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Eosinophilic Esophagitis: Etiology and Therapy

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eosinophilic esophagitis, dysphagia, eosinophilic gastrointestinal disease, gastroesophageal reflux disease, esophageal stricture, esophageal dilation

Abstract

Eosinophilic esophagitis (EoE) is a relatively recently identified but now frequently encountered antigen/immune-mediated disease which places significant burden on patients and the healthcare system. With its growing prevalence and recognition by healthcare providers in multiple disciplines, substantial progress has been made regarding the diagnostic criteria, clinical evaluation, tools for disease assessment, and immune pathways related to pathogenesis. Current treatment goals focus on the amelioration of inflammation and prevention of remodeling consequences using proton pump inhibitors, swallowed topical steroids, elimination diets, and esophageal dilation. Ongoing research holds promise for more efficacious and targeted therapies as well as a personalized approach to the care of patients with EoE.

INTRODUCTION

eos/hpf: eosinophils per high-power field

Eosinophilic esophagitis (EoE) is an allergen/immune-mediated disease characterized by esophageal mucosal eosinophilia and esophageal dysfunction. Rarely recognized when it was first described nearly three decades ago, EoE has become a major cause of upper gastrointestinal morbidity (1) with associated decrement in quality of life and increases in healthcare utilization and cost (2). Paralleling the increase in incidence and occurrence in the clinical environment, there has been a remarkable amount of discovery regarding the underlying etiology, natural history, and treatment of the disease.

EPIDEMIOLOGY

EoE was initially described in the 1990s in three adult and pediatric case series (3–5), where increased esophageal eosinophilia seen on biopsy presented with a unique clinical phenotype. Since the initial reports of EoE, the incidence of the disease has been rising and has outpaced changes in endoscopic and biopsy utilization (6). Global populations have seen dramatic increases in EoE cases, with areas reporting fivefold increases of cases over 4 years (7) and >100-fold increases of cases over a 14-year period (8). Recent meta-analysis data suggest a pooled incidence rate of 3.7/100,000/year, with a higher incidence in adults (7/100,000/year) as compared to children (5.1/100,000/year) (9). Data from the same study suggest a pooled prevalence of 22.7/100,000, again higher in adults (43.4/100,000) than in children (29.5/100,000) (9). In the United States, a recent study using a health claims database representing approximately 50% of the population covered by employer-sponsored insurance plans identified a prevalence of 79/100,000 (10). Not only is the rise in cases dramatic, but the numbers may even be higher, since patients with proton pump inhibitor–responsive esophageal eosinophilia (PPI-REE) may have been excluded (see below).

DIAGNOSIS

Criteria

EoE is characterized by clinical symptoms of esophageal dysfunction and esophageal eosinophilia, defined by ≥15 eosinophils per high-powered field (eos/hpf) on biopsy. Before solidifying a diagnosis of EoE, clinicians should consider other etiologies of esophageal eosinophilia (**Figure 1**) (11).

Proton Pump Inhibitor–Responsive Esophageal Eosinophilia

Gastroesophageal reflux disease (GERD) is one such etiology known to cause esophageal eosinophilia. In an effort to distinguish GERD from EoE, the initial consensus guideline published in 2007 included lack of response to proton pump inhibitor (PPI) therapy or normal esophageal pH monitoring in the diagnostic criteria for EoE (12). However, data and experience that emerged in the following years suggested that patients presenting with esophageal dysfunction and esophageal eosinophilia without a GERD phenotype responded to PPI therapy (13). The subsequent consensus recommendations published in 2011 introduced the idea of PPI-REE as an entity distinct from EoE (14). Subsequent studies, however, demonstrated that PPI-REE and EoE are virtually indistinguishable conditions, with shared clinical, endoscopic, histologic, biomarker, and gene expression profiles. Moreover, patients with PPI-REE responded to diet and steroid therapy, primary treatments used for EoE (11). At the same time, translational research found that PPIs were capable of acid-independent suppression of allergic inflammatory pathways

