CME

ACG Clinical Guideline: Diagnosis and Management of Eosinophilic Esophagitis

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Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease of the esophagus. It is diagnosed in the setting of symptoms of esophageal dysfunction and an eosinophilic predominant infiltrate in the esophagus. The condition is rapidly increasing in incidence and prevalence and is commonly encountered in gastroenterology and allergy practices, emergency departments, and primary care settings. Over the past decade, there have been paradigm shifts in disease diagnosis and management, increases in knowledge about EoE risk factors, natural history, and pathogenesis, and development of validated outcome metrics. This updated American College of Gastroenterology Clinical Guideline uses Grading of Recommendations, Assessment, Development, and Evaluation methodology to make recommendations across domains of diagnosis, treatment, monitoring and assessment of response, and pediatric-specific considerations. Proton pump inhibitors, topical steroids, empiric diet elimination, a biologic, and esophageal dilation are all recommended treatments; feeding therapy is used adjunctively in children with food aversion or feeding dysfunction. Monitoring with clinical, endoscopic, and histologic assessments is recommended to assess for treatment response and follow patients over time with maintenance therapy. When evaluating and following patients with EoE, consideration should be given to assessing and controlling both the inflammatory and fibrostenotic aspects of disease.

KEYWORDS: eosinophilic esophagitis; eosinophilic oesophagitis; treatment; monitoring; pediatrics; maintenance thearpy; diet elimination; proton pump inhibitors; topical steroids; biologics; dilation

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic allergen-induced, type 2 immune-mediated disease of the esophagus characterized by symptoms of esophageal dysfunction and an eosinophilic predominant infiltrate in the esophagus (1–5). The condition is rapidly increasing in incidence and prevalence (6,7), likely because of environmental factors interacting with genetic and epigenetic changes (8). These increases have outpaced endoscopy and biopsy rates and led to a substantial healthcare burden (9–13). What was once a case-reportable and rare disease (14,15) has become a frequently encountered condition in gastrointestinal (GI) and allergy practices, in the emergency department presenting as food impactions, and in the endoscopy suite. It is also likely that we are just seeing the "tip of the iceberg" of EoE cases (16).

This American College of Gastroenterology (ACG) Clinical Guideline is an update of the 2013 version (17). Since that time there have been paradigm-shifting changes in disease diagnosis and management, increases in knowledge about EoE risk factors, natural history, and pathogenesis (18–23), development of validated outcome metrics (24–30), a disease severity classification system (31), and updated nomenclature (32). EoE has been established as an adaptive immune T-cell–mediated type-2

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inflammatory disease, initiated when allergens interact with and penetrate an esophageal barrier that has intrinsic or acquired defects, with eosinophils acting as one of a number of pathogenic effector cells that lead to clinical manifestations of inflammation, remodeling, and fibrosis (18,21,33,34). In the setting of diagnostic delay, untreated or incompletely treated disease, or gaps in care, EoE progresses from an inflammatory to a fibrostenotic phenotype in most, but not all, patients (35–39). From the standpoint of diagnosis, the previous ACG guidelines focused on the controversy related to proton pump inhibitor (PPI) responsive esophageal eosinophilia (PPI-REE) and required failure of a PPI trial before definitive EoE diagnosis (17). However, new data have changed this framework (40), with subsequent consensus guidelines clarifying and streamlining the diagnostic algorithm, eliminating the PPI trial, and positioning PPIs as a treatment for EoE rather than a diagnostic criterion (3,41–43). From the treatment standpoint, there have been major advances in therapeutic options with an explosion of clinical trials (44), culminating in 2 topical steroids and 1 biologic being approved for EoE and with a robust pipeline of novel candidate therapies (45–47), as well as a larger body of data on dietary interventions (48). Because EoE is chronic, treatment generally must be long term.

In writing these updated guidelines, we aimed to create practical and evidence-based recommendations that encompassed major changes in the field, but that were also actionable and applicable across the range of patients with EoE and practice settings (Table 1). In doing so, we also tried to reinforce existing and recently published consensus statements (49–52), when appropriate, because some detailed aspects of EoE care were beyond the scope of this guideline. Since much of day-to-day practice is not supported by extensive evidence, we also present a set of key concepts to accompany the recommendations, which provide additional practical suggestions and expert opinion (Table 2). Finally, these guidelines are established to support clinical practice and suggest preferable approaches to a typical patient with EoE based on the currently available published literature. When exercising clinical judgment, particularly when treatments pose risks, healthcare providers should incorporate this guideline in addition to patient-specific medical comorbidities, health status, and patient preferences to arrive at a patient-centered care approach.

METHODS

The guideline panel members were selected based on their clinical, scientific, and methodological expertise. Panel members included adult (E.D., D.K., N.G., and I.H.) and pediatric (A.M. and G.F.) gastroenterologists and an allergist (S.A.), all with expertise in the diagnosis and treatment of EoE, and 2 methodologists (B.S. and S.S.) with expertise in Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). The full guideline panel met at regular intervals to develop clinically relevant questions structured as Population, Intervention, Comparison, and Outcome (PICO) statements that were amenable to systematic review. The PICO questions encompassed a range of topics related to EoE diagnosis, management, maintenance therapy, monitoring, and considerations for pediatric patients. These were iteratively refined to a final set for evidence review. A qualified medical librarian conducted the systematic review for each of the *a priori* PICO questions using PubMed (see Supplementary Appendix, Supplementary Digital Content 1, http://links.lww.com/AJG/D461 for search strategies). The medical librarian also manually searched the references of any systematic reviews and meta-analyses and cross-checked the output with a list of known randomized clinical trials (RCTs) and other studies provided by the guideline authors; these added checks further maximized literature capture. For treatment-related PICOs, and because a formal meta-analysis was beyond the scope of this guideline, we used the recently updated Cochrane systematic review and meta-analysis of EoE treatment trials, which included 41 RCTs in the field and included a comprehensive literature search that was up to date through March 3, 2023 (44). We then updated the literature search from that date forward to ensure that any new therapeutic trials were included in this guideline. For all other PICOs, PubMed was searched since inception. After the literature search was complete, the content authors identified the studies with the highest level of evidence most pertinent to each of the PICO questions and provided these to the GRADE methodologists for the formal level of evidence assessment.

This guideline document is structured in the format of recommendations and key concepts considered to be clinically important by the content authors. The GRADE process was used to assess the quality of evidence for each recommendation statement (Table 3) (53–56). The quality of evidence is expressed as high (we are confident in the effect estimate to support a particular recommendation), moderate, low, or very low (we have very little confidence in the effect estimate to support a particular recommendation) and is determined based on 5 parameters: the risk of bias of the studies; evidence of publication bias; heterogeneity among studies; directness of the evidence; and precision of the estimate of effect (54). The strength of the recommendation is expressed as either strong (recommendations) or conditional (suggestions) based on the quality of evidence, risks vs benefits, feasibility, and costs, additionally considering perceived patient and population-based factors (55). We also highlighted key concepts, which are statements that are not amenable to the GRADE process, either because of the structure of the statement or the available evidence (or lack thereof). In some instances, key concepts are based on extrapolation of evidence and expert consensus. Key concepts are framed as "advice" or "considerations" and often include definitions, epidemiological statements, or clinical approaches, rather than diagnostic or management recommendations. A narrative summary of evidence for each section provides important details for the data and rationale supporting the recommendation and key concept statements. Table 1 provides a summary of recommendations, and Table 2 provides a summary of the key concepts discussed in this guideline document.

DIAGNOSIS OF EOE

Recommendation

1. We recommend that EoE is diagnosed based on the presence of symptoms of esophageal dysfunction and at least 15 eosinophils per high-power field (eos/hpf) on esophageal biopsy, after evaluating for non-EoE disorders that cause or potentially contribute to esophageal eosinophilia (quality of evidence: low; strength of recommendation: strong).

Summary of evidence. Although the diagnostic approach to EoE has evolved since the first guidelines in 2007 (1–3,17,41), the conceptual definition of the condition is the same: EoE is an allergen/immune-mediated clinicopathologic condition characterized clinically by symptoms of esophageal dysfunction and

Table 1. EoE recommendations

Statement	Quality of evidence	Strength of recommendation
Diagnosis		
1. We recommend that EoE is diagnosed based on the presence of symptoms of esophageal dysfunction and at least 15 eos/hpf on esophageal biopsy, after evaluating for non-EoE disorders that cause or potentially contribute to esophageal eosinophilia	Low	Strong
2. We recommend using a systematic endoscopic scoring system (e.g., the EoE Endoscopic Reference Score) to characterize endoscopic findings of EoE at every endoscopy	Low	Strong
3. We recommend obtaining at least 6 esophageal biopsies from at least 2 esophageal levels (e.g., proximal/mid and distal), targeting EoE endoscopic findings, if possible, to assess for histologic features consistent with EoE	Low	Strong
4. We recommend that eosinophil counts be quantified on esophageal biopsies from every endoscopy performed for EoE	Low	Strong
Treatment		
PPIs		
5. We suggest PPIs as a treatment for EoE	Low	Conditional
Topical steroids		
6. We recommend the use of swallowed topical steroids as a treatment for EoE	Moderate	Strong
7. We suggest the use of either fluticasone propionate or budesonide in patients with EoE being treated with topical steroids	Low	Conditional
Dietary elimination		
8. We suggest an empiric food elimination diet as a treatment for EoE	Low	Conditional
9. We do not suggest currently available allergy testing to direct food elimination diets for treatment of EoE	Very low	Conditional
Biologics		
10. We suggest dupilumab as a treatment for EoE in individuals 12 years of age or older who are nonresponsive to PPI therapy	Moderate	Conditional
11. We suggest dupilumab as a treatment for EoE in pediatric patients (ages 1–11 years) who are nonresponsive to PPI therapy	Low	Conditional
12. We cannot make a recommendation for or against cendakimab, benralizumab, lirentelimab, mepolizumab, or reslizumab as a treatment for EoE	—	—
13. We suggest against using omalizumab as a treatment for EoE	Low	Conditional
Small molecules		
14. We suggest against the use of cromolyn and montelukast as a treatment for EoE	Very low	Conditional
Esophageal dilation		
15. We suggest the use of endoscopic dilation as an adjunct to medical therapy as a treatment for esophageal strictures causing dysphagia in patients with EoE	Low	Conditional
Maintenance therapy		
16. We suggest continuation of effective dietary or pharmacologic therapy for EoE to prevent recurrence of symptoms, histologic inflammation, and endoscopic abnormalities	Low	Strong
Monitoring and evaluation of response		
17. We recommend evaluating response to treatment of EoE with assessment of symptomatic and endoscopic and histologic outcomes	Low	Strong
Pediatric-specific considerations		
18. In children with EoE and dysphagia, we suggest an esophagram for evaluation of fibrostenotic disease	Very low	Conditional
19. We suggest evaluation by a feeding therapist and/or dietician as an adjunctive therapeutic intervention in children with EoE and feeding dysfunction	Very low	Conditional

EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; PPI, proton pump inhibitor.

Table 2. Key concepts in EoE diagnosis and management

Key concept	Comment
Diagnosis	
We advise eliciting a careful history of symptoms of esophageal dysfunction, including dietary avoidance and modification behaviors	These behaviors can mask the severity of symptoms
Providers should consider assessing for features that may increase risk of EoE including multiple atopic disease and family history	This may help detect otherwise unsuspected EoE cases
We advise performing endoscopy on no treatment (e.g., no dietary restriction and no PPI) when EoE is suspected to maximize diagnostic sensitivity	Diet and medications, including intranasal or inhaled steroids for rhinitis, sinusitis, or asthma, may partially or completely treat EoE and lead to a falsely negative examination
Providers should consider obtaining information on other EoE histologic features in addition to the eosinophil count	Features such as basal zone hyperplasia, dilated intercellular spaces, and lamina propria fibrosis can indicate ongoing disease activity even in the absence of prominent eosinophilia
Providers could consider assessing baseline EoE disease severity with the I-SEE	In the future, this tool may be used to help standardize management and monitoring strategies
Treatment	
PPIs	
We advise "high-dose" PPI use for EoE treatment	
We advise providers to counsel patients as to the rationale for PPI use in EoE	Patients without heartburn or reflux symptoms could be confused as to why a PPI is prescribed without this explanation
Topical steroids	
We advise that induction with swallowed topical steroids with budesonide and fluticasone improve symptoms, histology, and endoscopic disease activity in adolescents and adults with EoE	Options for swallowed topical steroids include the EMA-approved budesonide orodispersible tablet and FDA-approved budesonide oral suspension as well as off-label use of asthma preparations adapted for esophageal delivery
We advise administration of topical steroids after meals or before bedtime with nothing to eat or drink after 30–60 minutes to help maximize medication dwell time in the esophagus	If patients drink or eat right after medication administration, the medication will be cleared from the esophagus and will be less effective
In young children, providers should consider use of a slurry or suspension, rather than an inhaler device	Inhaler devices can be difficult for young children to use correctly
Diet elimination	
Providers may consider starting with a less-restrictive empiric elimination (i.e., 1FED or 2FED) as the initial diet therapy choice	Patient preference for diet selection should be incorporated in a shared decision-making process
We advise providers to collaborate with a dietician or nutritionist for patients undergoing dietary elimination	Dieticians can help with education, label reading and contaminant avoidance, food substitutions, meal planning, and other activities to help maximize success and adherence
After an initial response to dietary elimination, we advise a structured food reintroduction process	A food reintroduction process is needed to identify food triggers
Symptoms should not be used in isolation to determine food triggers	Endoscopy with biopsy is required after each food is reintroduced to assess whether eosinophilia has recured
Biologics	
We advise providers to use dupilumab as step-up therapy in difficult-to-treat patients, and providers should consider using it in patients with EoE with multiple atopic conditions that would also meet requirements for dupilumab use	The position of dupilumab in the EoE treatment algorithm is being determined
Esophageal dilation	
We advise endoscopists to have a high level of suspicion for strictures and esophageal narrowing in EoE, especially in patients with dysphagia or dietary avoidance/modification behaviors	Strictures and luminal narrowing can be difficult to detect on endoscopy
We advise a "start low and go slow" approach for esophageal dilation	Table 7 outlines a general approach for performing dilation
We advise that dilation be combined with an anti-inflammatory treatment	Dilation does not impact the underlying inflammatory disease activity in EoE

