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CLINICAL PRACTICE GUIDELINES

AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis

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This document presents the official recommendations of the American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (JTF) on the management of eosinophilic esophagitis. The guideline was developed jointly by the AGA's Clinical Practice Guideline Committee and the JTF with approval of both the boards of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology; and approved by both the AGA Governing Board and JTF Governing Boards. Development of this guideline and its accompanying technical review was fully funded by both the AGA Institute and the JTF, with no additional outside funding. The development process followed a standard peer review process as well as a 30-day public commenting period.

Eosinophilic esophagitis (EoE) was first characterized as a distinct clinical entity by Attwood and Straumann in the early 1990s.[1] While understood to be a food antigen-driven Th2 inflammatory condition, there is a large body of evidence that EoE patients have aeroallergen sensitization and concurrent atopic diseases, including asthma, allergic rhinitis, and eczema. There is a close interaction between these organ-specific diseases and potential for common triggering antigens in EoE and other atopic conditions. A dramatic rise in the recognition of EoE in the United States, first in pediatrics and subsequently in adults, was paralleled by an increase in publications on EoE.[1] The past 25 years have witnessed the emergence of the field from small case series and observational studies to larger, international, multicenter, randomized controlled trials (RCTs) of both medical and dietary therapies.[2] This guideline provides evidence-based recommendations focusing on the clinical management of EoE for both pediatric and adult allergists and gastroenterologists. Unless specified, the recommendations are applicable to the short-term treatment of EoE, as the current evidence base is primarily composed of trials extending from 2 to 16 weeks. With the exception of the recommendation on esophageal dilation, the guidelines are based on the failure to achieve histologic remission of <15 eosinophils/high power field (eos/hpf) as the definition of treatment effect.[2] Additional relevant outcome metrics, including symptoms and endoscopic features, could not be synthesized due to the use of varying and largely unvalidated instruments, variable study methodology, and a large degree of heterogeneity in reporting of outcomes. In forming the estimate of the effect for observational studies lacking a contemporaneous control group, the 8-week, placebo-controlled arm rate for failing to achieve histologic remission from topical glucocorticosteroid studies (86.7%) was used to allow comparison. In recommendations that this historical control group was used, the quality and strength of evidence was downgraded for using this

Abbreviations used in this paper: **AGA, American Gastroenterological Association; CI, confidence interval; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos/hpf, eosinophils/high power field; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IL, interleukin; JTF, Joint Task Force for Allergy-Immunology Practice Parameters; PICO, population, intervention, comparator, and outcomes; PPI, proton pump inhibitor; RCT, randomized controlled trial; RR, risk ratio.**

Most current article

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indirect comparator. For these recommendations, risk ratios (RRs) are presented by applying the baseline risk from the untreated control arms from steroid RCTs to the RR. As was reported in the technical review, use of this comparator should not be viewed the same as a direct control group comparison, but as an approximated measure that is permissible under Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.

The guideline was developed utilizing a process outlined elsewhere.[3] Briefly, both the AGA and JTF process for developing clinical practice guidelines incorporates GRADE methodology[3] and best practices as outlined by the Institute of Medicine.[4] GRADE methodology was utilized to prepare the background information for the guideline and the technical review that accompanies it.[2] GRADE uses the PICO format, which frames a clinical question by defining a specific population (P), intervention (I), comparator (C), and outcomes (O). The PICO questions focused on the use of therapeutics in patients with EoE. Each of the selected PICO questions was addressed in this review using the GRADE framework using evidence profiles, except for the last 2 PICO questions, which were addressed using a GRADE narrative review format. All recommendations were formulated using the GRADE evidence to decision framework (Tables 1–3). Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. A unique aspect of this guideline and the corresponding technical review was their development through a collaboration between AGA and JTF, which is composed of the American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology. In addition, representatives of both pediatric and adult medicine were included as well as a patient with EoE. This collaborative guideline reflects the interdisciplinary nature of EoE that integrates clinical and investigative efforts of multiple domains and builds on prior consensus recommendations published in both the allergy and gastroenterology literature.[5,6]

Recommendations

Question 1. Should Proton Pump Inhibitors Be Used in Patients With Esophageal Eosinophilia?