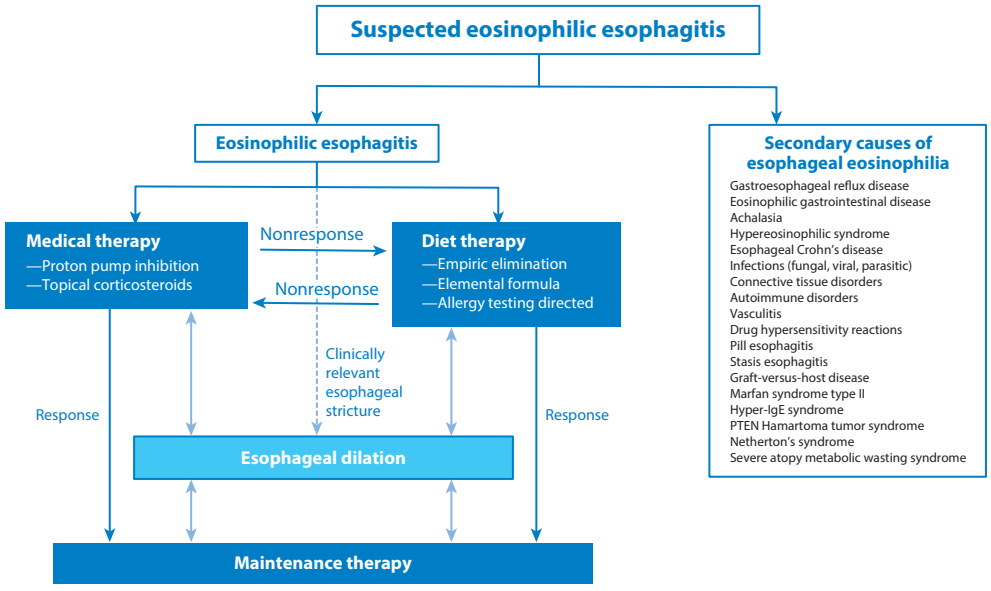

Figure 1

Diagnosis and treatment of eosinophilic esophagitis (EoE). Once EoE is differentiated from other causes of esophageal eosinophilia, treatment options include medical therapy, diet therapy, and esophageal dilation. Figure adapted with permission from Reference 74.

in cultured esophageal epithelial cells (15). As a result of the evidence supporting PPI-REE and EoE as similar entities and in an effort to avoid treatment response to define a disease, the updated international diagnostic criteria have removed the PPI trial as a diagnostic requirement (11).

CLINICAL FEATURES

Symptoms

The clinical presentation of EoE differs between children and adults. In the early years of life, symptom presentation can be vague and includes feeding difficulties and food refusal (16). Children over the age of 5 often note vomiting or pain (17). Adolescents and adults predominantly present with dysphagia (18), frequently also directly presenting with food impactions (19). Not only is dysphagia a common presenting symptom of EoE, but EoE is the second most commonly identifiable cause of dysphagia, the first being GERD (20).

Endoscopy

As outlined by recent guidelines (11), once the clinical presentation is suggestive of EoE, esophagogastroduodenoscopy is the next recommended test of choice. Endoscopy allows confirmation of diagnosis through direct tissue sampling. Furthermore, endoscopic features can strongly support the diagnosis and assess the severity of EoE. In 2013, the EoE Endoscopic Reference Scoring system (EREFS) was developed to better describe the features of EoE during endoscopy, including edema, rings, exudates, furrows, and strictures (21). The EREFS system is a widely used classification and grading system that has been validated and shows a high degree of accuracy in the diagnosis of EoE in children and adults (21). While classic endoscopic features of EoE can help support the diagnosis, a minority of EoE patients, under 5% in prospective studies, may have a normal endoscopy; therefore, biopsy of the esophagus in all suspected cases is recommended.

EREFS: Eosinophilic Esophagitis Endoscopic Reference Scoring

Histopathology

EoE-HSS: Eosinophilic Esophagitis Histologic Scoring System

Esophageal inflammation in EoE is currently defined by the diagnostic threshold of ≥15 eos/hpf on biopsy. However, eosinophil counts alone do not always capture the full extent of disease. For example, esophageal remodeling often leads to fibrosis of the lamina propria in children (22) and adults, which can affect symptom burden without significant eosinophilic inflammation. Consequently, several other histologic characteristics, aside from eosinophil counts, are now considered indicators of disease in EoE. The Eosinophilic Esophagitis Histologic Scoring System (EoE-HSS) developed by Collins et al. (23) incorporates eight histologic features including eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intracellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis. The EoE-HSS can distinguish treated from untreated EoE biopsy specimens and importantly includes eosinophil-independent variables such as basal zone hyperplasia and dilated intracellular spaces (23). Given the importance of features in addition to eosinophil counts, the EoE-HSS has been incorporated into clinical trials as an outcome measure.