Table 2. (*continued*)

Key concept	Comment
Maintenance therapy	
We advise providers to counsel patients that because EoE is chronic, disease activity almost universally recurs when treatment is stopped	This provides a clinical rationale for maintenance treatment
For patients on pharmacologic treatments, providers should consider identifying the lowest effective dose for long-term use	Any dose reduction decision should be individualized
Monitoring and evaluation of response	
We advise providers to not monitor symptoms alone in patients with EoE to assess treatment response	Monitoring symptoms alone is not sufficient in EoE as symptoms do not strongly correlate with endoscopic or histologic features of disease activity
Providers may consider using a histologic response threshold of <15 eos/hpf	The improvement in eosinophil count should be considered in the context of improvement of other histologic features, endoscopic findings, and symptoms
Providers may consider monitoring for adrenal insufficiency in selected patients with EoE on topical steroids for EoE and steroid medications for other conditions	Topical steroid monotherapy is unlikely to lead to clinically important adrenal insufficiency
Pediatric-specific considerations	
We advise that growth (height and weight), development (including eating skills), and nutrition (proper intake of nutrients) are treatment goals in children with EoE	These goals are in addition to symptomatic, endoscopic, and histologic improvement goals
Providers should consider quality of life of both the patient and family in selecting the management plan for children with EoE	These considerations will likely impact feasibility as well as adherence

1FED, single-food elimination diet; 2FED, 2-food elimination diet; EMA, European Medicines Agency; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; FDA, US Food and Drug Administration; PPI, proton pump inhibitor.

histopathologically by a marked esophageal eosinophilic infiltrate. The current diagnostic criteria were established by international consensus during the AGREE (A Working Group on PPI-REE) Conference and are reinforced by other guideline-making bodies (3,42,43); we reinforce that consensus here. Although it is beyond the scope of this guideline to review the full

Table 3. Grading of Recommendations, Assessment, Development, and Evaluation: strength of recommendations, quality of evidence, and implications for the patients and clinicians (54,56)

Strength of recommendation	Criteria
Factors influencing the strength of the recommendation include the quality of the evidence, clinical and patient-reported outcomes, risk of harm, and costs/healthcare resource utilization	
Strong	Strong recommendations are offered when the desirable effects of an intervention clearly outweigh the undesirable effects Implications from a patient and clinician perspective: *Patients*: Most individuals in this situation would prefer the recommended course of action and only a small proportion would choose an alternative *Clinicians*: Most patients should receive the recommended course of action or an alternative with similar strength of recommendation
Conditional	Conditional recommendations are offered when trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced Implications from a patient and clinician perspective: *Patients*: Some individuals would want the suggested course of action, whereas others may not. A discussion regarding pros, cons, and available alternatives is appropriate to reach an individualized patient-specific decision *Clinicians*: A shared decision-making model through a discussion regarding the available evidence and alternative options is appropriate, taking into consideration the values and preferences of the patient
Quality of evidence	**Criteria**
High	We are very confident that the true effect closely aligns with that of the estimate of the effect
Moderate	We have a moderate level of confidence in the estimate of effect. It is likely that the true effect is close to the estimate of the effect
Low	Our confidence in the effect estimate is limited. The true effect could differ from the estimate of effect
Very low	We have very little confidence in the effect estimate. The true effect may be substantially different from the estimate of effect

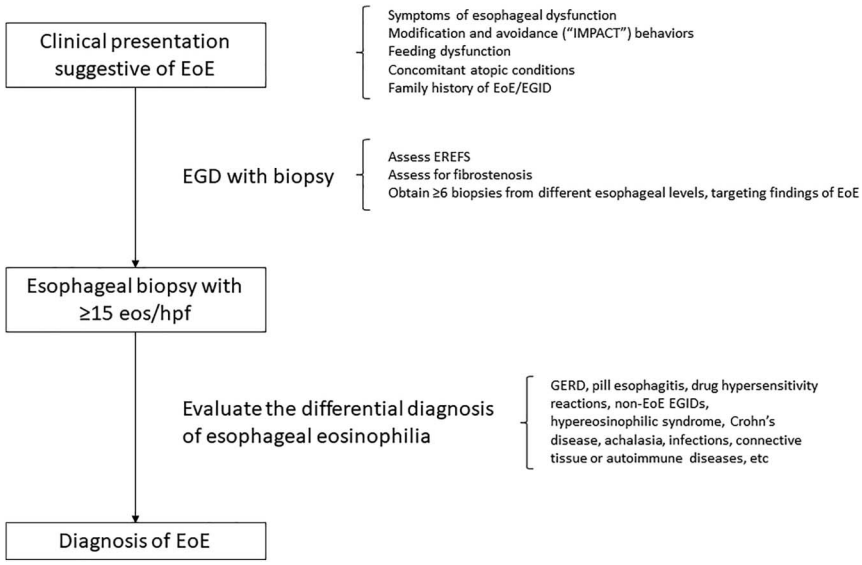

Figure 1. Diagnostic algorithm for EoE. EGD, esophagogastroduodenoscopy; EGID, eosinophilic gastrointestinal disease; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; EREFS, EoE Endoscopic Reference Score; GERD, gastroesophageal reflux disease.

evidence base supporting the diagnostic guidelines, the critical change since the 2013 ACG guidelines was to eliminate the requirement for a PPI trial for EoE diagnosis and to remove the term PPI-REE. This was based on extensive data showing that before treatment, patients who responded to PPIs were similar clinically, endoscopically, histologically, immunologically, and molecularly to patients with EoE without PPI response (40,57–64), and that PPIs were likely treating EoE through novel mechanisms independent of gastric acid suppression alone (65–68).

EoE is diagnosed with the following 3 criteria: (i) symptoms of esophageal dysfunction; (ii) at least 15 eos/hpf on esophageal biopsy; and (iii) an evaluation for non-EoE disorders that cause or potentially contribute to esophageal eosinophilia (Figure 1). For the first step, symptoms vary by age (69–72). In adolescents and adults, dysphagia and food impaction are most common, although heartburn and chest pain can be present as well. In infants and younger children, poor growth, failure to thrive, feeding intolerance, failure to progress to solid foods, increased time needed for eating, or food refusal can be seen, and in school-aged children, abdominal pain, vomiting, regurgitation, and heartburn are common. All symptoms of EoE are nonspecific and have a broad differential diagnosis. However, special attention should be paid when eliciting symptoms of dysphagia because patients can use food avoidance and modification behaviors to minimize these symptoms over long periods, leading to diagnostic delays (73–78). This avoidance may be carried to the level of an avoidant/restrictive food intake disorder (79,80). Providers can use the "IMPACT" acronym to assess for these types of behaviors (Table 4), and in pediatrics, detailed questioning can help to elucidate vomiting vs regurgitation vs dysphagia (see pediatric section, below) (81). It should be considered that food refusal, increased time to complete meals, and regurgitation in children could be signs of occult dysphagia that are difficult to elicit because of chronologic or developmental age. Other subtle EoE-related symptoms include meal-triggered chest pain and prompt esophageal regurgitation of swallowed food.

In addition to symptoms, the presence of other atopic diseases, including immediate-type food allergies, asthma, eczema (atopic dermatitis), and allergic rhinitis, should increase the suspicion of EoE. At least 60%–80% of patients with EoE will have concomitant allergic conditions, but the more atopic comorbidities a patient has, the more likely they are to have EoE (82–84). Notably, 1 study found that more than a third of patients seen in allergy clinics have unrecognized dysphagia or other typical EoE symptoms (85), although no data yet exist to support screening in this population. Like atopy, having a family history of EoE should increase the clinical suspicion for EoE in a symptomatic patient because it can cluster in families with family members of known EoE cases often having unrecognized esophageal symptoms (86). Although other environmental and early life risk factors have been established for EoE (87–94), there are no data to support screening or prevention in higher risk groups. To aid with diagnosis, several clinical prediction tools have been developed that have a high level of discrimination between patients with vs without EoE (95–100), and a new tool to assess disease severity in EoE, the Index of Severity in EoE (I-SEE), has been developed and is undergoing validation for clinical use (31,101,102).

Recommendation

2. We recommend using a systematic endoscopic scoring system (e.g., the EoE Endoscopic Reference Score [EREFS]) to characterize endoscopic findings of EoE at every endoscopy (quality of evidence: low; strength of recommendation: strong).

Summary of evidence. Endoscopic evaluation is critical in EoE for diagnosis, assessing treatment response, and long-term monitoring of disease activity. Typical findings of EoE include edema (decreased vascularity), fixed esophageal rings, white exudates, linear furrows, strictures, luminal narrowing, mucosal fragility ("crepe-paper mucosa"), and mucosa that feels firm when biopsies are acquired ("tug" or "pull" sign) in patients with

Table 4. "IMPACT" behaviors to assess while taking a dysphagia history

Behavior	Description
Imbibe fluids	Drinking a lot of liquids to help get each bite down smoothly
Modify foods	Cutting foods into small pieces or pureeing foods
Prolong meal times	Eating slowly and being the "last one at the table"
Avoid hard texture foods	Meats, crusty breads, and foods with sticky consistencies are often removed from the diet to minimize symptoms
Chew excessively	Thorough chewing to achieve a mush-like consistency to allow easier swallowing
Turn away tablets/pills	Pill dysphagia is a subtle symptom of EoE and may be the only indication of swallowing dysfunction

EoE, eosinophilic esophagitis.
Adapted from Hirano and Furuta. Gastroenterology. 2020;158(4):840–51 (81).

fibrosis (29,103–109). Although these findings are not pathognomonic and, therefore, are not a formal diagnostic criterion, 1 or more are nearly universally present when specifically assessed and substantially raise the suspicion of EoE (106,110,111).

A careful endoscopic examination is mandatory for all suspected esophageal diseases, and for EoE, this includes taking substantial time to visualize the entire esophagus after intubation (so as not to rub off or displace exudates), fully insufflating the esophagus, gently washing off mucous, saliva, or debris, and gauging esophageal caliber (112), which can include retroflexion at the gastroesophageal junction to estimate stricture diameter in this area (see dilation section, below).

A critical aspect of the examination is assessing EoE findings using the EREFS (29), a recommendation also endorsed by recent guidelines by the American Society for Gastrointestinal Endoscopy (ASGE) (49). EREFS specifically classifies 5 key EoE features by severity, including edema, rings, exudates, furrows, and strictures. These features are graded by severity, with a scheme yielding a score range of 0–9, with each feature scored by the worst appearing area of the esophagus (Figure 2). EREFS has been validated internally and externally (29,113,114), has been shown to distinguish EoE from non-EoE disorders with high discrimination in both children and adults (110,111,115), and correlates with treatment response as seen in multiple clinical trials (45–47,116–121). Thresholds for treatment response have also been proposed (122,123). Just as the Prague classification and the LA grade provide a common vocabulary for Barrett's esophagus and erosive esophagitis, respectively, EREFS provides this standard categorization for EoE and should be used in patients with suspected and established EoE.

Recommendation

3. We recommend obtaining at least 6 esophageal biopsies from at least 2 esophageal levels (e.g., proximal/mid and distal), targeting EoE endoscopic findings, if possible, to assess for histologic features consistent with EoE (quality of evidence: low; strength of recommendation: strong).