In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition over no treatment. *(Conditional recommendation, very low-quality evidence)*

Twenty-three observational studies that evaluated the histologic response to proton pump inhibitors (PPIs) reported an overall, unweighted histologic response rate of 42%. PPIs failed to induce histologic remission in approximately two-thirds of treated patients, compared with >85% of patients treated with placebo (RR, 0.66; 95% confidence interval [CI], 0.61–0.72). A high degree of inconsistency makes it difficult to provide a precise estimate of an absolute effect size and raises important concerns regarding variation in the criteria for patient selection, study design, as well as PPI duration, dosing, and formulation. Furthermore, most studies were noncomparative, single-arm, retrospective studies. Based on these factors, the strength of the recommendation was lowered. Nevertheless, a clinical benefit to the use of PPI monotherapy may be evident for certain patients. It is important to note that a European and an International consensus recommendation have recently removed the PPI trial from the diagnostic criteria of EoE.[7,8] After the exclusion of secondary causes of esophageal eosinophilia, symptomatic esophageal eosinophilia is now viewed as synonymous with EoE. PPIs are positioned as an effective, primary therapeutic option for certain patients with EoE. Based on their longstanding safety profile and ease of administration, patients may prefer to start with this form of therapy before trials of glucocorticosteroids or elimination diets. It should be emphasized that direct comparison of the efficacy of PPI and other medical or dietary EoE therapies is limited because, up to this time, most trials in EoE have excluded patients with esophageal eosinophilia that responded to a PPI (formerly denoted as PPI-responsive esophageal eosinophilia).

Question 2. Should Topical Glucocorticosteroids Be Used in Patients With Eosinophilic Esophagitis?

In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment. *(Strong recommendation, moderate quality evidence)*

Eight double-blind placebo-controlled studies enrolling 437 patients followed for a mean of 8 weeks compared treatment with topical budesonide or topical fluticasone to placebo.[2] It is of note that most of these studies required that patients first fail a PPI trial or excluded patients with known gastroesophageal reflux disease, which may not reflect routine clinical practice or the most current consensus-driven recommendations. Two of the trials used formulations of topical steroids developed specifically for esophageal delivery (tablet or liquid), whereas the remainder utilized ingested formulations designed for the treatment of asthma. As the result of a review process described in the technical guidelines, a single pooled estimate is presented here, despite many methodologic differences between these studies, including the relative potency and bioavailability of the agents used, method of administration, definition of response, dose, and differences that can occur in pediatric vs adult patients. All such factors may limit generalizability of this recommendation. Topical glucocorticosteroids failed to induce histologic remission in approximately one-third of treated patients, compared with >85% of patients treated with placebo (RR, 0.39; 95% CI, 0.26–0.58).[2] The certainty of this estimate is moderate; it

Table 1. GRADE Definitions on Strength of Recommendation

Strength of recommendation	For the patient	For the clinician
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to help individuals make decisions consistent with their values and preferences.
Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.

was downgraded for inconsistency due to heterogeneity of the studies. In short-term studies of $\leq$3 months, there was no increased risk of adverse events in patients treated with steroids compared with placebo (RR, 1; 95% CI, 0.85–1.19), although local viral and fungal infections and very limited description of adrenal suppression have been described in certain populations. Longer-term studies prospectively assessing the safety of topical glucocorticosteroid use, including adrenal function and growth suppression in children, are ongoing. It is relevant to consider that the same inhaled steroid agents are considered very safe for use in children and adults with asthma and are routinely used in the primary management of this disease. While no medications have been yet approved for treatment of EoE by the Food and Drug Administration, the European Medicines Agency approved a budesonide tablet formulation for EoE in 2018.

Question 3. Should Systemic Glucocorticosteroids Be Used in Patients With Eosinophilic Esophagitis?

In patients with EoE, the AGA/JTF suggests topical glucocorticosteroids rather than oral glucocorticosteroids. *(Conditional recommendation, moderate quality evidence)*

There has only been a single randomized trial of topical vs systemic glucocorticosteroids in 80 children with EoE.[2] Prednisone was given at a dose of 1 mg/kg twice a day, while fluticasone was given at a dose of 2 puffs 4 times a day (110 μg/puff for those aged $<$ 10 years and 220 μg/puff for those aged 11–18 years) for 4 weeks, followed by tapered dosing over 8 weeks. The primary end point was the histologic response, which was based on a score consisting of the percentage of basal cell hyperplasia and eosinophil density (eos/hpf). Both groups had similar histologic improvement, defined as a 1-point drop in this score. However, this score showed statistically greater improvement in the prednisone-treated group compared to the fluticasone-treated group at 4 weeks. The clinical significance of this difference, however, is unclear, given that symptomatic improvement was similar in both groups with 72% response rates in the prednisone arm vs 65% in the fluticasone arm. Relapse rates were also similar at 45% in both groups at week 24. Systemic complications were increased at 40% in the prednisone group, including weight gain and cushingoid appearance, compared with a 15% rate of oral candidiasis in the fluticasone group. Based on the similar effectiveness and well-characterized side effects of systemic glucocorticosteroids, topical glucocorticosteroids are preferred over prednisone for treatment of children with EoE. Similarities in disease pathogenesis and clinical manifestations in children and adults with EoE support the extension of the recommendation to adult populations. The potential benefits of systemic glucocorticosteroids in EoE patients that are refractory to topical glucocorticosteroids are currently unknown.