Barium Esophagram

Radiographic examinations can provide valuable information on the fibrostenotic features of EoE, which may be missed on endoscopy (24, 25). Barium esophagrams, in particular, can help to visualize strictures as well as narrow-caliber esophagus. Prior work has shown that barium esophagrams are more sensitive than endoscopy at identifying strictures (25). For example, in one study, endoscopy detected esophageal strictures in only one-third of patients with EoE with luminal diameters ≤13 mm (25). Endoscopy, however, has significantly greater sensitivity for the detection of inflammatory features of edema, furrows, and exudates than an esophagram.

Reflux Testing

Once considered as distinct clinical entities, GERD and EoE are now recognized as having considerable clinical and histologic overlap and interactions. Given the high prevalence of GERD in nearly 20% of the population (26), this overlap is expected. Classic presentations allow diagnosis of each disease process; EoE typically presents in young, atopic males where endoscopy often shows edema, rings, exudates, furrows, and/or strictures, and biopsies reveal a higher degree of esophageal eosinophilia, whereas GERD typically presents in patients with heartburn and regurgitation where endoscopy may be normal or show esophagitis or Barrett's esophagus (27). Though patients with GERD may have esophageal eosinophilia, the degree is usually less (<15 eos/hpf) than in EoE. However, in a subset of patients, the presenting symptoms, endoscopy, and eosinophilic counts may make it difficult to distinguish GERD from EoE. In cases where the distinction is clinically relevant, ambulatory pH monitoring may be helpful (27).

Impedance Planimetry

As understanding of EoE has progressed, technology has also been developed to better understand the remodeling consequences of EoE. The Functional Luminal Imaging Probe is a novel tool now used in the evaluation and management of patients with EoE. The tool utilizes impedance planimetry to determine esophageal distensibility, defined by esophageal cross-sectional area as a function of intraluminal pressure during volumetric distension (28). Esophageal distensibility has been shown to be significantly lower in patients with EoE than in controls (28). Esophageal

distensibility can also be used as a quantitative biomarker of disease severity. In a cohort of patients with EoE, esophageal distensibility was reduced in patients with food impactions as compared to solid-food dysphagia alone (29). Utilization of impedance planimetry may provide guidance for management of patients and clinical trials by serving as a quantitative marker of disease severity and risk of future complications.

Novel Activity Measures

In an effort to measure disease activity in patients with EoE and improve management, several instruments and novel activity measures have been created. Many assessment tools for children and adults have been created and validated to capture patient-reported outcomes related to symptoms, behavioral modifications with food consumption, and quality of life (30). Such validated tools allow standardization of patient reporting, which can inform therapeutic endpoints for clinical trials.

Improvement of eosinophilic inflammation is viewed both in practice and in clinical trials as a therapeutic goal. Novel tools now exist to assess inflammatory activity and to decrease the burden associated with repeated and invasive endoscopic evaluation with biopsies. The Esophageal String Test™ is a small, swallowed capsule which deploys a string into the esophagus and can collect secretions containing quantifiable eosinophil-derived proteins (31). Measurements of eosinophil-derived proteins have been shown to correlate with eosinophilic counts captured via tissue biopsy (31). The Cytosponge™ is also an ingestible capsule but contains a compressed mesh which expands when swallowed and then is withdrawn, thereby capturing fragments of esophageal epithelium (32). Eosinophilic counts collected by the Cytosponge™ have also positively correlated with eosinophilic counts by biopsy (32). Both these devices offer a less invasive modality of measuring esophageal inflammatory activity.

PATHOGENESIS

The presence of eosinophils in the esophagus corresponds to pathology, as this luminal site is normally devoid of this cell type. EoE is thought to develop through a multifaceted interplay of environmental factors through food and/or aeroallergens, host factors such as an allergic background, and an underlying genetic predisposition (**Figure 2**) (33). Genome-wide analysis studies demonstrated susceptibility elements at 5q22 (thymic stromal lymphopoietin) and 2p23 (CAPN14). In select hosts, an immune response is thought to be triggered primarily by ingested food allergens, leading to a cellular response by T helper type 2 cells. This pathway leads to activation of cytokines, namely interleukin (IL)-5 and IL-13. IL-5 is involved in eosinophil synthesis and trafficking, and increased IL-13 leads to production of specific proteins, notably eotaxin-3 via epithelial cells. Eotaxin-3 is a primary regulator of eosinophils within the gastrointestinal tract (33, 34). IL-13 is also known to induce proteases that impair the epithelial barrier (35), which in turn reduce expression of key adhesion molecules important in the maintenance of the epithelium (36). Mast cells, additionally, have been implicated in the inflammatory pathway and tissue remodeling in EoE (22, 37). The understanding of the pathogenesis of EoE has led to the development of therapeutic options targeting specific activated cytokines, receptors, and cell types.