Summary of evidence. EoE is a patchy disease histologically (124). Previous studies have shown marked variability in eosinophil counts both between and within biopsies, with some microscope fields appearing normal and others appearing highly inflamed

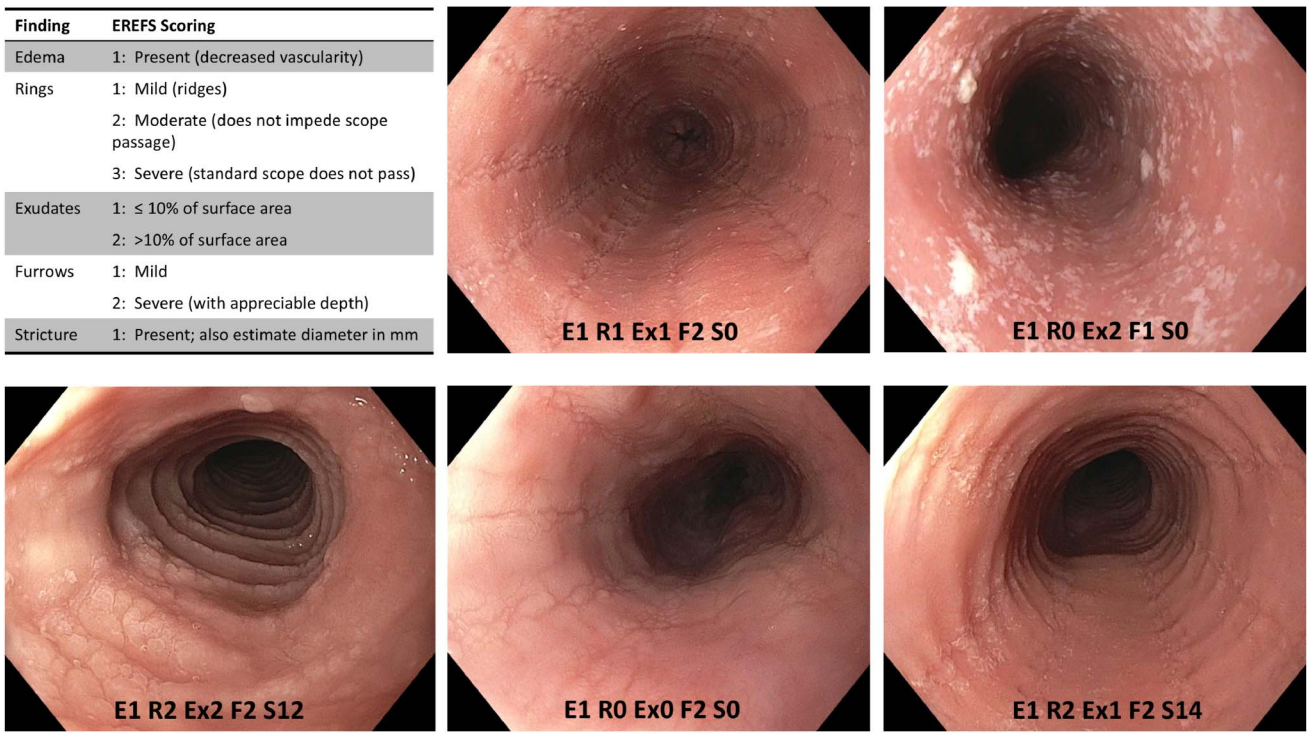

Figure 2. EREFS with example scoring. EREFS, EoE Endoscopic Reference Score.

(125,126). Therefore, it is possible to miss the diagnosis if too few biopsies are obtained. Previous studies have demonstrated that with 6 or more biopsies, the diagnostic sensitivity approaches 100% (127,128). In addition, targeting biopsies in areas of endoscopic findings of furrows or exudates, rather than normal-appearing areas, will increase the biopsy yield for diagnosis (129). From a practical standpoint, obtaining at least 2–4 biopsies from at least 2 distinct esophageal areas (typically the proximal and distal halves of the esophagus), while targeting areas of visual inflammation (if present), is the preferred approach (3,49). In addition, it is important to obtain biopsies at the time of food impaction when urgent or emergent endoscopy is performed, which can be performed safely after the bolus is cleared, a practice endorsed by ASGE guidelines (49,130–134). Since patients are frequently lost to follow-up after food impactions and biopsy rates at this time are traditionally low, the diagnosis of EoE may be missed or delayed if biopsies are not obtained at that time (130).

Recommendation

4. We recommend that eosinophil counts be quantified on esophageal biopsies from every endoscopy performed for EoE (quality of evidence: low; strength of recommendation: strong).

Summary of evidence. As the established diagnostic biomarker for EoE, it is important to quantify the peak eosinophil counts from esophageal biopsies obtained in patients with suspected or established EoE. Although the threshold of 15 eos/hpf in at least 1 hpf is used for diagnosis (3), more detail than ">15 eos/hpf" is needed for subsequent patient management. Although the exact eosinophil count is not necessarily associated with disease severity (e.g., a patient with 200 eos/hpf is not twice as symptomatic or severe as a patient with 100 eos/hpf), for subsequent monitoring, it is important to know, e.g., if a patient has gone from 200 to 150 eos/hpf, or from 200 to 20 eos/hpf after treatment to gauge the anti-inflammatory effect. Although all 4 of these samples could be read out as >15 eos/hpf without quantification, in the latter case, there may be a substantial treatment response, and in the former case, there is no important histologic response. An additional point about eosinophil counts is that they can vary by the size of the microscope high-power field used such that a given eosinophil density (in eos/mm^2) can yield different counts based on the hpf size (135). Therefore, it may be preferable to report eosinophil density for consistent comparisons across studies and clinical settings (in which case, the diagnostic threshold is ~60 eos/mm^2), although this change has not currently been made in practice.

Although the eosinophil has traditionally been the cell of focus in EoE given that it is readily visible on standard hematoxylin and eosin staining, it is just one of many cells infiltrating the esophagus in EoE. There is now extensive literature on the role of mast cells in EoE, T cells of several subtypes, basophils, NK cells, and fibroblasts (136–150). In addition, results from recent trials of eosinophil-depleting agents (see below) have shown ongoing clinical symptoms and endoscopic signs of EoE despite depletion of eosinophils (151,152), suggesting that EoE is not an eosinophil-dependent disease in some cases, which has also been corroborated by recent animal model work (153,154).

There is, therefore, ongoing interest in clinically evaluating other histologic findings associated with EoE. The EoE Histologic Scoring System (EoEHSS) assesses the severity (grade) and extent (stage) of 8 histologic features, only 1 of which is degree of eosinophilic infiltration (30). Although the EoEHSS has primarily been used as a clinical trial metric (155–158), there is an expanding body of literature highlighting the importance of findings such as persistent basal zone hyperplasia or lamina propria fibrosis as drivers of ongoing symptoms despite decreases in eosinophil counts (138,159–161). Thus, reporting whether these features are present or absent with EoEHSS could become important clinically in the future.

MANAGEMENT

The goals of EoE treatment are to improve patient symptoms and quality of life, improve or normalize the endoscopic and histologic appearance of the esophagus, normalize growth and development in children, maintain nutrition, and prevent complications such as food impaction, esophageal stricturing, and perforation. To do this, both the inflammatory and fibrostenotic aspects of the disease need to be addressed. Pharmacologic or dietary therapies can treat the inflammatory component and can also lead to improvements in esophageal caliber (162). Esophageal dilation is used to treat strictures and luminal narrowing. Because the field lacks comparative efficacy clinical trials for the different treatment approaches, the decision of which treatment to use is individualized based on disease characteristics and patient preference using a shared decision-making framework (163). In general, we advise that a single anti-inflammatory therapy is initially selected, and treatment response is assessed by clinical, endoscopic, and histologic disease activity. A suggested treatment and monitoring algorithm is presented in Figure 3, and specific details about monitoring and outcomes are also discussed below.

Proton pump inhibitors

Recommendation

5. We suggest PPIs as a treatment for EoE (quality of evidence: low; strength of recommendation: conditional).

Summary of evidence. The rationale for using PPIs for treatment of EoE goes beyond the antisecretory effect. PPIs have multiple effects beyond blocking the proton pump (164), and in EoE, several potential novel mechanisms have been described, including decreasing expression of eotaxin-3 (the main cytokine that recruits eosinophils to the esophagus) (65,66), improving esophageal barrier function (67), and helping to maintain esophageal epithelial transcriptional homeostasis (68). It is important to explain this rationale for PPI use to patients with EoE, so they are not confused by the well-known reflux indication of this medication class and in turn have compromised adherence, e.g., because of lack of reflux symptoms.

In terms of efficacy, 2 small, randomized trials have assessed PPIs for the treatment of EoE in comparison with a topical steroid, but no studies have compared PPIs with placebo. In the first trial, 30 adult patients with EoE were randomized to esomeprazole 40 mg daily or fluticasone 440 μg by mouth twice a day swallowed from an inhaler for 8 weeks (165). Esomeprazole led to a significant decrease in eosinophil count (45.8 ± 30.7 to 22.1 ±

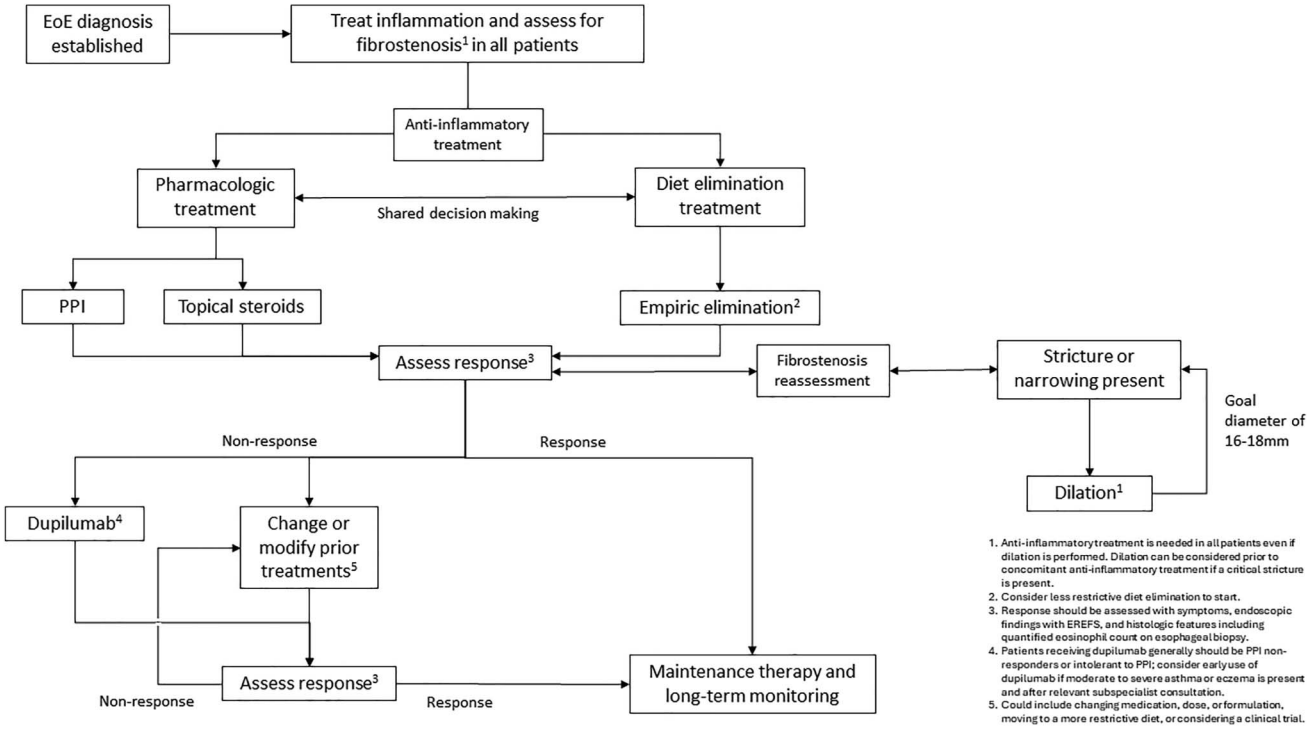

Figure 3. Management algorithm for EoE. After the diagnosis of EoE is established, all patients should be treated for inflammation and, in a parallel process, be assessed for whether fibrostenosis is present. Specific anti-inflammatory treatment is chosen and whether esophageal dilation should be performed is determined. Response assessment and follow-up for maintenance therapy and monitoring should be structured. EoE, eosinophilic esophagitis; EREFS, EoE Endoscopic Reference Score; PPI, proton pump inhibitor.

20.6 post-treatment; $P = 0.02$), which was generally similar to the effect of fluticasone. Dysphagia symptoms, as measured by a nonvalidated score, demonstrated a nonsignificant decrease. In the second trial, 42 adults with EoE were also randomized to esomeprazole 40 mg daily or fluticasone 440 μg swallowed from an inhaler twice daily for 8 weeks (166). There was no significant change in the biopsy eosinophil count in the esomeprazole group (42.9 ± 18.9 vs 30.5 ± 33.7; $P = 0.17$), but 33% of patients reached the endpoint of <7 eos/hpf. Dysphagia symptoms, measured with the Mayo Dysphagia Questionnaire score, significantly improved with esomeprazole therapy (19 ± 21 vs 1.4 ± 4.5 $P = 0.001$). Similarly, there was an improvement in endoscopic signs of EoE, including stenosis, rings, furrows, and plaques without statistical analysis performed; the trial was performed before development of EREFS.

With respect to pediatric patients with EoE, 1 study randomized 64 children to omeprazole 1 mg/kg twice daily (max dose 20 mg twice daily) plus a 4-food elimination diet (4FED; cow's milk, soy, egg, and wheat) vs omeprazole monotherapy for 8–12 weeks (167). Eosinophil count was reduced in the omeprazole-only group from 44.5 to 12 eos/hpf, but the effect of omeprazole on symptoms or endoscopic findings was not reported. No trials have evaluated the combination of steroids and PPIs, although some topical steroid trials have patients with ongoing PPI use (168).