Question 4. Should an Elemental Diet Be Used in Patients With Eosinophilic Esophagitis?

In patients with EoE, the AGA/JTF suggests using elemental diet over no treatment. *(Conditional recommendation, moderate quality evidence)*
Comment: Patients who put a higher value on avoiding the challenges of adherence to an elemental diet and the prolonged process of dietary reintroduction may reasonably decline this treatment option.

The relevant data on efficacy of elemental diets (amino acid–based formulas) for treatment of EoE are derived from 6 single-arm, observational studies without control group comparators, which indicate that very few (6.4%) of these subjects on elemental diet failed to achieve histologic remission (defined as $<$15 eos/hpf).[2] This contrasts with failure to achieve histologic remission in 86.7% of a historical placebo comparison group from glucocorticosteroid trials, resulting in an estimated RR of 0.07 (95% CI, 0.05–0.12).[2] Adult studies had a lower proportion of participants achieving histologic remission than pediatric studies.[2]

Difficulty adhering to elemental diets for reasons such as taste, nutritional concerns, practical implementation within

Table 2. GRADE Definitions on Quality of Evidence

Quality	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

the context of overall dietary alternatives, breadth of avoidance in this style of diet, and cost are of concern. Harms include interference with development of oral motor skills in children, social isolation created by dining restrictions, the potential need for gastrostomy tube, costs of elemental formula, and burden of repeated endoscopies during gradual food re-introduction. From a food allergy perspective, there may be some risk of developing de novo IgE-mediated food allergy in previously tolerant patients on elimination diets for EoE, as has been noted in isolated case reports in EoE as well as in atopic dermatitis.[9,10] There is insufficient literature beyond a handful of case reports describing such events to determine whether such risk exists, and further studies are needed to evaluate this concern. Elimination diets of any type should be used with discretion and for as short a period as is suitable to treat the underlying EoE. Consultation with a board-certified allergist who is skilled in the management of IgE-mediated food allergy should be a strong consideration.

Therefore, although the evidence for efficacy of elemental diets is of moderate quality due to possible large effects, we suggest a conditional recommendation for elemental diet. Clinicians should consider patient age and preferences for alternative medical and dietary management therapeutic options when considering elemental diets.

Question 5. Should an Empiric Food Elimination Diet Be Used in Patients With Eosinophilic Esophagitis?

In patient with EoE the AGA/JTF suggests using an empiric six-food elimination diet over no treatment. *(Conditional recommendation, low quality evidence)*
Comment: Patients who put a higher value on avoiding the challenges of adherence to diet involving elimination of multiple common food staples and the prolonged process of dietary reintroduction may reasonably decline this treatment option.

Ten studies reported the effectiveness of an empiric, 6-food elimination diet with an overall, unweighted histologic response rate of 68%, although these also suffered from the same limitations of elemental diet studies in that all were single-arm, observational studies.[2] The RR for failure to achieve histologic remission relative to placebo based on historical controls was 0.38 (95% CI, 0.32–0.43).2 While uniformly beneficial from these observational studies, certainty in the effect estimate was rated down, as none of the studies were controlled trials. Although these studies were reported as "6-food" elimination diets, the inclusion of both tree nuts and peanuts as well as finned fish and shellfish could be considered as 8 separate food groups. Furthermore, this approach entails a higher number of actual foods because of the multiple different types of tree nuts, finned fish, and shellfish. In addition, 2 studies eliminated foods to which patients had abnormal skin testing and 1 also eliminated corn, rice, and legumes.

Several practical concerns limit the utilization of empiric elimination diets in EoE. Heterogeneity in response rates could reflect selection bias and potential for exclusion of patients with limited adherence to the diet. Incomplete or inconsistent diet reintroduction may reflect the challenges in adherence and activity assessment defining disease relapse (symptoms vs pathology) during the reintroduction process. As is common to any form of elimination diet, the time, risk, and financial burden of repeated endoscopies are also potential implementation barriers, as is long-term adherence after the identification of specific food trigger(s) in the re-introduction process, and the possible development of de novo IgE-mediated food allergy upon re-introduction.[11]