ALLERGY EVALUATION

Food antigen triggers are the principal allergic factor in the development of EoE, as evidenced by the efficacy of diet therapy in treating the disease. Prior studies have demonstrated that

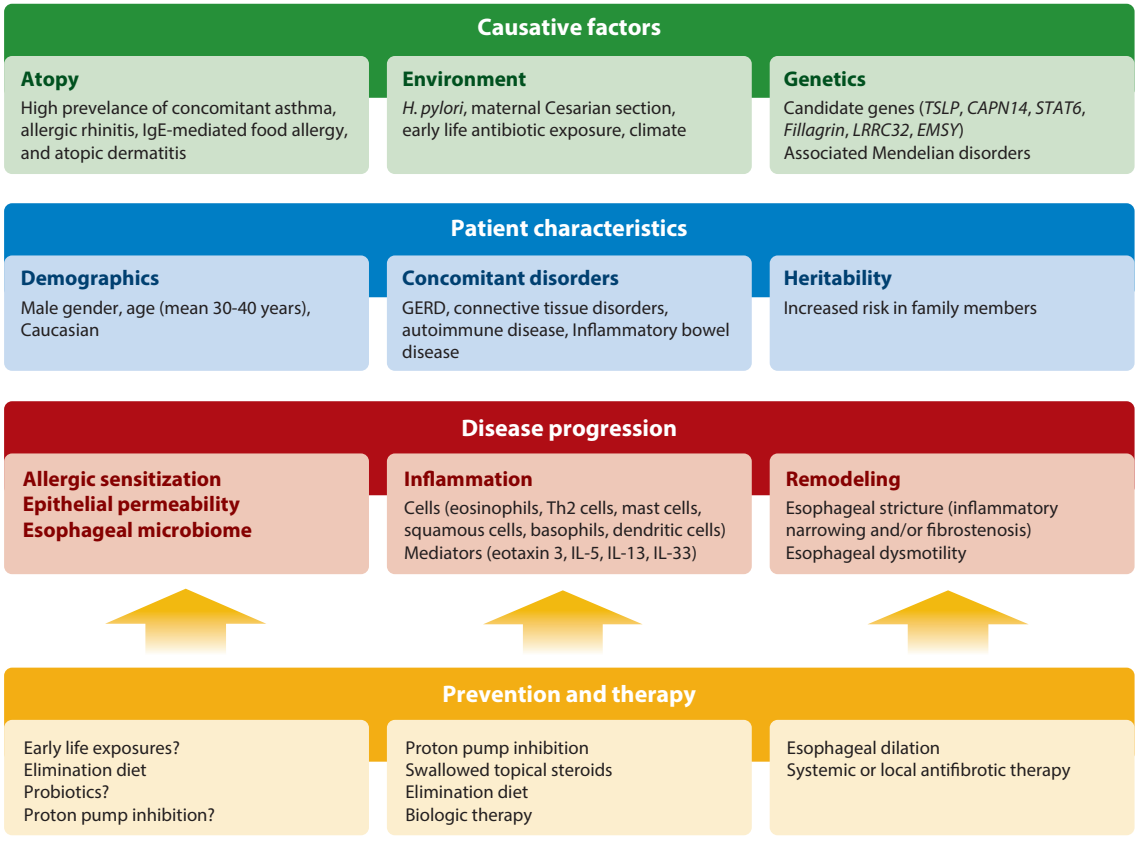

Figure 2

Roles of patient, environmental, and genetic factors in the development of eosinophilic esophagitis. Abbreviation: GERD, gastroesophageal reflux disease.

aeroallergens can also exacerbate EoE, with seasonal variation in symptom activity. Some studies indicate that up to 80% of adults may be atopic, having concomitant asthma, allergic rhinitis, atopic dermatitis, or IgE-mediated food allergy (38). The evaluation and treatment of concomitant atopic diseases can optimize the successful management of the EoE patient. Allergists also can direct the use of systemic therapies that have been approved by the US Food and Drug Administration (FDA) for the treatment of atopic dermatitis, asthma, and allergic rhinitis. While not approved for EoE, several of these agents have shown efficacy in phase II clinical trials in EoE. While testing for food allergens has had limited success for predicting food triggers in EoE, allergists can assess IgE-mediated hypersensitivity to foods avoided during empiric elimination protocols and provide guidance during the food-reintroduction process.

