy tube, costs of elemental formula, and difficulties related to undergoing repeated endoscopies requiring sedation and biopsy.5

**Clinical Burden**

Patients with EoE report substantial clinical burden,43 and experience impaired QOL because of the progressive nature of the disease and the impact on daily life.1,44 Adults with EoE may have restrictive symptoms, including dysphagia and food impaction, which impairs their ability to eat, whereas children with EoE commonly refuse food and can fail to thrive.1,44 Additionally, patients with EoE may need repeat endoscopies, and those with more advanced disease may require rescue therapies, including endoscopic dilation, at the emergency department for symptomatic relief.45,46

Concomitant type 2 inflammatory conditions, such as allergic disorders, also are common in patients with EoE and can increase disease burden. Allergic disorders were reported in over 90% of patients in a multisite single-visit registry of patients with EoE in the United States. Of the 705 patients (age range: 0.9-56.2 years) enrolled between May 2011 and March 2016, the most common allergic disorder was food allergy (67.0%), followed by allergic rhinitis (60.3%), atopic dermatitis (46.4%), asthma (45.4%), allergic conjunctivitis (31.2%), urticaria (26.2%), food anaphylaxis (27.1%), and angioedema (13.2%) (Figure 3).6

Similarly, the results of a longitudinal study of electronic medical record (EMR) data from 130,435 patients in the Children’s Hospital of Philadelphia medical network found that prior diagnosis of a type 2 inflammatory disease increased the risk of EoE diagnosis. The investigators reviewed birth cohort data from January 1, 2001, to December 31, 2017, and found that of the 139 children who developed EoE, the presence of atopic dermatitis, IgE-mediated food allergy, and asthma all were independently and cumulatively associated with a subsequent diagnosis of EoE: atopic dermatitis (HR 3.2, 95% confidence interval [CI] 2.4-4.0), IgE-mediated food allergy (HR 2.4, 95% CI 1.7-3.2), and asthma (HR 1.9, 95% CI 1.5-2.3).45

**FIGURE 3.** Percentage of Patients With Comorbidities in a Multicenter Study of Patients With Eosinophilic Esophagitis

![Proportion of patients (%)](image)

**EoE,** eosinophilic esophagitis; **GERD,** gastroesophageal reflux disease. *Data are from a multisite single-visit registry of 705 patients with EoE in the United States (age range: 0.9-56.2 years), enrolled between May 2011 and March 2016.6*
Economic Burden

According to a matched, case-control analysis of commercial medical and pharmaceutical insurance claims data from 2009 and 2010, the estimated total annual health care costs for EoE are more than $500 million (based on a prevalence of 56.7 cases per 100,000 individuals [age range: 0-64 years]), and up to $1.3 billion (based on a prevalence of 153.2 cases per 100,000 individuals). Taking inflation into account, this amount translates to approximately $665 million to $1.73 billion in 2020 (based on an estimated inflation rate of about 33%, determined by the Consumer Price Index for Medical Costs and dollars alone, without regard to other influences, such as new treatments). These figures reflect the costly diagnosis and management strategies for EoE, such as multiple upper endoscopies with biopsies (Figure 4). For example, during the 2-year period, patients with EoE (n = 8135) had significantly more claims for upper endoscopies than those without EoE (n = 32,540) (2 claims vs 0.1 claims; P < .001; age range for all patients: 0-64 years).

Humanistic Burden

The impact of EoE on health-related QOL has been shown to increase with disease severity. For example, in a study conducted between March 2013 and May 2014, patients with EoE for at least 17 years who needed an endoscopy for diagnosis, further confirmation of a suspected diagnosis, or monitoring of previously diagnosed EoE were invited to recall their QOL and symptom severity over the last 7 days using validated instruments. Results indicated that the presence of dysphagia was correlated with decreased QOL and increased disability. Similarly, the results of a 2011 qualitative study of patient-reported outcomes in 24 adults with EoE found that they were most worried about the impact of EoE on their ability to eat (87% of patients), concerns regarding dysphagia (67%), and the impact of EoE on their social relationships (65%). About half of the patients (49%) were worried about available treatments.

More recently, the results of a 2019 cross-sectional, internet-based survey of adult patients with EoE (n = 243) and adult caregivers of pediatric patients with EoE (n = 270) showed that more than 42% reported low shared decision-making in regard to their EoE treatments and only 38% felt content with their current treatment.

Conclusions

Early diagnosis and effective treatment of EoE is essential for reducing the clinical, economic, and humanistic impact of this disease. Current treatment options (diet therapy, esophageal dilation, PPIs, and topical swallowed corticosteroids) do not specifically target type 2 inflammation in EoE. As the prevalence of EoE continues to increase, it is imperative to understand existing unmet needs to optimize all aspects of its management, including long-term care.

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REFERENCES


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