Several trials were reviewed utilizing empiric elimination diets that limited the number of avoided foods to 1, 2, or 4, given data by Kagalwalla et al suggestive that peanut/tree nut and finfish/shellfish reintroduction after 6-food elimination diet was associated with low rates of disease recurrence, and that not all major allergens needed to be removed initially.[2] Although this approach potentially reduces the burden of repeated endoscopies during the reintroduction process and can improve lifestyle and adherence, the effectiveness appears to be lower.[2] Nevertheless, the emerging data on less-restrictive diets may increase both provider and patient preference for an empiric elimination diet in EoE. Furthermore, less-invasive procedures, such as transnasal endoscopy (which does not require sedation), as well as nonendoscopic, office-based methods to assess disease activity through assessment of surrogate markers, are under development and could obviate the need for repeated biopsy sampling during the

Table 3. American Gastroenterological Institute and Joint Task Force on Allergy-Immunology Practice Parameters Guideline Recommendations on the Management of Eosinophilic Esophagitis

Recommendation	Strength of recommendation	Quality of evidence
1. Recommendation: In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition over no treatment.	Conditional	Very low quality
2. In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment.	Strong	Moderate
3. In patients with EoE, the AGA/JTF suggests topical glucocorticosteroids rather than oral glucocorticosteroids.	Conditional	Moderate
4. In patients with EoE, the AGA/JTF suggests using elemental diet over no treatment.	Conditional	Moderate
Comment: Patients who put a higher value on avoiding the challenges of adherence to an elemental diet and the prolonged process of dietary reintroduction may reasonably decline this treatment option.		
5. In patients with EoE, the AGA/JTF suggests using an empiric, 6-food elimination diet over no treatment.	Conditional	Low
Comment: Patients who put a higher value on avoiding the challenges of adherence to diet involving elimination of multiple common food staples and the prolonged process of dietary reintroduction may reasonably decline this treatment option.		
6. In patients with EoE, the AGA/JTF suggests using an allergy testing-based elimination diet over no treatment.	Conditional	Very low quality
Comment: Due to the potential limited accuracy of currently available, allergy-based testing for the identification of specific food triggers for EoE, patients may prefer alternative medical or dietary therapies to an exclusively testing-based elimination diet.		
7. Recommendation: In patient with EoE in remission after short-term use of topical glucocorticosteroids, the AGA/JTF suggests continuation of topical glucocorticosteroids over discontinuation of treatment.	Conditional	Very low quality
Comments: Patients who put a high value on the avoidance of long-term topical steroid use and its possible associated adverse effects, and/or place a lower value on the prevention of potential long-term undesirable outcomes (ie, recurrent dysphagia, food impaction, and esophageal stricture), could reasonably prefer cessation of treatment after initial remission is achieved, provided clinical follow-up is maintained.		
8. Recommendation: In adult patients with dysphagia from a stricture associated with EoE, the AGA/JTF suggests endoscopic dilation over no dilation.	Conditional	Very low quality
Comment: Esophageal dilation does not address the esophageal inflammation associated with EoE.		
9. Recommendation: In patients with EoE, the AGA/JTF recommends using anti–IL-5 therapy for EoE only in the context of a clinical trial.	No recommendation	Knowledge gap
10. Recommendation: In patients with EoE, the AGA/JTF recommends using anti–IL-13 or anti–IL-4 receptor α therapy for EoE only in the context of a clinical trial.	No recommendation	Knowledge gap
11. Recommendation: In patients with EoE, the AGA/JTF suggests against the use of anti-IgE therapy for EoE.	Conditional	Very low quality
12–15. Recommendation: In patients with EoE the AGA/JTF suggest using montelukast, cromolyn sodium, immunomodulators, and anti-TNF for EoE only in the context of a clinical trial.	No recommendation	Knowledge gap

Table 4. Knowledge and Evidence Gaps in the Management of Eosinophilic Esophagitis

Use of uniform end points among clinical trials to facilitate meaningful comparisons between therapies
Understanding the mechanisms and management of persistent symptoms despite histologic remission
Defining the extent and implications of variations in clinical outcomes for individual patients
Head-to-head studies comparing therapies to inform an algorithmic approach
Effectiveness of combinations of treatments (eg, PPI + diet, PPI + steroids, steroids + diet, steroids + dilation)
Prospective data on the natural history of EoE to inform decisions regarding maintenance therapy
Longer-term studies evaluating the efficacy of maintenance medical and diet therapies
Measurement of quality of life and nutritional status as outcomes
Use of biomarkers for diagnosis and monitoring
Validation of office-based, nonendoscopic disease monitoring methods for EoE activity
Appropriate timing of esophageal dilation in relation to use of medical or diet therapy (eg, should esophageal dilation only be performed after initiation of medical or diet therapy)
Impact of a baseline history of food exposure and related symptoms on the interpretation of allergy testing
Interaction between oral immunotherapy for food allergy and EoE
Impact of other associated atopic diseases (IgE-mediated food allergy, pollen food allergy, atopic dermatitis, asthma, allergic rhinitis)
Effectiveness of environmental allergen avoidance and immunotherapy

reintroduction process, thereby increasing the practical application of elimination diet for EoE.[12]

Question 6. Should Allergy-Based Testing Be Used for the Purpose of Identifying Food Triggers in Patients With Eosinophilic Esophagitis?