NATURAL HISTORY

An understanding of the natural history of EoE informs decisions regarding the appropriate management (1). Existing studies provide disparate views on the long-term consequences of EoE. The first study to address the issue described 30 adults followed for a mean of 7.2 years in the absence of medical or diet therapy for EoE (39). Dysphagia and esophageal eosinophilia persisted in

nearly every patient. The study highlighted the chronic nature of EoE in adults and the apparent lack of clinical progression over the several-year follow-up period. Subsequent, symptom-focused outcome studies have supported a relatively benign course to EoE, with absent or mild dysphagia in the majority of patients (1). These favorable outcomes may have been affected by the use of medical or diet therapies and esophageal dilation. Furthermore, patients typically adapt to the slow, progressive esophageal remodeling by means of modification in eating behaviors. Multiple studies focusing on endoscopic outcomes have raised substantial concerns about progression of fibrostenosis in the majority of patients with over a decade of untreated disease (40, 41). The longer-term follow-up in these reports combined with a more objective endoscopic measure of disease activity likely provide a more accurate depiction of the longitudinal consequences of EoE.

The natural history of EoE, therefore, involves chronic inflammation that leads over time to progressive fibrostenosis in many but not all patients (1). This progression appears to be gradual, allowing many patients to adopt coping strategies that often limit symptom reporting. In addition, genetic factors and individual host factors contribute to variability in disease progression. Spontaneous remission does occur but appears to be uncommon.

TREATMENT

Therapeutic Endpoints

The treatment of EoE seeks to relieve symptoms, improve histopathology, reverse existing disease complications, and prevent future disease consequences. While improved symptom assessment is an intuitive primary objective, it is important to emphasize limitations to this approach in both clinical practice and trials. Excessive mastication, extended meal-times, ingestion of liquids during meals, and avoidance and/or modification of harder-textured, dry solids can mitigate the intensity of dysphagia and thereby lead to erroneous assessment of disease activity in adults. Another limitation arises from the relationship between symptoms and esophageal remodeling. Esophageal remodeling related to chronic inflammation manifests as esophageal strictures that are a major determinant of symptom outcomes of dysphagia and food impaction (42). Medical and diet therapies that significantly reduce esophageal inflammation may not effectively reverse existing esophageal strictures. In contrast, esophageal dilation can effectively manage esophageal strictures, thereby alleviating dysphagia in the absence of improvement in esophageal inflammation (43).

Randomized controlled trials have demonstrated that measuring EoE activity using esophageal mucosal eosinophil density offers an objective and quantifiable measure with a high degree of interobserver agreement and with minimal placebo response. Outcomes are commonly defined by a reduction in mucosal eosinophilia, but the method used to calculate eosinophil density has varied considerably. Furthermore, a variety of target thresholds have been used, including endpoints of <15, <10, <6, and <5 eos/hpf in some studies and percent reduction in eosinophil density in others. The EoE-HSS, which incorporates histopathology beyond eosinophil density, provides a more comprehensive characterization of mucosal inflammation in EoE for clinical trials (23). While it is tempting to consider histology as the primary determinant of therapeutic efficacy, the correlation between symptoms and pathology is poor, owing to the limitations described above.

Based on the recognition of limitations to both symptom and histologic outcomes in the assessment of disease activity in EoE, a three-pronged approach that incorporates measures of symptoms, histology, and endoscopic features is recommended (44). Endoscopic features, as delineated by the EREFS system, identify remodeling aspects of disease, including esophageal rings and strictures that are associated with symptom outcomes of dysphagia and food impaction risk and are not demonstrable on mucosal biopsies. Application of EREFS in randomized placebo-controlled clinical trials has demonstrated the responsiveness of EREFS to medical and diet therapies for EoE.

For the purpose of clinical trials, core outcome measures incorporating symptoms, histology, and endoscopy are under development to standardize disease activity assessment.