Numerous single-arm uncontrolled and observational studies have examined the use of PPIs in EoE (169). A systematic and meta-analysis performed in 2016 of 33 of these studies (11 prospective and 22 retrospective) across 188 children and 431 adults reported a pooled clinical response of 60.8% (95% confidence interval [CI] 48.38%–72.2%) and histologic remission (<15 eos/hpf) of 50.5% (95% CI 42.2%–58.7%) (170). PPIs were more effective in prospective than retrospective studies (52.6% vs 39.1%) and when administered twice daily compared with once daily (55.9% vs 49.7%), but without statistical significance. However, the types and doses of PPI used were not reported in most studies, but when reported, there was substantial variability in the specific PPI (omeprazole, n = 119; esomeprazole, n = 71; rabeprazole, n = 41; and lansoprazole, n = 5) as well as in doses, frequency, and treatment duration, limitations which precluded making definitive recommendation about specific PPI type or dosing.

From a practical standpoint, we suggest initial treatment for EoE with "high-dose" PPI, essentially using doses that are double the approved reflux dosing (Table 6), and either once daily or divided doses before meals can be used based on considerations of adherence because dosing efficacy data are variable. For example, a retrospective cohort study of 305 newly diagnosed patients with EoE receiving varying doses of omeprazole demonstrated an overall rate of histologic remission of 42.3%. Histologic remission was significantly higher with 20–40 mg twice daily dosing (53%–54%) than 20–40 mg once daily (10%–12%; $P < 0.0001$) (171). There are also data demonstrating that when the PPI dose is reduced to once daily in patients demonstrated to be in histologic remission on twice-daily dosing, 30% of initial responders relapsed but regained histologic remission after escalation of the PPI back to twice daily (172). By contrast, a prospective cohort study showed that >80% of PPI-responsive patients maintained histologic remission after stepping down from omeprazole 40 mg twice daily to 40 mg daily to 20 mg daily (173). Therefore, using once-daily doses in patients with EoE is certainly a possibility. For

example, in a study of 51 patients, there was a 61% histologic response rate to once-daily esomeprazole 40 mg, which is a PPI that is minimally metabolized by CYP2C19 (174). Finally, a lack of initial response to PPI does not necessarily indicate complete lack of response. Several studies have described partial response to PPIs in a subgroup of patients or use of PPIs after successful steroid therapy in initial PPI responders (175–177).

A key question is whether there are predictors of response to PPIs such that their use or avoidance can be personalized for initial medical therapy in patients with EoE. Although a meta-analysis found a trend toward greater efficacy of PPIs in patients with abnormal acid exposure on pH monitoring (170), the overall predictive value of abnormal pH monitoring to predict PPI response is low (174). The presence of gastroesophageal reflux disease also does not predict response to PPIs, and PPIs can be effective even in patients with proven response to steroids or diet elimination (178,179). Other factors studied that may mitigate against successful treatment with PPIs include the presence of allergic rhinitis (172), rapid CYP2C19 metabolism, although this may be overcome with PPI dose escalation (172,180), and *STAT6* polymorphisms (180–182). A predictive model identified younger age, lower body mass index (BMI), and higher blood eosinophil counts as additional risk factors for nonresponse (183).

Another clinical concern relates to adverse effects from long-term PPI use. A full discussion of PPI safety is beyond the scope of this guideline. However, although many potential adverse reactions have been reported, the relative risks of most of the reported complications are low enough such that confounding cannot be eliminated and many recent and well-conducted studies have not confirmed these associations. For example, the most comprehensive study, a randomized, double-blind trial examining PPI risks over a 10-year period in 17,598 participants did not find an increased risk in chronic kidney disease, dementia, pneumonia, bone fracture, chronic obstructive pulmonary disease, or diabetes mellitus (184). The only increased risk was associated with *Clostridium difficile* infection. As a result, the benefit of PPIs in EoE outweigh the risks, although providers prescribing PPIs for EoE should actively explore and discuss any concerns patients may have since unaddressed concerns could impact adherence.

Finally, a potassium-competitive acid blocker (PCAB) has been preliminary studied in EoE, but data are limited, and potential mechanisms are not clear (185). The largest study, performed in Japan, was a retrospective analysis of 118 patients either treated with vonoprazan or PPIs (including rabeprazole 10 mg, rabeprazole 20 mg, and esomeprazole 20 mg) (186). Patients in the PCAB group achieved a 72.7% symptomatic response, a 2-point reduction in EREFS, and complete histologic remission in 39.4%, which was overall similar to the results obtained with PPIs. Based on these data, PCABs will likely be formally studied in EoE. There are no data to suggest that H2 receptor blockers have efficacy in EoE.

Topical steroids

Recommendation

6. We recommend the use of swallowed topical steroids as a treatment for EoE (quality of evidence: moderate; strength of recommendation: strong).

Summary of evidence. Swallowed topical corticosteroids (STCs) were the first medical therapy for EoE with clinical effectiveness reported in a small, pediatric case series in 1998 (187). The concept was to coat the esophagus with an anti-inflammatory medication, analogous to how a steroid cream might be applied to the skin in atopic dermatitis. This initial report was followed by larger retrospective and prospective trials and ultimately publication of over 13 randomized, double-blind, placebo-controlled clinical trials in children and adults with EoE (45,46,116–119,168,188–194). Most trials excluded patients with response to PPI therapy. Every STC trial, regardless of whether budesonide or fluticasone was used, demonstrated significant histologic efficacy compared with placebo, with meta-analyses estimating response rates in the 60%–70% range, although heterogeneity in the degree of response exists (44,52,195). Focusing on recent phase 3 trials of STC, histologic efficacy, defined by achieving <15 eos/hpf, ranged from 62% to 95% for trials of budesonide oral suspension (BOS, 2 mg b.i.d.) and budesonide orodispersible tablet (BOT, 1 mg b.i.d.) formulations, respectively (45,46). BOS was approved for EoE by the US Food and Drug Administration (FDA) in 2024, and BOT was approved for EoE by the European Medicines Agency in 2018. A third pharmaceutical agent developed for EoE, fluticasone propionate orally disintegrating tablet, reported histologic response (<15 eos/hpf) in 75% (3 mg QHS) to 95% (1.5 mg b.i.d.) in a phase 2b clinical trial (119). This agent is currently in phase 3 clinical trials (NCT04281108 and NCT05634746). The reasons for the variable histologic response using agents developed for esophageal delivery are unclear, but histologic and symptomatic inclusion criteria varied as did the duration of treatment (6–12 weeks), concomitant use of PPI therapy or topical steroids for non-EoE indications, prevalence of previous exposure to off-label STC formulations for EoE, and previous use of esophageal dilation. Although meaningful comparisons are not possible owing to the differences in study designs, off-label use of asthma preparations of corticosteroids adapted for esophageal delivery have comparable histologic efficacy with preparations designed for esophageal delivery (44,52,195).

Although most, but not all, placebo-controlled trials of STC demonstrated significant improvement in symptoms of dysphagia, the response rates were variable. Early studies of STC that failed to demonstrate symptom improvement used nonvalidated patient-reported outcome (PRO) instruments and were underpowered owing to the sizable placebo symptom-response rates common to trials in EoE (190,192). Comparisons of symptom responses related to different formulations of STC are not possible, given the different PROs used by the trials. By contrast, endoscopic improvement using EREFS has uniformly been achieved in phase 2 and 3 RCTs. Of note, most of the industry-supported, placebo-controlled trials of STC have been in adolescent and adult populations because of the challenges with symptom measurement in children. Nevertheless, the histologic response rate in pediatric studies has been comparable with adult studies (44).

STCs have demonstrated an overall favorable safety profile. The most common side effect of STC is oral and/or esophageal candidiasis. Again, focusing on phase 3 trials of STC developed for esophageal delivery, the rates of candidal infection range from 3.8% for BOS to 23.7% for BOT (45,46). Of note, many cases of suspected candidal infection were not confirmed on histology, and most patients were asymptomatic. Management options

include intermittent use of antifungal agents (topical clotrimazole or oral fluconazole), dose reduction of STC, or cessation of STC depending on the presence of associated symptoms and severity. Interestingly, 1 report notes a correlation of steroid effectiveness to the occurrence of candidal esophagitis (196). Adrenal insufficiency is uncommon, identified in ≤5% in induction trials of BOS and BOT in adults and a large pediatric observational study (197). A systematic review that included randomized controlled trials as well as retrospective and prospective observational studies with varying length of exposure to STC noted an overall rate of adrenal insufficiency of 15.8% (198). The definition of adrenal dysfunction varied by studies with some using morning cortisol and others using adrenocorticotropic hormone stimulation testing. Regardless, symptom manifestations of adrenal insufficiency are even less common across trials of STC (199). The low occurrence of adrenal dysfunction in placebo-controlled induction trials is not surprising, given the short duration of exposure (6–12 weeks) and limited bioavailability of the agents studied. Based on these data, testing for adrenal function is not necessary for short-duration use but might be considered for continuous, long-term administration or in patients on multiple corticosteroid formulations (see monitoring section, below).

For this recommendation statement, the quality of evidence regarding STC for histologic improvement and remission is high, but for other endpoints (e.g., clinical response), the evidence is moderate or borderline low/moderate; data are also more extensive for adults/adolescents as compared to children. Thus, considering the safety profile of STC, the strength of this recommendation was rated strong with moderate quality of evidence.

That said, cost and access remain important considerations for patients particularly now with the FDA and European Medicines Agency approval of formulations of budesonide. Off-label use of fluticasone and budesonide suspension by prescription or compounding pharmacies remain options (200–202). For suspension preparations, the concentration of budesonide as well as volume and viscous properties of the vehicle (honey, sucralose, etc) may affect the effectiveness and have not been compared in trials. Although use of the powder packets of fluticasone contained in Diskus preparations is a more logical form for esophageal delivery than ingestion of the propellant from a meter-dose inhaler (MDI), a retrospective study using fluticasone powder did not demonstrate superiority compared with MDI in the basis of histologic efficacy (203).

Several studies have attempted to identify predictors of histologic response to STC, but there is no single marker that is currently used in practice. Esophageal dilation was found to be associated with nonresponse (204,205), and patients with what is termed the "extremely narrow caliber" esophagus have also been shown to have approximately a third of the odds of responding to steroids as those without this phenotype (206), although a proportion of these patients may ultimately be treated successfully (207). From the molecular standpoint, a single nucleotide polymorphism in the *TGF-β* gene was associated with nonresponse (208), but differences in gene expression have not identified single genes or multiple gene panels that can predict steroid response (209,210). However, a set of differentially methylated genes was identified and then independently validated to predict nonresponse (211,212), but this is not currently available for routine clinical use.

Recommendation

7. We suggest the use of either fluticasone propionate or budesonide in patients with EoE being treated with topical steroids (quality of evidence: low; strength of recommendation: conditional).

Summary of evidence. There is 1 comparative efficacy study examining the 2 most common formulations of STC used in EoE before the development of the esophageal-specific agents—budesonide mixed into a slurry (oral viscous budesonide [OVB]) and fluticasone swallowed from an MDI (213). In this randomized, double-blind, double-dummy, clinical trial, newly diagnosed patients with EoE (who were primarily PPI nonresponsive) either received OVB 1 mg b.i.d. plus a placebo inhaler (n = 56), or fluticasone inhaler 880 μg b.i.d. plus a placebo slurry (n = 55) over an 8-week treatment period. Although patients in each group had favorable histologic, endoscopic, and symptomatic outcomes after treatment, the differences between the OVB and MDI groups were not significant. For example, histologic response (<15 eos/hpf) was achieved in 71% and 64% in the OVB and MDI groups, respectively and post-treatment dysphagia scores and EREFS were also similar. Based on this, OVB was not felt to be superior to MDI and either budesonide or fluticasone could be used for initial STC treatment. These trial data echoed results from a previous systematic review and meta-analysis or previous (non-comparative) clinical trials that showed pooled histologic treatment responses of 77% and 68% for budesonide and fluticasone, respectively (195), similar to retrospective cohort studies (214–216) and a more recent meta-analysis (217).

This recommendation implies that either budesonide or fluticasone is a reasonable choice for initial STC treatment in EoE. However, it is important to note that the data supporting this recommendation did not use either of the approved budesonide formulations discussed above (BOT or BOS) as neither was available when the trial was conducted. Similarly, the fluticasone dissolvable tablet is in phase 3 testing, and none of the newer formulations have been subject to comparative effectiveness studies. In addition, the efficacy and role of novel steroid delivery methods, including a mometasone-impregnated membrane (NCT04849390) and a long-acting injectable fluticasone formulation (NCT05608681), are yet to be determined.