In patients with EoE, the AGA/JTF suggests allergy testing-based elimination diet over no treatment. (*Conditional recommendation, very low quality evidence*)
Comment: Due to the potential limited accuracy of currently available, allergy-based testing for the identification of specific food triggers, patients may prefer alternative medical or dietary therapies to an exclusively testing-based elimination diet.

Like elemental and empiric elimination diets, the evidence-base for using allergy-based testing to identify food triggers in patients with EoE is limited to single-arm, observational studies that have noncomparative study designs. Testing-based diets involve the scientific rationale of identifying a potential immune-mediated mechanism of food allergy involving either food-specific IgE or cell-mediated pathways, as opposed to empiric diets, which simply presume importance of common allergens as the trigger without identifying their direct role in the pathogenesis of the disease process. Twelve single-arm studies reported that 49.2% of subjects on an allergy testing–based elimination diet failed to achieve histologic remission (defined as <15 eos/hpf). The estimated RR for failure to achieve histologic remission relative to placebo based on historical controls was 0.57 (95% CI, 0.33–0.73).2 An important limitation in pooling these studies involves the degree of inconsistency due to different testing techniques (eg, skin-prick testing, serum-specific IgE testing, patch testing, or combinations of these) used in different studies. A sensitivity analysis failed to show any statistically significant difference between studies that used patch testing and those that did not; however, a sensitivity analysis excluding studies using serum-specific IgE was not performed. There may be a potential role for aeroallergen testing and treatment in EoE, which is presently being evaluated. Similar to potential risks for other dietary elimination strategies, there may be challenges with long-term adherence to dietary elimination and a potential risk of de novo IgE-mediated food allergy upon re-introduction.

Question 7. Should Maintenance Therapy Be Recommended in Patients With Eosinophilic Esophagitis?

In patient with EoE in remission after short-term use of topical glucocorticosteroids, the AGA/JTF suggests continuation of topical glucocorticosteroids over discontinuation of treatment. (*Conditional recommendation, very low quality evidence*)
Comments: Patients who put a high value on the avoidance of long-term topical steroid use and its possible associated adverse effects, and/or place a lower value on the prevention of potential long-term undesirable outcomes (eg, recurrent dysphagia, food impaction, and esophageal stricture), could reasonably prefer cessation of treatment after initial remission is achieved, provided clinical follow-up is maintained.

The chronicity and potential for disease progression provide the rationale for maintenance therapy of EoE. Retrospective natural history studies, placebo data from RCTs, and observational cohort studies support the likely chronic nature of symptoms and histopathology of EoE if either it is untreated or treatment is discontinued. Spontaneous disease remission has been reported but is uncommon in either pediatric or adult series, with limited description in the literature. Moreover, the available data in adults, albeit retrospective and subject to certain biases, have demonstrated the potential for long-term progression

from inflammation to esophageal strictures in a proportion of EoE patients with untreated disease.[1]

At this time, there are a paucity of studies and, therefore, very limited evidence, to define what constitutes effective maintenance therapy in EoE.[2] Only 1 very small trial randomized patients to a year of low-dose budesonide (0.25 mg twice a day) or placebo. While a significant reduction in eosinophil density was noted with active drug compared to placebo, only 36% of patients maintained an eosinophil density <5 eos/hpf at 1 year, and no dose-finding study supported the choice of the 0.25 mg twice a day as appropriate or sufficient vs other amounts. The use of a low maintenance dose of budesonide compared to the induction dose of 1 mg twice a day likely reduced the efficacy, although development of steroid-tolerance or selection of steroid-refractory patients is plausible. Additional single-arm observational studies of topical steroids also reported a high proportion of patients with histologic recurrence, but most also utilized dosing lower than administered during induction. In contrast, 3, single-arm observational studies of PPIs noted sustained histologic response in the majority of adults, despite dose reduction. Very limited data are available on the long-term effectiveness of elimination diets.