Proton Pump Inhibitors

As mentioned, recent clinical guidelines no longer mandate a PPI trial to establish a diagnosis of EoE and instead identify PPIs as a viable therapeutic option for EoE (11, 45). PPIs have an overall histopathologic response of 42% based largely on observational studies with significant heterogeneity in effect size (13). A prospective uncontrolled case series reported that the majority of EoE patients who respond to initial high-dose PPI therapy maintain response with dose reduction. Small case series, however, have noted loss of initial PPI response upon long-term follow-up. The CYP2C19 genotype indicating hypermetabolism of PPI therapy has been associated with loss of initial PPI response (11, 45). Nonetheless, the safety and ease of administration of PPIs position them favorably as a first-line treatment option.

Swallowed Topical Steroids

Swallowed topical corticosteroids are a common primary therapy for both children and adults with EoE, with efficacy consistently demonstrated in several randomized double-blind placebo-controlled trials. Overall, about two-thirds of patients enrolled in placebo-controlled trials demonstrated a histologic response (13).

Drawbacks to corticosteroids include lack of an FDA-approved preparation for EoE and absence of a readily available formulation optimized for esophageal delivery in the United States. In 2018, the European Medicines Agency approved a budesonide tablet for EoE. Adverse side effects have been limited to oropharyngeal and esophageal *Candida* infections, but systemic effects including adrenal insufficiency and bone density are being carefully evaluated. *Candida* infections have been largely asymptomatic and incidental findings at the time of systematic follow-up protocols in clinical trials. The known safety profile of topical steroids used for allergic rhinitis and asthma, combined with the lower bioavailability of swallowed compared to inhaled steroids, provides reassurance while we await prospectively collected long-term safety data.

Diet Therapy

Diet therapy is considered a first-line treatment strategy in both adults and children (5, 46–48). Three different approaches to diet therapy in EoE have been utilized: an elemental, or amino acid–based, formula, which eliminates common food allergens; an allergy-directed diet based on food allergy testing; and an empiric elimination diet which excludes the most common food allergens known to trigger EoE (**Table 1**). The goal of diet therapy is not to stay on a restrictive diet indefinitely but rather to identify a limited number of specific food triggers and thereby personalize diet therapy for long-term maintenance.

Elemental diet therapy was first described in a pediatric cohort in the late 1990s (5) and continues to be used predominantly in children, with limited use in adults (49). This dietary approach has been shown to be the most effective in terms of reduction of histologic eosinophilia (50). Despite the superior efficacy of the elemental diet as highlighted in prior meta-analysis studies, practical limitations of this treatment approach include cost, taste of formula, and time required to complete food reintroduction (50). Due to these concerns, elemental diet is not utilized as first-line diet therapy in adults.

Given the role of food allergens in the development of EoE, many attempts have been made to develop personalized, allergy-directed diet therapy. In this approach, office-based testing,

Table 1 Diet therapy for eosinophilic esophagitis (EoE)

Type	Description	Efficacy[a]	Advantages/disadvantages	Global considerations for all dietary approaches
Elemental	Amino acid–based formula, eliminates common food allergens	91%	Most effective diet therapy Limited palatability Costly Identification of a specific food trigger can take many months Multiple endoscopies are needed during reintroduction	Identification of food trigger(s) obviates need for chronic medication use Allergen-free food costs and accessibility are limitations Cost and burden of repeat endoscopies to identify food trigger must be considered Multidisciplinary team (allergist, dietician, gastroenterologist) optimizes approach Patient motivation to pursue dietary intervention is an important consideration
Empiric elimination	Most common foods eliminated in six-food elimination diet (SFED): milk, wheat, soy, egg, nuts, seafood Step-up (2→4→SFED) and step-down approaches described	72% (SFED)	Allows consumption of most table foods Identification of a specific food trigger can take several months Multiple endoscopies are needed during reintroduction to identify histologic activity	
Allergy-directed	Elimination of selective foods based on results of office-based allergy testing	46%	Limited accuracy for IgE-based testing in identifying foods triggering EoE Improved methods to identify allergic triggers are needed	

[a]Based on meta-analysis data; efficacy defined as a histologic response of <15 eosinophils/high-powered field (50).

including skin-prick testing, atopy patch testing, or IgE testing, helps to identify allergens which are then eliminated from the diet. Although a logical way to identify food triggers, allergy-directed diet therapy has shown limited improvement in symptoms and histology (51, 52). Likewise, allergy testing was not found to be predictive of food triggers in either of the two largest adult dietary studies utilizing an empiric elimination approach (47, 48). Another more recent adult study looked at the use of atopy patch testing in directed diet therapy for EoE and found that atopy patch testing did not reliably predict food triggers identified by food elimination diet in adult patients with EoE (53). Results of these and other studies highlight that the available office-based allergy testing tools are not effective methods to determine the trigger foods to avoid in adult EoE and should not be used to direct dietary avoidance in EoE (50).