Dietary elimination

Recommendation

8. We suggest an empiric FED as a treatment for EoE (quality of evidence: low; strength of recommendation: conditional).

Summary of evidence. Knowing that the pathogenesis of EoE is food antigen-driven in most people provides the foundation for dietary elimination treatment. Dietary therapy was first found to be effective for EoE in 1995 in an initial case series of 10 children with esophageal eosinophilia and lack of response to antireflux therapy (218). All 10 children were treated with elemental formula and had decreased intraepithelial eosinophil counts, improvement or resolution of symptoms, and recurrence of presenting symptoms with food challenges. Larger retrospective pediatric studies followed which produced similar results (219–222). These early studies, which comprise most of the data on elemental dietary therapy, supported the concept that EoE is triggered by food antigens. Building on the pediatric data, the first prospective study of an elemental diet in adult patients with EoE

found that although 72% responded histologically, symptoms and strictures did not improve significantly (223). A technical review summarizing these data showed that the histologic response rate to an elemental diet was 93.6% compared with 13.3% using a historical placebo comparison group taken from swallowed topical corticosteroid data (52), results similar to the pooled rates of >90% for histologic response in a different meta-analysis (224).

Despite the high response rates for the elemental formula, there are several limitations to this approach (225). The poor palatability of the formula can decrease adherence and necessitate percutaneous gastrostomy placement to allow sufficient volume to be consumed. Furthermore, the extremely restrictive nature of the diet has implications for quality of life and feasibility. For example, in an adult observational study, more than one-third (38%) of patients failed to adhere to the diet (223). The use of elemental formula necessitates monitoring by a registered dietitian for nutritional deficits and potential weight loss. Cost is also a major issue. Not only is the elemental formula itself expensive, with insurance coverage available in only a minority of states in the United States, but there is a need for multiple repeated endoscopies in a lengthy reintroduction process to identify food triggers. Because of these reasons, treatment with an elemental diet is not the favored dietary approach in most patients and is generally reserved for infants and patients with severe and refractory EoE without other options. Instead, an empiric elimination diet, where the foods that are statistically most likely to trigger EoE are avoided, is preferred as a first-line treatment.

Of the empiric diet therapies available for EoE, the 6-food elimination diet (6FED) has been the best studied (226). For this diet, the common allergens of animal milk (sometimes referred to simply as "dairy"), wheat, soy, egg, nuts/peanuts, and fish/shellfish are empirically removed. Initially studied in a pediatric patient population, the 6FED provided clinical and histologic improvement in EoE with more favorable acceptance, cost, and adherence compared with an elemental diet (221). The 6FED has also been demonstrated to be effective in adults. A prospective study of 50 patients with EoE demonstrated that 70% achieved histologic remission (≤10 eos/hpf) and 94% had reduced symptom scores (227). Wheat and milk were the most implicated food antigens in this cohort after reintroduction (60% and 50% of cases, respectively). Follow-up studies have demonstrated the practicality of using 6FED in clinical practice in a larger cohort, with complete remission of 54%–58%, and after food reintroduction was completed, 69% of patients had only 1 food trigger identified (228). In addition, efficacy in a European study using 6FED plus elimination of legumes and cereal grains, of 67 patients with EoE, 73% achieved histologic remission (<15 eos/hpf) (229). With food reintroduction, a single food trigger antigen was identified in 36% of patients, 2 triggers in 31%, and 3 or more triggers in 33%, with milk being the most common trigger (62%), followed by wheat/cereals (29%), egg (26%), and legumes (24%). Based on these data and multiple other observational studies, several meta-analyses estimated an approximately 70% histologic response rate for 6FED (52,224,226).

Despite efficacy of 6FED, significant challenges remain, including the restrictive nature of this diet and the need for multiple endoscopies to identify food triggers (48). These limitations prompted research into less-restrictive elimination diets and a "step-up" diet approach. A multicenter Spanish study evaluated the step-up approach, starting with a less-restrictive dairy and wheat elimination (2-food elimination diet [2FED]), that achieved remission in 43% of children and adults in the study (230). Patients who did not respond to the 2FED moved on to a 4FED (avoidance of dairy, wheat, egg, and soy), and if they did not respond to 4FED, moved on to a 6FED with histologic responses similar to previous results. It is important to note that although some patients elected not to move to the next step-up in diet restriction, this process was more efficient, reducing endoscopic procedures and trigger identification time by 20%. A subsequent modeling analysis suggested that a step-up dietary elimination approach maximized efficiency in identifying food triggers while optimizing the number of endoscopies required (231). The strongest data to date supporting a less-restrictive upfront diet elimination comes from 2 randomized trials. The first compared single food elimination with milk (1FED) with 6FED in adults with EoE and found that histologic response rates (<15 eos/hpf) were similar between the 2 approaches (34% vs 40%; $P = 0.58$) (232). However, more patients randomized to 6FED achieved complete remission (≤1 eos/hpf) compared with 1FED, although the complete remission rate was low (19% vs 6%; $P = 0.03$). Patients who did not respond to 1FED completed salvage therapy with 6FED with a 43% response. The second trial compared 1FED with 4FED in children younger than 18 years and also found similar rates for histologic response (44% vs 41%; $P = 1.0$), although 4FED was superior in reducing symptoms (233). Retrospective cohort studies in the pediatric population using 1FED showed histologic response rates of more than 50%–60% (234,235). An additional randomized trial found the addition of elemental formula to the 4FED helped to improve quality of life but did not lead to greater histologic response compared with 4FED alone (236).

For this recommendation statement, the quality of evidence is low because of heterogeneity of data and lack of placebo-controlled studies, with the acknowledgement that placebo-controlled diet studies are challenging to conduct. This recommendation also considers the number of publications and meta-analyses that show dietary intervention is highly effective and should be offered to patients as an alternative to medical therapy, so they can make an informed decision about their care. In clinical practice, the optimal choice for empiric diet therapy (Table 5) is ultimately the one that patients and families can successfully adhere to and have the resources to complete and one with which the provider is familiar. There is no "one size fits all" approach for empiric diets, so discussion should include the effectiveness of each empiric approach, the situation of the patient and family and whether this can support diet elimination, the process of repeat endoscopic evaluation for food reintroduction, and the overall length of each approach. Different case scenarios, diet choices, and approaches to reintroduction (48,225,237–239) are presented in the Supplementary Appendix (see Supplementary Digital Content 1, http://links.lww.com/AJG/D461).

It is important to convey the concept to patients that after an empiric diet is chosen, with the exception of the 1FED, if there is histologic response (usually <15 eos/hpf) after the initial 6- to 8-week course of diet elimination, then a process of reintroduction begins to identify food triggers (48). The general approach is to add a food or food group back for 6–8 weeks and repeat an endoscopy. If a patient has been nonadherent or has had known food contamination, then it is important to do a "washout" for several weeks (2–6 weeks depending on the amount/nature of the contamination) and push back the endoscopy to account for this. If histologic response is sustained, the food is not a trigger and can

Table 5. Dietary elimination therapy options

Diet	Details[a]	Efficacy range
1FED	Dairy elimination alone; also referred to as animal milk elimination[b]	35%–45%
2FED	Dairy and wheat elimination	40%–45%
4FED	Dairy, wheat, egg, and soy elimination	40%–50%
6FED	Dairy, wheat, egg, soy, nuts, and seafood elimination	40%–70%
Elemental formula	Amino acid–based hypoallergenic formula	>90% (if adherent)
Allergy test-directed	Not recommended[c]	—

1FED, single-food elimination diet; 2FED, 2-food elimination diet; 4FED, 4-food elimination diet; 6FED, 6-food elimination diet; EoE, eosinophilic esophagitis; Ig, immunoglobulin.
[a]See Supplementary Appendix (see Supplementary Digital Content 1, http://links.lww.com/AJG/D461) for approach to food reintroduction.
[b]Some patients may opt for a wheat-only elimination as the first choice.
[c]Do not order serum IgE or IgG testing, or perform skin prick or patch tests to direct an EoE diet; an allergist may perform these tests for other reasons as clinically indicated after evaluation.

be continued in the diet. If there is a histologic flare (≥15 eos/hpf), then the food is a trigger and should be re-eliminated indefinitely, at which point another food is added back and the process is repeated. One approach to food reintroduction is to add back foods systematically, starting with foods that are the least likely to trigger EoE (240,241). Dietary elimination is optimized by working with a registered dietician or nutritionist with knowledge about EoE, consulting a feeding therapist if avoidant-restrictive food intake disorder or other feeding dysfunction is present (see pediatric section, below), and recognizing that some food-related symptoms are not due to EoE (242). Consultation with an allergist should be pursued if there is a concern for loss of tolerance on food avoidance and if the patient has concurrent immunoglobulin (Ig)E-mediated food allergies and is considering oral immunotherapy (243) (see below). Once food triggers are identified, patients can be maintained long-term on diet elimination (see maintenance section, below).

Recommendation

9. We do not suggest currently available allergy testing to direct FEDs for treatment of EoE (quality of evidence: very low; strength of recommendation: conditional).

Summary of evidence. Allergy test-directed elimination diets have been a theoretically appealing alternative to empiric elimination and elemental formula—if an allergy test is positive, it should imply that a given food should be eliminated. However, EoE is a delayed-type hypersensitivity lymphocyte-driven type 2 immunity in which IgE is dispensable, and accordingly, studies of elimination diets based on skin prick, patch, or serum Ig allergy test results have had limited success in predicting EoE food triggers. Therefore, these tests should not be done to direct food elimination in EoE. For example, a pediatric study showed skin prick testing for the 2 most common EoE triggers, milk and wheat, was less than 30% sensitive for identifying these triggers in patients with EoE (244,245). In another study, elimination diets directed by multimodal allergy testing failed to achieve either clinical or histologic remission in 67% of adult patients with EoE (246). A larger prospective study of 50 adults with EoE undergoing an empiric 6FED found that skin prick testing predicted only 13% of identified food triggers (227). Similarly, poor concordance was demonstrated in a study of 67 adults undergoing 6FED and in a prospective study of 5 different types of allergy tests (229,247). Targeted elimination diets, therefore, have the lowest response rates in meta-analyses (52,224). Given the inaccuracy of available allergy testing, particularly skin prick testing, patch testing, and serum IgE or IgG testing, to predict food triggers in EoE, and with the lower response rates compared with empiric elimination diets, allergy test-based diets are not currently recommended and serum IgE or IgG food panels should not be ordered for EoE.

Finding more accurate methods to predict food triggers in EoE has been an active area of investigation. Based on the finding that esophageal tissue in patients with EoE had a marked increase in IgG4 compared with controls (248), investigators wondered whether it could be used for predicting treatment response or food triggers (249). Supporting this theory, the 1FED vs 6FED clinical trial found that milk-specific IgG4 was associated with response to milk elimination (232). The correlation of milk-specific IgG4 levels and T-cell stimulation to milk proteins with milk as a clinical trigger has been demonstrated in children with EoE (250). Similarly, a larger panel of 5 food triggers (milk, wheat, egg, soy, and peanut) assessed by food-specific IgG4 in esophageal biopsies plus peripheral blood T-cell stimulation with proteins from these foods had an accuracy of 53%–75% (251); an RCT of this approach using an 18-food panel is now underway (NCT05543512). A smaller prospective cohort study evaluating the efficacy of food-specific serum IgG4-directed elimination diet led to histologic remission in 45% (252). Although potentially promising, more research is needed before these novel testing paradigms can be implemented in clinical practice.

Although allergy testing is not recommended to identify food predictors in guiding diet elimination in EoE, there are important roles for the allergist in consultation and collaboration for both dietary elimination and care of patients with EoE (243,253). For instance, there have been case reports that pediatric patients who have avoided foods for many years may develop sensitization to these foods and be at risk of immediate-type reactions, including anaphylaxis, during reintroduction (254–256). Therefore, if patients have avoided foods and are embarking on a food reintroduction process, or if there is a concern for loss of tolerance to foods regardless of the length of food avoidance, consultation with an allergist is helpful to determine safety of food

Table 6. Medication dosing for initial treatment

Medication	Dosing
PPIs	
Children	2 mg/kg per day (or 1 mg/kg twice daily)
Adults	Double the approved reflux dose per day (e.g., omeprazole 20 mg twice daily or 40 mg daily or other PPI equivalent)
Topical steroids	
Budesonide[a]	
Children	1–2 mg/d (depending on age, height, and weight; can be divided twice daily)
Adults	2–4 mg/d[b] (can be divided twice daily)
Fluticasone[c]	
Children	110–880 μg/d (depending on age, height, weight) in a divided dose
Adults	1760 μg/d in a divided dose
Dupilumab	
15–<30 kg	200 mg subcutaneously every other week
30–<40 kg	300 mg subcutaneously every other week
≥40 kg	300 mg subcutaneously every week

EoE, eosinophilic esophagitis; PPI, proton pump inhibitor.
[a]If asthma preparations are being adapted for EoE, the goal is to mix the aqueous budesonide to a syrup-like consistency, using sucralose, honey, maple syrup, or similar with a goal total volume of approximately 10 mL.
[b]Note that approved dosing for budesonide oral suspension is 2 mg twice daily.
[c]Doses are for fluticasone given from a multidose inhaler; if the disk device is used, dosages should be adjusted based on whether a 100- or 250-μg device is used.

reintroduction unsupervised at home vs in the office with oral food challenges. Given potential seasonal variation noted with EoE and that diet elimination may have decreased effectiveness during pollen season (257–260), allergists can also provide insight into the role of aeroallergens and how this might impact dietary elimination and timing of endoscopy.