Until more data are available, the continued use of PPIs, topical glucocorticosteroids, or elimination diets are reasonable options, and this is a very preference-sensitive area of management. As there was limited evidence on PPI or diet therapies, the guideline recommendation was written to include topical glucocorticosteroids only. The limited data, as well as uncertainties in the natural history of EoE, provide very low confidence in the estimated benefits of long-term therapy for EoE, but must also be balanced with the risks of potential disease recurrence in individual patients when treatment is discontinued.

Question 8. Should Esophageal Dilation Be Used in Patients With Eosinophilic Esophagitis?

In adult patients with dysphagia from a stricture associated with eosinophilic esophagitis, the AGA/JTF suggests endoscopic dilation over no dilation, *(Conditional recommendation, very low-quality evidence)*
Comment: Esophageal dilation does not address the esophageal inflammation associated with EoE.

The systematic review in the accompanying technical report identified symptom improvement in 87% of patients who underwent esophageal dilation.[2] The assumption that no clinical improvement would occur if dilation was not performed likely overestimates this treatment benefit, given the reported symptom–placebo response noted in controlled trials. Furthermore, the evidence was considered low quality due to the retrospective, single-arm design of all but 1 of the reports, and the lack of a standard definition for what constitutes clinical improvement.[2,13] There is no associated benefit in terms of histologic improvement in eosinophilia with dilation, and dilation is considered a point of care option for the endoscopist.

Despite the initial case reports of increased complications from dilation in EoE, large series using a more conservative dilation approach in experienced centers found that major complications were not increased over rates expected from dilation of non-EoE, benign esophageal strictures.[2] The technical review identified no mortality associated with dilation. The pooled rate of perforation was 0.4%, hospitalization was 1.2%, and significant gastrointestinal hemorrhage was 0.1% after dilation. Most of the perforations were before 2009, with subsequent improvement in perforation rate after this time period, which was speculated to be the result of the adoption of a more conservative dilation approach. The most common adverse event reported was chest discomfort or pain. Of note, a patient questionnaire reported chest pain in 74% of patients after dilation, while retrospective chart review identified chest pain in only 7%, consistent with under-reporting of this dilation-associated outcome.[14]

For individual patients that place a higher value on the avoidance of the uncommon complications of dilation, it may be reasonable to use medical or dietary therapy before using dilation. Although strictures may be present in many EoE patients, it has not been demonstrated that these patients will necessarily respond better to dilation as opposed to alternative therapies. Esophageal strictures in EoE may be related to both inflammation and fibrosis, with the former being amenable to medical or diet therapy.[15,16] Retrospective case series have identified lower utilization of esophageal dilation among patients treated effectively with medical therapy. Esophageal dilation alone as a treatment modality for patients with EoE and daily dysphagia has only been reported in a small retrospective series and required maintenance dilation on average every 2 years.[17] The limited available data support the use of medical/diet therapy in combination with periodic dilation as necessary for adults with EoE and esophageal stricture.

Question 9. Should Anti–Interleukin-5 Therapy Be Used in Patients With Eosinophilic Esophagitis?

In patients with EoE the AGA/JTF recommends using anti–interleukin-5 therapy only in the context of a clinical trial. *(No recommendation; knowledge gap)*

Given the role of interleukin (IL)-5 in the maturation and release of eosinophils, there is a biologically plausible mechanism to support the use of anti–IL-5 therapy in patients with EoE. Three RCTs have been conducted, 2 using mepolizumab (1 involving adults and 1 in children) and 1 using reslizumab (children).[2] Participants in each study had higher baseline levels of esophageal eosinophilia and had frequently failed clinical management with other therapies. The results from the mepolizumab and reslizumab studies were combined for the purpose of GRADE analysis, despite

difference in ages of enrollees of these trials and similar mechanisms of action of these therapies, although formal noninferiority between the drugs has not been studied. While a reduction in tissue eosinophilia was observed, very few participants achieved prespecified histologic remission with <15 eos/hpf. More than 90% of patients in treatment groups failed to achieve histologic remission (RR, 0.92; 95% CI, 0.84–1.00). Symptomatic improvement was evaluated differently in each study and not grouped for GRADE analysis; however, a significant improvement in symptoms compared with placebo was not observed. No significant safety issues occurred in any of the trials.

Anti–IL-5 therapies are currently approved for use in moderate to severe persistent eosinophilic asthma. Initial studies in asthmatics demonstrated a reduction in tissue eosinophilia, but lack of clinical improvement. Follow-up studies that focused treatment on a more-specific patient population with steroid-resistant refractory eosinophilic asthma were needed to better understand potential clinical benefit. In a similar fashion, additional studies in patients with EoE are needed before use in clinical practice can be recommended.