Studies have shown that using an empiric elimination diet approach has comparable effectiveness in children and adults (50). In this dietary treatment, the six most common food allergens are eliminated: milk, wheat, soy, egg, nuts, and seafood. Second to elemental diets, this approach is considered next most effective and much more palatable (50). Studies of the six-food elimination diet (SFED) showed wheat and milk to be the most common triggers (47, 48), with many patients reporting only one trigger (47). Identifying more common dietary triggers has allowed the development of tailored elimination diets (54–56), including four-food elimination diets (FFED) eliminating milk, wheat, eggs, and either soy or legumes (54, 56) and single-food elimination removing milk (57). Considering this, novel approaches are also looking at the "step-up" versus "step-down" elimination diets for adults (58). In the step-up approach, rather than starting by eliminating all six foods at once, patients are encouraged to eliminate the two most common foods for a period of six weeks followed by an endoscopy. If they do not achieve histologic remission, patients proceed to the FFED and, based on response, potentially advance to the SFED. The advantages to

such an approach are clear if the food trigger is identified early on. However, if the trigger is not identified in the first round, the length of pursuing elimination diet therapy may be prolonged. Since there are many different approaches to empiric elimination, it is important to discuss them all with patients and come up with an individualized approach.

Diet therapy in patients with EoE has practical advantages. Avoidance of food allergens eliminates the need for chronic medication to help control the disease. Diet therapy has the advantage of affecting the underlying cause of the disease by food allergen avoidance rather than treating symptoms and histology with topical corticosteroids. While diet therapy has several practical advantages, there are limitations that should be reviewed with patients (**Table 1**). Food cost and accessibility is one consideration, as prior studies have demonstrated that allergy-friendly foods consumed on an elimination diet cost more and are more likely found in specialty food stores (59). The need for repeated endoscopies to identify food triggers is another major limitation of diet therapy. The number of foods eliminated at the start of the diet determines the number of follow-up endoscopies needed overall, and this should initially be discussed with patients. Novel measures of eosinophilic activity as described above may help offset this burden in the future. When counseling patients about pursuing diet therapy, it is essential to provide the infrastructure to help patients navigate this process. Patients should have access to a multidisciplinary team including a registered dietician who can provide nutritional support and education and monitor for potential contamination (55, 60).

Esophageal Dilation

Esophageal dilation is an effective strategy to manage symptoms of dysphagia resulting from strictures associated with EoE. Initial concerns about high risks of complications of esophageal perforation in small case series have not been supported by larger retrospective series and meta-analyses (13). The overall reported risk of perforation with dilation in EoE is similar to that for benign esophageal stricture dilation. An important caveat regarding the low reported risks is that the evidence is derived primarily from retrospective series and dominated by the experience from esophageal centers that have adopted a cautious approach to dilation in EoE.

Additional and Emerging Therapies

Montelukast has previously been investigated because of its allergic targeting properties, though it is not commonly recommended due to limited histologic efficacy. Additionally, the mast cell stabilizer cromolyn sodium is felt to have anti-eosinophilic properties. There has been limited evidence to support the use of oral cromolyn as a treatment for EoE (61). With increasing knowledge regarding the pathogenesis of EoE and identification of key factors in the immune response, several immune-targeted and monoclonal antibody treatment options are being developed with efficacy demonstrated in phase II clinical trials (**Table 2**).