Biologics

Recommendation

10. We suggest dupilumab as a treatment for EoE in individuals 12 years of age or older who are nonresponsive to PPI therapy (quality of evidence: moderate; strength of recommendation: conditional).

Summary of evidence. Dupilumab is a monoclonal antibody against the interleukin (IL)-4 receptor alpha (IL-4rα) that blocks the effect of both IL-4 and IL-13, cytokines that are central to the type 2 inflammatory cascade (261). The medication, which is a subcutaneous injection, has been previously approved as add-on therapy for moderate to severe asthma and atopic dermatitis and is also approved for chronic rhinosinusitis with nasal polyposis and prurigo nodularis. Because of the shared pathogenetic components between atopic dermatitis and EoE, a phase 2 proof-of-concept study was conducted that showed improvement with dupilumab compared with placebo for symptoms of dysphagia, histologic response, and endoscopic severity after 12 weeks of treatment (120). Based on these data, an international phase 3 RCT was conducted on 321 subjects that consisted of 3 parts (47,262). In part A, 300-mg weekly dupilumab was compared with placebo for 24 weeks; in part B, weekly dupilumab was compared with every other week administration and to placebo for 24 weeks; part C was an active extension with ongoing treatment to 52 weeks. The coprimary endpoints were histologic remission, defined as ≤6 eos/hpf, and the absolute change from baseline in dysphagia frequency and severity, as measured by the validated Dysphagia Symptom Questionnaire. For inclusion, patients had to be 12 years and above and at least 40 kg and PPI nonresponders. In addition, patients who needed esophageal dilation at the screening endoscopy or who had severe stricturing such that a standard adult scope could not pass were excluded. In part A, 60% achieved histologic remission with dupilumab compared with 5% in placebo ($P < 0.001$); similar remission rates were seen in part B with both weekly and every other week dosing, and rates were maintained in part C with ongoing dupilumab use. For symptoms, there was a significantly larger decrease in dysphagia symptoms with weekly dupilumab dosing compared with placebo in part A (21.9 point decrease in Dysphagia Symptom Questionnaire compared with 9.6, $P < 0.001$), and this was again seen with weekly dosing in part B, but every other week dosing was not different than placebo. In addition, endoscopic severity (measured by EREFS) and histologic severity (measured by EoEHSS) were significantly improved with both weekly and every other week dosing compared to placebo. Based on the symptom data, weekly 300-mg dosing (Table 6) was approved by the FDA in 2022, for patients at least 12 years of age and weighing at least 40 kg, with additional approvals following throughout the world.

For this recommendation statement, although the quality of evidence was moderate (2 RCTs), a conditional recommendation was favored for dupilumab because of cost and issues with generalizability stemming from 1 phase 3 study with a population of patients with established and moderate to severe EoE. Specifically, these patients were characterized by a mean duration of EoE before study entry of 5 years, approximately 40% had required esophageal dilation, all were PPI nonresponders, and approximately 70% had previously been treated with topical steroids, half of whom were either nonresponsive or intolerant to this medication class.

The safety profile for dupilumab has been established for other atopic diseases, and in general, it is a relatively well-tolerated medication (263–265). With the anti-IL-4rα mechanism, it does not seem to increase risk of infections, and screening for tuberculosis, HIV, or hepatitis is not required before starting the medication. Clinically important immunogenicity has not been reported, and therapeutic drug monitoring is not recommended currently. In the EoE trials, the most common side effects were related to injection site discomfort, erythema, or reactions (47,120,262,266). In non-EoE trials, arthralgias have been reported (263–265). In the subanalyses from the pivotal trial cited above, response rates were similar regardless of ongoing PPI use or previous steroid response (267,268).

With the recent approval, data related to real-world efficacy are increasingly being published, primarily as case series and cohort studies. The largest of these evaluated 46 patients with severe EoE, who likely would not have qualified for the phase 3 study because of critical strictures and esophageal dilation

requirement (269). Despite being refractory to all previous treatments, these patients had a similar histologic response rate (~60%) as in the pivotal trial and had concomitant endoscopic and symptom improvement. Notably, they also had an improvement in esophageal caliber and reached their largest dilation size, a result that echoes a subanalysis from the phase 2 study where a 2- to 3-mm improvement in esophageal diameter compared with placebo was noted with dupilumab (and in the absence of esophageal dilation), as measured by the endoluminal functional lumen imaging probe (EndoFLIP) (120).

Recommendation

11. We suggest dupilumab as a treatment for EoE in pediatric patients (ages 1–11 years) who are nonresponsive to PPI therapy (quality of evidence: low; strength of recommendation: conditional).

Summary of evidence. Dupilumab was studied in 102 children aged 1–11 years in a 2-part randomized trial of 2 dosing regimens (higher exposure and lower exposure) compared to placebo (270). In the first part, the 2 doses were compared to placebo for a 16-week treatment period, and the primary outcome was histologic response, again defined as ≤6 eos/hpf, with additional outcomes of endoscopic severity, growth, and symptom improvement. The second part was an active treatment phase for an additional 36 weeks. After 16 weeks of treatment, histologic response rates were 68%, 58%, and 3% for the higher dose, lower dose, and placebo groups, respectively ($P < 0.001$). Endoscopic severity and growth were significantly improved with dupilumab compared with placebo, and there was a trend for improved patient- and caregiver-reported symptoms as well. In addition, responses seen at week 16 were maintained through 52 weeks of treatment. Based on these data, in February 2024 the FDA approved the use of dupilumab patients with EoE aged 1–11 years and weighing at least 15 kg. There are 2 different dosages based on weight, both at a frequency of every other week, in contrast to the weekly dose in patients 12 years and above (Table 6). The safety profile in this study was consistent with the safety seen in the adolescent and adult EoE trial, as well as seen in other programs of dupilumab.

For this recommendation statement, the quality of evidence was rated as low, given the single and modestly sized trial, and lack of significant improvement in nonvalidated patient-reported outcomes, acknowledging the difficulty of conducting a placebo-controlled trial in a pediatric population. A conditional recommendation was favored because of cost and issues with generalizability stemming from a single phase 3 study that enrolled patients with a more moderate to severe and treatment-refractory disease profile, similar to the considerations for the evidence assessment in the adult population.

Recommendation

12. We cannot make a recommendation for or against cendakimab, benralizumab, lirentelimab, mepolizumab, or reslizumab as a treatment for EoE.

Summary of evidence. A number of targeted biologics have been or are being studied for use for EoE (271) and are either experimental, not clinically available, or do not have sufficient evidence in either direction to recommend for or against use in EoE.

Cendakimab is a monoclonal antibody against soluble IL-13, a type 2 cytokine that plays a strong role in EoE pathogenesis, and, therefore, decreases signaling through the IL-13 receptors. A phase 2 study of this medication (then called RPC-4046) randomized patients to receive 1 of 2 doses of cendakimab or placebo, given as a weekly subcutaneous injection for 16 weeks (121). The study met the primary endpoint with a significant decrease in mean eosinophil counts and saw improvements in histologic response and endoscopic severity compared with placebo. For the higher dose group, there was a strong trend toward dysphagia symptom improvement in all patients and a significant improvement compared with placebo in the steroid-refractory subgroup. The medication is currently being tested in a phase 3 study of EoE (NCT04753697).

Benralizumab and lirentelimab are antibodies directed against the IL-5 receptor alpha and the siglec-8 receptor, respectively, and lead to near complete eosinophil depletion, although mepolizumab and reslizumab are antibodies against soluble IL-5, a type 2 cytokine important for eosinophil maturation and activation. All have been examined either in phase 3 or phase 2 studies of EoE, and results were similar, with prominent histologic response rates (including very high rates with benralizumab and lirentelimab, which completely deplete eosinophils) compared with placebo (151,152,272–275). However, symptom response was generally not significantly higher than placebo, and in some studies, endoscopic improvement was either modest or not seen. These results raise the question of what processes drive disease activity in the absence of eosinophils and have implications for outcome metrics for EoE (see below). However, given the prominent antieosinophil effect of these medications, future research may be warranted with different treatment paradigms (e.g., combination therapy; maintenance therapy; steroid-sparing therapy; and targeted therapy in patients with hypereosinophilic syndrome or eosinophilic asthma overlap).

Recommendation

13. We suggest against omalizumab as a treatment for EoE (quality of evidence: low; strength of recommendation: conditional).

Summary of evidence. Omalizumab is an antibody against IgE and is approved for asthma and chronic urticaria. Given the allergic pathogenesis of EoE, omalizumab was tested in a randomized placebo-controlled clinical trial of EoE, but there were no differences in outcomes between the active medication and the placebo group, although IgE levels decreased as expected with treatment (248). Although the trial did not show benefit in EoE, it did confirm that EoE is not IgE-mediated and reported a novel increase in IgG4 in EoE as a possible pathogenic mechanism. Of note, omalizumab has been approved for IgE-mediated food anaphylaxis in children down to 12 months of age, and this efficacy underscores different mechanisms between food anaphylaxis and EoE.

We also note that other biologics have been used in EoE, including infliximab and vedolizumab (276–278). However, because these are case reports or case series, we are not able to make GRADE recommendations for these treatments, and these should

Table 7. Approach for esophageal dilation in EoE

Esophageal dilation can be considered for all patients with EoE and an esophageal stricture with dysphagia
The immediate endpoint of endoscopic dilation is the appearance of a mucosal disruption, best termed "dilation effect," or reaching the target diameter
In adult and adolescent patients with EoE, a goal luminal diameter that relieves dysphagia and food impaction (typically ≥16 mm) should be achieved over ≥1 sessions based on the initial caliber of the lumen and effect noted during dilation
In patients with EoE, different dilation techniques chosen based on stricture characteristics and endoscopist preference are acceptable for performing dilation therapy
Using an initial dilator size that may underestimate the esophageal caliber, relooking after the dilation, and then working to larger sizes until dilation effect is seen, is a reasonable approach
In patients with fibrostenotic EoE, dilation therapy should occur in conjunction with effective medical or diet elimination anti-inflammatory therapy because dilation alone does not impact EoE disease activity
Empiric dilation may be performed for patients with EoE with persistent dysphagia in the presence of a normal-appearing esophageal diameter by endoscopy and histologic remission achieved with medical or dietary therapy

EoE, eosinophilic esophagitis.
Adapted from Aceves et al. Gastrointest Endosc. 2022;96(4):576–92.e1 (49).

not be used clinically for EoE treatment outside of appropriate research settings.

Small molecules

Recommendation

14. We suggest against the use of cromolyn and montelukast for the treatment of EoE (quality of evidence: very low; strength of recommendation: conditional).

Summary of evidence. Because EoE has a mixed inflammatory cell infiltrate (T cells, eosinophils, mast cells, and basophils), inhibition of specific components of these inflammatory responses has been therapeutically targeted with small molecules (279). However, data supporting the use of small molecules in EoE are limited by small sample size and lack of placebo-controlled trials, although the field is quickly evolving with several novel but experimental agents under study.

The most documented small molecule used in EoE in the literature is montelukast, a leukotriene receptor antagonist. Leukotrienes are responsible for bronchoconstriction, vascular permeability, and eosinophil infiltration in the setting of asthma, aspirin exacerbated respiratory disease, and allergic rhinitis, and are also increased in EoE. There have been multiple observational studies evaluating the effects of leukotriene inhibitors in EoE (280–282), but only one that was blinded and placebo-controlled (283). In this trial, patients were placed on swallowed topical steroids for 6 weeks and then randomized to either montelukast (n = 21) or placebo (n = 20). Symptoms of dysphagia were evaluated for 24 weeks by telephone interview, but both the placebo and montelukast groups demonstrated similar symptomatic response rates.

Mast cell stabilization with cromolyn was investigated in a small (n = 16) randomized trial compared with placebo, but cromolyn did not show a significant reduction in esophageal eosinophilia or symptoms (284).

Other small molecules have been studied for EoE, but data are too scant to recommend use or treatments remain in early phase trials. These included azathioprine or 6-mercaptopurine (285), losartan (NCT03029091), etrasimod (286), and IRL1104 (287).

Dilation

Recommendation

15. We suggest the use of endoscopic dilation as an adjunct to medical therapy as a treatment for esophageal strictures causing dysphagia in patients with EoE (quality of evidence: low; strength of recommendation: conditional).

Summary of evidence. An esophageal stricture is often viewed as a transmural and fibrotic process and in EoE focal constrictions of the esophagus ("strictures") as well as more diffuse and longitudinal narrowing ("narrow caliber esophagus") can be seen. Studies using endoscopic ultrasonography have demonstrated expansion of the esophageal mucosa, submucosa, and muscularis propria in patients with EoE (288–290). It is likely that the esophageal wall thickening in EoE is composed of both inflammation and fibrosis. For EoE, this subepithelial inflammation may explain why short-term medical therapy can increase esophageal caliber and reduce the need for dilation and occurrence of food impactions (291–293). Unfortunately, an imaging technique that reliably differentiates inflammation from fibrosis in the esophageal wall does not exist currently.