Question 10. Should Anti–Interleukin-13 Therapy Be Used in Patients With Eosinophilic Esophagitis?

In patients with EoE, the AGA/JTF recommends using anti–IL-13 or anti–IL-4 receptor-α therapy for EoE only in the context of a clinical trial. *(No recommendation; knowledge gap)*

The IL-4 and IL-13 pathway is known to be involved in Th2 inflammatory conditions by directing eosinophil production, prolonged survival, and trafficking into tissues. Anti–IL-4 and anti–IL-13 therapy has shown benefit in Th2-associated conditions, such as atopic dermatitis and asthma, and there is a biologically plausible pathway for use in EoE. IL-13 is overexpressed in the esophageal mucosa and induces a gene expression profile that closely resembles the EoE transcriptome.

Three clinical trials have evaluated the efficacy of biologic therapy directed at the IL-13 pathway in EoE. One RCT involving 25 adult participants evaluated the use of anti–IL-13 therapy with QAX576 in EoE.[2] This study did not meet its primary end point of a >75% decrease in peak eosinophil counts 12 weeks after starting therapy. Mean esophageal eosinophil counts decreased compared with placebo, but no significant difference was observed in symptoms. Two additional RCTs that utilized monoclonal antibodies targeting the IL-13 pathway were not included, as the full articles were not available at the time of this systematic review, both of which showed promise. The first was a phase 2 study using RPC4046, a monoclonal antibody against IL-13 that demonstrated histologic and endoscopic efficacy compared to placebo in 99 adults with EoE.[18] The second study using dupilumab, a monoclonal antibody against the IL-4 receptor-α inhibiting the signaling of both IL-13 and IL-4, demonstrated symptom, histologic, and endoscopic efficacy compared to placebo in 47 adults with EoE.[19] While these newer preliminary results appear favorable, the use of anti–IL-13 therapy in EoE is not recommended for clinical use outside of a clinical trial at this time.

Question 11. Should Anti-IgE Therapy Be Used in Patients With Eosinophilic Esophagitis?

In patients with EoE the AGA/JTF suggests against the use of anti-IgE therapy for EoE. *(Conditional recommendation; very low-quality evidence)*
In patients with EoE, the AGA/JTF recommends topical steroids over no treatment *(strong recommendation, moderate quality evidence).*

IgE is involved in anti-helminthic responses and mediates type 1 hypersensitivity reactions. However, IgE is not known to be directly involved in the development or recruitment of eosinophils. Anti-IgE therapy is currently approved for use in patients with moderate to severe persistent atopic asthma and in patients with chronic urticaria who are refractory to first-line therapy.

There has been 1 RCT involving 30 adult participants evaluating use of anti-IgE therapy in EoE.[2] This study did not demonstrate any change in esophageal eosinophilia or reduction in symptoms. Based on limited evidence and lack of a biologically plausible mechanism, use of anti-IgE therapy in EoE is not recommended for clinical use. A conditional recommendation against use was made for anti-IgE therapy because of the quality of the RCT and the inclusion of the primary end point evaluated in this guideline (<15 eos/hpf). Other interventions, such as montelukast (did not include eos/hpf) and cromolyn sodium (very low sample size), had very major limitations and therefore insufficient evidence to recommend against and, therefore, no recommendation was made about their use.

Questions 12–15. Should Montelukast, Cromolyn, Immunomodulators, or Anti-TNF Therapy Be Used in Patients With Eosinophilic Esophagitis?

In patients with EoE, the AGA/JTF suggest using montelukast, cromolyn sodium, immunomodulators, and anti-TNF only in the context of a clinical trial. *(No recommendation; knowledge gap)*

Given the few studies and low quality of evidence, use of montelukast, cromolyn, immunomodulators, and anti-TNF therapies are not recommended for clinical use.[2] These therapeutic agents have been grouped together for the purposes of this guideline based on limited evidence for a

mechanistic role of their biologic markers in the development of EoE and limited studies surrounding each therapy.

Montelukast is a leukotriene receptor antagonist approved for use in the treatment of persistent asthma and exercise-induced bronchospasm. There is 1 RCT with adult participants (n = 41) comparing montelukast with placebo for maintenance therapy after histologic remission was already achieved and did not show any difference in symptoms. A histologic outcome was not included in the study design.

Cromolyn is a mast cell stabilizer that can prevent the release of inflammatory mediators in patients with allergic rhinitis and asthma. Mast cell and mast cell mediators have been implicated in EoE pathogenesis. There has been 1 RCT of cromolyn compared to placebo (n = 16), which demonstrated that only 1 patient treated with cromolyn achieved histologic remission.