Maintenance Therapy

Maintenance therapy is currently recommended for patients with EoE with the rationale of preventing progression of esophageal remodeling. The type of maintenance involves shared decision making that accounts for patient preferences, disease severity, and the initial therapy chosen. Loss of therapeutic response to PPI, steroids, and diet therapies has been reported in EoE patients with prolonged use. Thus, periodic endoscopy can verify continued histologic remission as well

Table 2 Emerging therapies for eosinophilic esophagitis

Therapeutic agent	Mechanism of action	Route of administration	Study design; patient cohort	Trial outcome
Mepolizumab (62–64)	Monoclonal antibody to IL-5	Intravenous	Open-label, single-arm, phase I/II; 4 adults (63)	Significant reduction in mean and peak esophageal eosinophil counts Significant improvement in peripheral blood eosinophilia
			Randomized phase II clinical trial; 11 adults (64)	No patients with reduction of peak eosinophils to <5 eos/hpf Significant reduction of mean eosinophil counts
			Randomized phase II clinical trial; 59 children (62)	8.8% of patients with peak eosinophil <5 eos/hpf Significant reduction of mean and peak eosinophil counts
Reslizumab (65)	Monoclonal antibody to IL-5	Intravenous	Randomized clinical trial; 226 children and adolescents	Significant reduction of peak eosinophil counts No significant improvement in symptoms
QAX576 (66)	Monoclonal antibody to IL-13	Intravenous	Randomized phase II clinical trial; 23 adults	Nonsignificant 40% response rate (defined as >75% decrease in peak eosinophil counts) Reduction in mean eosinophil counts
RPC4046 (67)	Monoclonal antibody to IL-13	Subcutaneous	Randomized phase II clinical trial; 99 adults	Significant reduction in mean eosinophil counts and endoscopic activity
Dupilumab (68)	Monoclonal antibody to IL-4α receptor	Subcutaneous	Randomized phase II clinical trial; 47 adults	Significant improvement in symptoms Significant reduction of peak eosinophil counts and endoscopic activity
Omalizumab (69)	Monoclonal antibody to IgE	Subcutaneous	Randomized phase II clinical trial; 27 adults, 3 children	No significant reduction in tissue eosinophil counts No significant reduction in symptoms
OC000459 (70)	Chemoattractant receptor-homologous molecule on Th2 cells (CRTH2) antagonist	Oral	Randomized phase II clinical trial; 26 adults	Significant reduction in eosinophil counts
AK002 (71)	Monoclonal antibody to SIGLEC-8 (depletes eosinophils)	Intravenous	Randomized phase II/III clinical trial in 65 patients with eosinophilic gastritis/gastroenteritis; subgroup of 25 adults with esophageal eosinophilic inflammation	Reduction in esophageal eosinophil counts in subset with esophageal involvement
Infliximab (72)	Monoclonal antibody to TNF-α	Intravenous	Open-label case series; 3 adults	Lack of resolution of eosinophilic tissue infiltration in steroid-dependent patients
Azathioprine/6-mercaptopurine (73)	Immunomodulator, purine analog	Oral	Uncontrolled case series; 3 adults	Induction of histologic and clinical remission in steroid-dependent patients

Abbreviations: eos/hpf, eosinophils per high-powered field; Th2, T helper type 2; TNF-α, tumor necrosis factor–α.

as interval development of strictures. Potential long-term adverse effects with swallowed topical steroids appear uncommon but are being prospectively assessed in maintenance trials.

FUTURE ADVANCES AND CONCLUSIONS

EoE has grown from a clinical curiosity to a well-recognized entity that poses both diagnostic and therapeutic challenges. The last two decades of EoE research have helped to not only define the disease pathogenesis but also advance different areas of treatment including topical corticosteroids, diet therapy, and biologic therapy. Management guidelines are evolving with an improved understanding of disease characteristics and phenotypic as well as genotypic subtypes. Despite this, there are currently no FDA-approved medications for EoE. While novel therapies are on the horizon, office-based techniques that will reduce the burden of repeated endoscopy are in development to assess EoE activity. Serologic and in vitro assays are being developed to identify specific food triggers and should replace the use of empiric elimination strategies. Ongoing research is also advancing the understanding and management of eosinophilic gastrointestinal disorders beyond the esophagus. Further investigations will lead to the implementation of personalized medicine that addresses heterogeneous patient populations.

DISCLOSURE STATEMENT

Dr. Nirmala Gonsalves serves on the advisory board for Allakos and receives royalties from Up to Date. Dr. Ronak V. Patel has nothing to disclose. Dr. Ikuo Hirano has served as a consultant for Adare, Allakos, Arena, AstraZeneca, EsoCap, Gossamer, Receptos, Regeneron, and Shire Pharmaceuticals. He has received research funding from Adare, Allakos, Receptos, Regeneron, and Shire Pharmaceuticals.

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