Esophageal dilation is a common procedure that can be routinely and safely performed by most general endoscopists. The effectiveness and safety of dilation in patients with EoE were detailed in systematic reviews and meta-analyses (294,295). Clinical improvement occurred in 95% of cases, and postprocedural hospitalization occurred in <1% and esophageal perforation in <0.5% of dilations. Furthermore, performance of dilation has become safer over time. Although safe and practical, a conditional recommendation as opposed to a strong recommendation is favored based on the low quality of evidence. To date, there has only been 1 RCT to evaluate esophageal dilation compared with no dilation among adults with EoE and stricture (296). This RCT was an unblinded single-center study that included only 31 patients and was downgraded because of imprecision, indirectness, and bias. All other studies of esophageal dilation in patients with fibrostenotic EoE have been uncontrolled observational studies, including cohort, case-control, and case series (52).

Consensus recommendations on the method for esophageal dilation in EoE are described in a recent guideline publication by the ASGE and were based on expert opinion (49) because the esophageal dilation experience in EoE is largely based on retrospective case series and clinical experience, as noted above. These consensus recommendations are summarized in Table 7. Although esophageal dilation has been reported as monotherapy in patients with EoE who have strictures or narrowing and are

refractory to all other treatments (297), this is not the preferred approach. This is because dilation improves esophageal caliber and symptoms of dysphagia but does not impact the underlying EoE disease activity or pathogenesis (298). Therefore, we advise pairing esophageal dilation with anti-inflammatory therapy based on data showing a decreased esophageal dilation requirement after histologic response (299–301).

A key point when approaching esophageal dilation is to recognize that detection of esophageal strictures in EoE can be difficult on endoscopic examination. Strictures are obvious when the esophageal lumen precludes or hinders passage of a standard endoscope; however, when other techniques are used to assess esophageal diameter more accurately, endoscopy is far less sensitive. For example, in a study using a structured esophagram protocol to measure the esophageal lumen diameter, endoscopy had poor sensitivity (14.7%, 95% CI 5.0%–31.1%) for detection of a narrowed esophagus and only modest specificity (79.2%, 95% CI 57.8%–92.9%) (302). Even at a cutoff diameter of $\leq$ 15 mm, endoscopy had a sensitivity of only 25.0% (95% CI 5.5%–57.2%). This insensitivity to stricture detection was further suggested by a 71% symptomatic response rate to dilation in patients without perceived esophageal narrowing at endoscopy. Similar data have also been published in children with EoE, where 55% of strictures noted on barium esophagram were not detected endoscopically (303). However, it should be noted that the specificity of the barium esophagram is also limited because of inability to control for intraesophageal luminal distension pressure (303,304).

Another technique of assessing for esophageal strictures that provides a more precise assessment of diameter with quantification of luminal distension pressure is impedance planimetry using the EndoFLIP probe (305). As this instrument measures esophageal wall compliance, areas of esophageal rigidity in the presence of subtle strictures may be detected. In patients with EoE, EndoFLIP seems to be more sensitive than endoscopy for detection of esophageal fibrotic change. For example, when applied to 33 patients with EoE and rings and furrows with vs without visible strictures, there was no difference seen in distensibility (306). This suggests either a discordance between endoscopic and EndoFLIP findings or a greater sensitivity of EndoFLIP for detecting esophageal stenosis and/or decreased distensibility associated with rings even in the absence of an endoscopically identified stricture. The latter scenario has been supported in a follow-up study in adults showing a correlation between esophageal distensibility and endoscopic ring severity measured by EREFS (307). EndoFLIP has also been used in a study of 59 children with EoE where the distensibility index correlated with grade 2 rings on endoscopy (308). However, although a distensibility index $<$4.5 mm^2 distinguished patients with and without endoscopically detected strictures, only 23% of pediatric patients had strictures detected (309). These data further underscore the increased sensitivity of EndoFLIP for esophageal stricture detection in EoE, and recently, a physiomechanical classification of EoE based on distensibility metrics and esophageal motility findings from FLIP has been explored (310). However, we note that to date, EndoFLIP has primarily been used at specialty centers in research settings and has not been routinely used in most clinical practices for EoE.

Maintenance therapy

Recommendation

16. We suggest continuation of effective dietary or pharmacologic therapy for EoE to prevent recurrence of symptoms, histologic inflammation, and endoscopic abnormalities (quality of evidence: low; strength of recommendation: strong).

Summary of evidence. The rationale for maintenance therapy in EoE is based on its natural history as a chronic disease, which is demonstrated in cohort studies and the placebo arms of clinical trials. When EoE treatment is stopped, disease activity nearly universally recurs regardless of the type of treatment used (288,311–313). Moreover, in the absence of treatment or with treatment interruptions, there is fibrostenotic progression in most, but not all, patients (35–39,314,315). Finally, as opposed to childhood food allergies, asthma, or eczema, patients with EoE do not "grow out" of EoE; EoE seems to be a final and irreversible step in the atopic march (84,316).

For topical corticoid steroid therapy, there have been 3 randomized withdrawal trials that support maintenance therapy. In the first, 28 patients 14 years of age and older who had gone into remission ($<$5 eos/hpf; symptom score of 2 points or less) with 15 days of budesonide at 2 mg/d (administered as a nebulized/swallowed delivery) were randomized to either continue budesonide at a dose of 0.25 mg twice daily or to receive placebo (288). After the 50-week follow-up period, 35.7% of the active treatment group remained in histologic remission ($<$5 eos/hpf) compared with 0% in the placebo group. The median time to clinical symptom relapse was also longer in the budesonide group ($>$125 days) compared with placebo (95 days). In a novel outcome metric, esophageal wall thickness was also significantly higher in the placebo group compared with controls, indicating ongoing transmural inflammation and remodeling. In a similarly designed trial of BOT, patients 18–75 years who were in clinicopathologic remission after 6 weeks of 1 mg BOT twice daily were randomized to either continue 1 mg twice daily (n = 68), decrease dosing to 0.5 mg twice daily (n = 68), or to placebo (n = 68) for 48 weeks (313). The primary outcome of maintenance of remission (defined as no clinical or histologic relapse, no food impaction requiring endoscopy, no dilation, and no withdrawal for any reason) was achieved in 75%, 73.5%, and 4.4% of the 1 mg twice daily, 0.5 mg twice daily, and placebo groups, respectively. In the placebo group, the median time to relapse was 87 days, compared with $>$350 days in the active treatment groups. A randomized withdrawal trial of BOS allocated patients aged 11 years and older who were in clinicopathologic remission after 12 weeks of 2-mg twice-daily treatment to either continued BOS 2 mg twice daily (n = 25) or placebo (n = 23) for 36 weeks (317). The proportion without relapse was numerically but not statistically significantly higher in the BOS groups compared with placebo (43.5% vs 24%; $P = 0.13$), a per-protocol analysis showed a larger delta (50% vs 16.7%; $P = 0.038$), and a *post hoc* analysis using a time-to-event analysis also supported the efficacy of maintenance therapy (318).

In addition to these trials, prospective and retrospective cohort data also support maintenance therapy with topical steroids. In the trial of OVB vs fluticasone MDI, those who were in histologic remission stopped treatment and were followed prospectively to assess durability of response (312). The median time to symptom recurrence was 244 days (of note, dilation was allowed in this study, which could explain the longer time to symptom relapse),

78% had histologic relapse (>15 eos/hpf) by 1 year, and 94% had some degree of eosinophilic infiltration on biopsy. Two adult retrospective trials demonstrated that treatment with STC for longer duration and higher doses resulted in significantly higher proportion of patients with histologic, symptom, and endoscopic remission and long-term treatment associated with "deep" (i.e., complete) remission (319,320); pediatric studies have shown similar results (321,322). Additional studies have shown decreased rates of food impaction with long-term steroid treatment (323), decreased rates of esophageal dilation (299,300), and increased rates of stricture progression with interruption of treatment (39,315). These data suggest that disease modification in EoE may be possible with successful long-term treatment. In general, it is reasonable to consider dose reduction with STC to use the lowest most effective dose confirmed by endoscopy and biopsy, and the data are strongest for this with BOT. However, it is important to note there is a loss of response to STC over time, and some data suggest that every other day dosing may not be effective (324,325).

Data also support long-term efficacy of PPIs and dietary elimination in EoE. In both children and adults, 70%–85% can maintain PPI response at 1 year (172,173,326). A study of the EoE CONNECT database found a 69% remission rate for patients treated for at least 6 months (327), and a more recent retrospective cohort study suggested that histologic and symptom PPI responses were maintained in more than 60% of adults at a mean follow-up time of 3.6 years (176). For diet elimination, long-term treatment is effective, but the clinical challenge is for patients to maintain adherence over time. Several studies have shown that even after trigger identification, approximately half are not able to maintain the diets longer term (229,328–330). One option that might help with diet adherence over time is to allow for "diet holidays." In patients who are travelling for vacation, having a busy time at work, facing winter holidays with increased social events, or having a special event where diet restriction is too cumbersome, we advise relaxing the diet restriction and bridging these times with medical therapy. Patients may then choose to stop medical therapy when they are ready to go back to diet elimination. Patients may welcome this approach to make events such as family vacations easier to navigate and it can potentially lead to longer-term success with diet therapy, although there are no data yet to support this approach. Of note, this approach may be more challenging for children as the desire to continue eating an EoE food trigger may be hard to overcome.

Emerging data with biologics also support maintenance therapy. In an open-label extension study of the anti-IL-13 antibody, cendakimab, histologic, endoscopic, and symptom responses were maintained with 52 weeks of additional ongoing treatment (331). Similarly, ongoing use of the IL-4Ra antibody dupilumab demonstrated continued histologic, endoscopic, and symptom efficacy in pediatric, adolescent, and adult patients treated for 52 weeks, and in some cases, response rates were higher at 52 weeks than at 24 weeks (262).

Monitoring and evaluation of response

Recommendation

17. We recommend evaluating response to treatment of EoE with assessment of symptomatic and endoscopic and histologic outcomes (quality of evidence: low; strength of recommendation: strong).

Summary of evidence. The goal of monitoring and evaluating response in patients with EoE is to answer the question of whether the patient "is better" (332). However, several complexities underly what seems to be a simple question. Since EoE is a chronic disease that universally recurs when patients stop treatment, and because there can be a loss of response to treatment over time, long-term monitoring is required (50). Although there are multiple domains in EoE, for clinical practice, we recommend assessing symptomatic, endoscopic, and histologic features to provide a complete picture of disease activity. Unfortunately, symptoms have only a modest correlation with biologic metrics of disease (333–335), which makes clinical evaluation alone more challenging. For example, symptoms can be improved in the presence of ongoing disease activity if patients have substantial modification or avoidance behaviors related to eating or if they have had esophageal dilation. Symptoms can also persist after inflammation related to EoE has been treated if there is an undetected esophageal stricture (for which barium esophagram could be considered), if an esophageal infection complicates STC treatment, or if there is superimposed esophageal hypervigilance, visceral hypersensitivity, or feeding dysfunction (336).

A recent set of consensus statements from a group of clinicians and researchers in the United States and Europe provided recommendations related to monitoring (50). Although PROs are not used routinely in practice, clinical assessment of symptoms during a patient encounter with detailed questions about dysphagia and related symptoms, IMPACT behaviors (Table 4), and feeding dysfunction is highly recommended. For endoscopy, EREFS should be used, and pre-treatment and post-treatment findings can be compared. Complete normalization of the esophagus corresponds to EREFS = 0, but a threshold of endoscopic response of EREFS ≤2 (using a 0–9 scale) has been proposed and evaluated (122,123). For histology, an eosinophil count of <15 eos/hpf (<60 eos/mm^2) is a reasonable goal for most patients (337,338), so esophageal biopsies should be performed at every endoscopy where EoE is being evaluated. For all assessments, understanding where a patient started in relation to where they are after treatment is important, and responses can sometimes be discordant or partial. Borrowing from inflammatory bowel disease, the concept of "deep remission" has been proposed and is defined as a complete response in all domains—symptom resolution, endoscopic remission, and histologic remission (319). Although this concept is the ideal and could be a goal for all patients, in practice, it can only be achieved in a subgroup of patients with EoE. For example, in a study of 351 patients in the Swiss EoE Cohort, only 33 (9.4%) achieved deep remission, and after treatment was stopped in these patients, relapse was noted at a median of 22 weeks (319). There are also specific growth and development considerations for monitoring in children (see pediatric section, below).

In terms of timing of monitoring, this can vary depending on the treatment and the individual features of the patient (50). In general, the recommendation is to perform an endoscopy to assess treatment response in 8–12 weeks after starting a new therapy such as PPI, STC, or FED. For dupilumab, the timing may range between 12 and 24 weeks based on clinical trial findings. At the time of endoscopy, a patient's symptoms can be assessed, EREFS can be noted, and esophageal biopsies obtained for histologic examination. The next step depends on whether a patient has had clinical complications such as (but not limited to) food impaction, perforation, strictures requiring dilation, or malnutrition. If

a patient is on the moderate to severe disease spectrum with these complications, follow-up should be individualized and may be at shorter intervals. If a patient does not have these complications, has an adequate response, and treatment is stable, regular clinical follow-up is recommended. Although there are few data to support timing of interval endoscopies, 1 report noted that if a patient has a gap in care (without clinic visits or endoscopies) for 2 years or more they are at risk of progression to fibrostenosis, with increasing risk of fibrostenosis with longer gaps (39). If the patient has an adequate response, but there is a change in treatment (e.g., dose reduction), then another repeat endoscopy should be performed to assess response to that treatment change.