Two immunomodulators (azathioprine and 6-mercaptopurine) have been retrospectively reported in a total of 4 patients with EoE but without any use of control subjects. All patients had EoE refractory to other therapies and multiple confounders that make it difficult to discern the impact of immunomodulatory therapy.[2]

TNF-related apoptosis-inducing ligand has been shown to promote inflammation in EoE. One observational case series described open-label use of anti-TNF in a clinical trial in 3 adult patients with EoE, all of whom had inadequate response to prior therapy.[2] The 3 case reports all reported different outcomes, including symptom scores, esophageal eosinophilia, and endoscopic changes. While interval improvement was observed, the differences in patient presentation, outcome measures, and lack of control subjects limit extrapolation of these findings.

Question 16. Should Repeat Esophagogastroduodenoscopy Be Used to Assess Patients With Eosinophilic Esophagitis After a Change in Treatment?

Numerous randomized, placebo-controlled trials of medical therapies for EoE included in this guideline and accompanying technical review have demonstrated significant improvement in symptom, endoscopic, and histologic end points using validated instruments.[2] Generally, the improvement in objective parameters of endoscopy and pathology have been more robust and consistent than the subjective improvement in symptom outcomes. Moreover, symptom and pathology outcomes are often discordant with one another, although disease remission currently remains anchored in histologic criteria. Evidence that the assessment of biologic activity with endoscopic and histologic parameters after treatment will reduce long-term disease complications is limited.[20] On the other hand, the use of symptom-based therapeutic assessment without esophagogastroduodenoscopy (EGD) and biopsy is limited and often misleading due to the ability of patients to modify dietary intake (ie, avoidance of hard-textured foods, excessive mastication, and prolonged meal times) to overcome objective histologic and endoscopic disease manifestations.[2,21] Dissociation between biologic activity and symptoms in adults is further compounded by the presence of strictures related to fibrostenosis that do not reflect mucosal inflammatory activity. This concept is evident in the symptom relief provided by esophageal dilation in the absence of improvement in esophageal inflammation.

The importance of the documentation of adequate suppression of mucosal inflammation after therapeutic intervention is indirectly supported by several retrospective studies that have associated prolonged, untreated disease with the increased prevalence of esophageal strictures.[1] In addition, retrospective case series have reported a reduction in frequency of esophageal dilation as well as food impactions, with improvement in pathology with topical glucocorticosteroids. Nevertheless, the supposition that reduction in esophageal eosinophilia will prevent progressive disease remodeling consequences requires confirmation in prospective, long-term studies. Similarly, although the use of endoscopic outcomes in gastroesophageal reflux disease and inflammatory bowel disease serve as precedents, their application to EoE needs further study to demonstrate their relevance to long-term disease outcomes.

While not a formal recommendation of this guideline, the use of repeat EGD with biopsy to assess disease activity after a change in therapy is reasonable. The criteria for histologic and endoscopic improvement after therapy are being actively investigated to identify core outcome metrics for both clinical trials and clinical practice.[2] Until such metrics are established, a threshold of <15 eos/hpf to define an adequate therapeutic response serves as a response criterion until a better measure is established.[3,22] The recommended frequency for EGD with biopsy during clinical follow-up is identified as a knowledge gap and may vary, depending on the severity of initial clinical presentation.

Question 17. What Is the Management of Patients Who Become Asymptomatic After Initial Proton Pump Inhibitor Treatment?

The recently published European and International consensus statements have removed the PPI trial from the diagnostic criteria for EoE.[7,8] Based on this revised definition of EoE, the use of repeat EGD with biopsy after PPI therapy would follow the same rationale as recommendation 16.

Conclusions

During the past 2 decades, EoE has emerged as a dominant cause of dysphagia worldwide. In concert with the rise in disease prevalence, an increasingly robust evidence base has provided insights into effective management strategies that are summarized in this guideline. At the same time, EoE is an evolving field with many unknowns and areas of controversy. Table 4 summarizes several knowledge and evidence gaps in the management of EoE that were identified in the creation of this document.

While swallowed, topical glucocorticosteroids were the only therapy to receive a strong recommendation, the evidence supported conditional recommendations for PPI and diet therapy as well as esophageal dilation. The use of novel, targeted biologic therapies for EoE are being actively evaluated. A common theme apparent in both the guideline and the accompanying technical review includes the need for uniform end points in clinical trials to facilitate meaningful comparisons between therapies. Furthermore, a deeper understanding of the natural history of EoE in both children and adults is needed to inform clinical decisions regarding the optimal use of disease monitoring and long-term, maintenance therapy. In the dawn of this new disease, much light has been shed and the future is bright.

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Conflicts of interest

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