Currently, response assessment in EoE relies on endoscopy with biopsies; although there are no noninvasive biomarkers that have been validated to assess response (339), several less- or minimally invasive techniques are available (340). Unsedated transnasal endoscopy is now used, particularly in children, to minimize anesthesia exposure and costs (341–345). It is safe, well tolerated, and can provide the endoscopic and histologic measures (EREFS and esophageal biopsies) to assess response. The Cytosponge, a spherical cytology brush contained in a capsule that is attached to a string, swallowed, allowed to expand over 5–10 minutes, and then pulled out of the esophagus to obtain a tissue sample has a sensitivity and specificity of 75% and 86%, respectively, compared with esophageal biopsies, is well tolerated, and has successfully been implemented for food reintroduction protocols in EoE (346–348). The Esophageal String Test is a string with a weighted capsule that is swallowed and absorbs detectable inflammatory factors while indwelling in the esophagus for 1 hour (349,350). When eotaxin-3 and major basic protein were measured in the string, the area under the receiver operator curve was 0.83 to distinguish active ($\geq$15 eos/hpf) from inactive ($<$15 eos/hpf) EoE. Other metrics that have also been used to assess treatment response include mucosal impedance and EndoFLIP (305,351–353); these are both used during an endoscopy and mostly restricted to specialized centers.

Assessment of response clinically, as described above, is different from assessing response for registration clinical trials designed for drug approval. The FDA has published guidance on endpoints for EoE trials and currently has a framework where coprimary endpoints are required (354). Although this framework allows for assessment of both biologic (i.e., eosinophil counts) and clinical (i.e., symptom) features of EoE disease activity and has led to 2 drug approvals, it is somewhat limiting. Furthermore, given the recent studies described above regarding lack of clinical response with eosinophil-depleting agents (151,152), the eosinophil count may not be the best biologic outcome in all cases. To address these issues, researchers, clinicians, and epidemiologists convened the Assessment of Clinical endpoints in Eosinophilic esophagitis for Novel Therapeutics (ASCENT) meeting (355) to discuss a range of potential endpoints for registration trials to further facilitate drug development and approval in EoE.

Pediatric-specific considerations

Recommendation

18. In children with EoE and dysphagia, we suggest an esophagram for evaluation of fibrostenotic disease (quality of evidence: very low; strength of recommendation: conditional).

Summary of evidence. Symptom assessment in children can be challenging when determining the need to perform a therapeutic dilation. Three factors related to this should be considered before a sedated endoscopy. First, although not as common as adults with EoE, esophageal narrowing and strictures can occur in children. Second, a limited body of literature describes the presence of endoscopically unrecognized esophageal narrowing and the positive impact of dilation in children. Third, the preparation and the performance of an unplanned dilation intraoperatively can be challenging as equipment is not always available.

Similar to adults (302,356), the assessment of the esophageal caliber preoperatively with an esophagram and barium-coated pill can be helpful in some children with symptoms that could be attributable to a narrow esophagus. For example, in a retrospective analysis, an esophagram detected esophageal narrowing in 55% of 22 children who did not have recognition of the narrowing endoscopically (303). In another case series, the use of a barium-coated pill detected a clinically significant esophageal narrowing in 3 children that was not observed with esophagram alone (304). Those children with unexplained feeding problems, dysphagia, food impaction, or family history of EoE-related stricture could be considered. In circumstances where a family is concerned about radiation, the use of EndoFLIP may be helpful (308), but of course, the risks of sedation and endoscopy need to then be weighed.

Factors yet to be clarified with respect to the use of the pill esophagram in children include length of barium pill retention that is abnormal, how symptoms correlate with esophageal narrowing, and the clinical importance of refusal to swallow a pill.

For this recommendation statement, the quality of evidence was very low because of the existence of only small uncontrolled observational studies subject to substantial bias and heterogeneity; the conditional recommendation balances the implications of undiagnosed stricture in pediatric patients with EoE and the relative safety of esophagram as a diagnostic tool.

Recommendation

19. We suggest evaluation by a feeding therapist and/or dietician as an adjunctive therapeutic intervention in children with EoE and feeding dysfunction (quality of evidence: very low; strength of recommendation: conditional).

Summary of evidence. A basic tenet of pediatrics is to assure normal growth and development. With respect to growth, progression along growth curves for linear and body mass needs to be assured. In circumstances when growth is not proceeding or when the exclusion of foods is necessary as a part of a therapeutic plan, consultation with a pediatric dietitian is important. In both of these circumstances, pediatric dietitians will ensure that proper calories and micronutrients are provided in a well-balanced and feasible plan that will be able to be adhered to within a family's home.

In some situations, consultation with a pediatric endocrinologist is advised for children not achieving growth milestones. Additional considerations for slow growth are the issues of steroid toxicity and adrenal dysfunction secondary to chronic steroid use. Growth failure secondary to topical steroids is unusual, more likely with the use of systemic steroids, and in the case of EoE, a child's growth typically accelerates after achieving remission (357). With respect to adrenal suppression, studies reveal a wide range of findings that tend to be confounded by method of adrenal testing, duration of STC exposure, and concomitant use of

other steroids. For EoE, the use of STC as a monotherapy is not typically associated with clinical symptoms of adrenal insufficiency (197,358).

A key feature of a child's development relates to the acquisition of skills necessary to chew and swallow foods. In this regard, whether a function of underlying disease activity or coping behaviors, feeding dysfunction is often present in children with EoE. In fact, up to 16.5% of pediatric patients with EoE have significant feeding disorders, and the overwhelming majority (93.9%) have learned maladaptive feeding behaviors (359). This includes poor acceptance of meals, refusing to try new foods, poor mealtime structure, and spitting out food after chewing or holding it in the mouth. In a study evaluating the nutritional state of 53 young (aged 1–7 years) patients with EoE, and 38 gastroesophageal reflux disease controls, there was no difference in mean BMI z score between the groups (360). Ferritin, prealbumin, parathyroid hormone, and vitamin D levels were also similar between the groups. Although these groups were similar anthropomorphically, up to one-third of pediatric patients with EoE presenting for care may have a diagnosis of failure to thrive (361). Therefore, although there is a relationship between feeding and nutrition, evaluation of anthropomorphics alone may not be sufficient to determine whether there are feeding issues beyond intake. Determining the variety of foods and textures, levels of mealtime stress, and grazing behaviors are also important to evaluate in addition to typical questions focused on dysphagia alone. For example, the feeding behaviors of pediatric subjects with EoE (n = 27) were evaluated compared with non-EoE control patients (n = 25) (72). Subjects with EoE demonstrated significantly increased consumption time when compared with healthy controls. Of note, there were no statistically significant differences in eating behaviors between active and inactive EoE. This suggests that even in remission, altered feeding behaviors persist.

Based on these data and principles of care, we advise that growth (height, weight, and BMI), development of eating skills, and nutrition (proper intake of nutrients) remain treatment goals in addition to symptomatic, endoscopic, and histologic improvement in children with EoE. With these goals in mind, referral to a registered dietician or pediatric feeding program may be required. Before referral to a feeding program, it is essential to ensure that EoE is in remission. Because pediatric feeding programs use positive reinforcement techniques (362), negative stimuli such as abdominal pain, reflux, or dysphagia with the meal may decrease acceptance of foods and ultimately attenuate the benefits of positive reinforcement. The current guidelines for pediatric feeding programs involve a multidisciplinary evaluation with medical, nutrition, feeding skill, and psychosocial component evaluation (363).

With respect to expected outcomes for pediatric patients, growth and development are of primary importance along with the clinical features of improvement in symptoms, endoscopic appearance, and histological features. The assessment of mucosal inflammation requires the use of endoscopic techniques with sedation in those who are not able to receive the unsedated transnasal approach described above. The use of general anesthesia during endoscopy has raised concerns about its impact on the developing brain, although these neurodevelopmental concerns are primarily based on animal models for exposures at high concentrations of sedatives for long periods, which are not reflective of conditions for standard sedated endoscopy. Regardless, all factors need to be addressed with parents in considering the risks and benefits of performing sedated endoscopy.

For this recommendation statement, the quality of evidence was very low because only small uncontrolled observational studies exist and are subject to substantial bias and heterogeneity; the conditional recommendation balances the clear need to ensure children with EoE are best positioned to achieve their optimal growth and development milestones.

GENERAL APPROACH TO EOE TREATMENT

An algorithm for EoE treatment is presented in Figure 3. In this algorithm, anti-inflammatory treatments and interventions for fibrostenotic EoE (dilation) are presented in parallel, as both aspects should be assessed and treated in all patients. This consideration of both the inflammatory and fibrostenotic aspects of EoE disease activity also mirrors the framework of the I-SEE (31). In a patient with dysphagia and esophageal stenosis or narrowing, dilation can be performed as discussed above. Moreover, if dysphagia symptoms persist despite what appears to be an adequate treatment response objectively (e.g., histologic and endoscopic responses), dilation could be considered. For anti-inflammatory treatment, the first distinction to make is whether pharmacologic or dietary elimination treatment will be used initially. Because there are no comparative efficacy studies to answer this question, shared decision-making should be used. If a medication is selected, either PPIs or STCs could be used, and we favor using a single anti-inflammatory agent as given the current lack of data on combination therapy. If an elimination diet is selected, empiric elimination should be used, and although most patients will opt to start with a less-restrictive diet (1FED or 2FED), more-restrictive diets could be selected based on patient preference. Endoscopy with biopsies should be performed in 8–12 weeks to assess treatment response, with the next steps depending on response. If there is a good response, then medications can be continued, doses decreased if appropriate and desired by the patient, and monitoring put into place, which would include endoscopy and biopsy to assess ongoing response after dose reduction. Because EoE is a chronic disease with no currently known cure, treatment should be continued long term. If there is nonresponse to pharmacologic treatment, dupilumab could be considered, and if there is nonresponse to dietary elimination, a more-restrictive diet could be considered or the patient could switch to pharmacologic options; clinical trials can also be considered for nonresponsive patients. For all treatments, cost and insurance coverage should be considered on an individual basis because there are scant cost-effectiveness data to currently support decisions. In cases where a patient with EoE has other atopic conditions that would meet indications for dupilumab use, dupilumab can be considered earlier in the treatment algorithm in consultation with a relevant specialist. In addition to this therapeutic approach, referral for adjunctive behavioral interventions is warranted in patients, particularly children, with EoE and concern for feeding dysfunction.

FUTURE DIRECTIONS

During the evidence review and writing process for these guidelines, knowledge gaps and areas for future research were identified (Table 8). These include comparative efficacy studies to help position different therapies in the treatment algorithm and biomarkers (particularly noninvasive biomarkers) for both monitoring treatment response and for predicting response with the

Table 8. Future research questions and knowledge gaps to address in EoE

Comparative effectiveness studies of EoE first-line treatments
Trials of biologics in populations not included in clinical trials to date (newly diagnosed patients; PPI-naive patients; severely fibrostenotic patients)
Identification of predictors of response to treatment
Application of predictors to personalization of therapy
Identification of phenotypes and endotypes associated with progression to fibrostenosis
Application of I-SEE to treatment and monitoring paradigms
Methods for identification of food triggers
Noninvasive biomarkers for monitoring response to therapy
Expansion of use of minimally and less-invasive methods for monitoring response to therapy
Role of combination therapy
Dose reduction strategies over time
Definition and implementation of quality indicators for EoE
Cost-effectiveness data for available EoE treatments
Positioning novel treatments in the EoE algorithm as they become available

EoE, eosinophilic esophagitis; I-SEE, Index of Severity in EoE; PPI, proton pump inhibitor.

goal of individualizing treatment choice (which may also involve use of genetic, epigenetic, and nongenetic predictors and modeling). Identification of phenotypes and endotypes associated with progression to fibrostenosis is also needed. Work is required for noninvasive and minimally invasive methods of monitoring to become used more widely in practice and to seek novel methods for identification of food triggers. With the development of I-SEE, studies are required to match disease severity with treatment and monitoring paradigms, perhaps in the context of different EoE phenotypes and endotypes. Education is also required to help decrease diagnostic delay and assist providers in optimizing their EoE diagnostic and treatment protocols. The pipeline of novel therapeutics in EoE is flowing, with multiple agents under study and potential therapeutic targets identified (TSLP/tezepelumab; mast cells/barzovolimab; IL-15; Janus kinase inhibitors; alpha-1 trypsin inhibitor; novel topical steroid delivery systems, etc). Despite these needs, tremendous advancements have been made in the field over the past decade to the benefit of both patients and providers, and the field is poised for more advances in the coming years.

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CONFLICTS OF INTEREST

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Dedication: We dedicate this guideline to Ikuo Hirano, our colleague, teacher, innovator, advocate, acronym master, inspiration, and friend. Ikuo Hirano's diplomacy, finesse, and steadfastness helped provide the background for its development. Ikuo Hirano's rigor, vision, and innovation shaped much of its basis. Ikuo Hirano's enthusiasm, creativity, and integrity shape the future iterations that will emerge from his mentees and research to come.

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