American Gastroenterological Association 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 on the Management of Eosinophilic Esophagitis. The guideline was jointly developed by the AGA’s Clinical Practice Guideline Committee and the Joint Task Force on Allergy Practice Parameters 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.

1. Disclose conflicts of interest:

Conflict of interest disclosure: All members were required to complete disclosure statement. By mutual agreement with the JTF, these statements are maintained at the American Gastroenterological Association Institute (AGA) headquarters in Bethesda, Maryland and pertinent disclosure are published with the report.

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Review. Dr. Stukus received consulting fees from Aimmune Therapeutics, Inc. and Before Brands to deliver unbranded educational symposia. Dr. Greenhawt is supported by grant #5K08HS024599-02 from the Agency for Healthcare Quality and Research, is an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrommune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech, Nutricia, Kaleo Pharmaceutical, Nestle, Aquestive, Allergy Therapeutics, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Aimmune, DBV, Before Brands, multiple state allergy societies, the ACAAI, the EAACI; is an associate editor for the Annals of Allergy, Asthma, and Immunology; and is a member of the Joint Taskforce on Allergy Practice Parameters. These relationships are unrelated to the work on this guideline and pose no conflict of interest. The recommendations involving medications undergoing clinical trials were written by members of the guideline committee without conflict of interest.
Eosinophilic esophagitis (EoE) was first characterized as a distinct clinical entity by Attwood and Straumann in the early 1990s. 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.\textsuperscript{1} The past 25 years has witnessed the emergence of the field from small case series and observational studies to larger, international, multi-center, randomized controlled trials (RCTs) of both medical and dietary therapies.\textsuperscript{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 comprised of trials extending from 2 to 16 weeks. The majority of recommendations are based on the failure to achieve histologic remission of < 15 eosinophils/high power field (eos/hpf) as the definition of treatment effect.\textsuperscript{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 control 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 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 reviewed in the technical report 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 GRADE methodology.
The guideline was developed utilizing a process outlined elsewhere. Briefly, both the AGA and the JTF process for developing clinical practice guidelines incorporates GRADE methodology and best practices as outlined by the Institute of Medicine. GRADE methodology was utilized to prepare the background information for the guideline and the technical review which accompanies it. GRADE uses the PICO format, which frames a clinical question by defining a specific Population (P), Intervention (I), Comparator (C), and Outcomes (O). The PICOs 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 except for last two PICO questions which were addressed using a narrative review format. 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 the development in a joint manner through a collaboration between AGA and Joint Task Force for Allergy-Immunology Practice Parameters (JTF) that is comprised of the American Academy of Allergy, Asthma & Immunology (AAAAI), American College of Allergy, Asthma and Immunology (ACAAI). 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 upon prior consensus recommendations published in both the allergy and gastroenterology literature.

Table 1. GRADE Definitions on Strength of Recommendation

<table>
<thead>
<tr>
<th></th>
<th>For the Patient</th>
<th>For the Clinician</th>
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<tbody>
<tr>
<td><strong>Strong</strong></td>
<td>Most individuals in this situation would want the recommended course of action and only a small proportion would not.</td>
<td>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.</td>
</tr>
</tbody>
</table>
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 towards a decision.

Table 2. GRADE Definitions on Quality of Evidence

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>High</strong></td>
<td>We are very confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td><strong>Very Low</strong></td>
<td>We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.</td>
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Table 3: AGA-JTF Guideline Recommendations on the Management of Eosinophilic Esophagitis (EoE)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
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<tbody>
<tr>
<td>1. Recommendation: In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition over no treatment</td>
<td>Conditional</td>
<td>Very low quality</td>
</tr>
<tr>
<td>2. In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>3. In patients with EoE, the AGA/JTF suggests topical glucocorticosteroids rather than oral glucocorticosteroids</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td>4. In patients with EoE, the AGA/JTF suggests using elemental diet over no treatment</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Comment:</strong> 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.</td>
<td></td>
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<tr>
<td>5. In patients with EoE, the AGA/JTF suggests using an empiric, six-food elimination diet over no treatment</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Comment:</strong> 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. In patients with EoE, the AGA/JTF suggests using an allergy testing-based elimination diet over no treatment</td>
<td>Conditional</td>
<td>Very low quality</td>
</tr>
</tbody>
</table>
**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 patients with EoE in remission following short-term use of topical glucocorticosteroids, the AGA/ITF suggests continuation of topical glucocorticosteroids over discontinuation of treatment.

**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 (i.e., recurrent dysphagia, food impaction, and esophageal stricture), could reasonably prefer cessation of treatment after initial remission is achieved, provided clinical follow-up is maintained.  

| **Recommendation:** In patients with EoE, the AGA/ITF recommends using anti-IL-5 therapy for EoE only in the context of a clinical trial | Conditional | Very low quality |
| **Recommendation:** In patients with EoE, the AGA/ITF recommends using anti-IL-13 or anti-IL-4 receptor alpha therapy for EoE only in the context of a clinical trial | No recommendation | Knowledge gap |
| **Recommendation:** In patients with EoE, the AGA/ITF suggests against the use of anti-IgE therapy for EoE | Conditional | Very low quality |
| **Recommendation:** In patients with EoE, the AGA/ITF suggest using montelukast, cromolyn sodium, immunomodulators, and anti-TNF for EoE only in the context of a clinical trial | No recommendation | Knowledge gap |

**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 (PPI) reported an overall, unweighted histologic response rate of 42%. PPIs failed to induce histologic remission in approximately 2/3 of treated patients, compared with >85% of patients treated with placebo, for a RR of 0.66, (95% 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 proton pump inhibitor (PPI) duration, dosing and formulation. Furthermore, most studies were non-comparative, 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 Following 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 long-standing safety profile and ease of administration, patients may prefer to start with this form of therapy prior to 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 since, 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 or PPIREE).
Question 2. Should topical glucocorticosteroids be used in patients with EoE?

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 eight weeks compared treatment with topical budesonide or topical fluticasone to placebo. It is of note that most of these studies required patients first fail a PPI trial or excluded patients with known GERD, which may not reflect routine clinical practice or the most current consensus-driven recommendations. Two of the trials used formulations of topical steroids specifically developed 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 herein, 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 may occur in pediatric versus adult patients. All such factors may limit generalizability of this recommendation. Topical glucocorticosteroids failed to induce histologic remission in approximately 1/3 of treated patients, compared with >85% of patients treated with placebo, for a RR of 0.39, (95% CI 0.26-0.58). The certainty of this estimate is moderate; it was downgraded for inconsistency due to heterogeneity of the studies. In short-term studies of three months or less, there was no increased risk of adverse events in patients treated with steroids compared with placebo (risk ratio of 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 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 EoE?**

| 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 versus 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 four time a day (110 ug/puff for those < 10 years of age and 220 ug/puff for those 11-18 years) for 4 weeks followed by tapered dosing over 8 weeks. The primary endpoint was the histological response which was based on a score consisting of the percentage of basal cell hyperplasia and eosinophil density (eos/hpf). Both groups had similar histological 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 versus 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 EoE?**

<table>
<thead>
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<td>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.</td>
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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 eosinophils/hpf).\(^2\) This contrasts with failure to achieve histologic remission in 86.7% of a historical placebo comparison group glucocorticosteroid, 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 the context of overall dietary alternatives, and 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 if such risk exists and further studies are needed to evaluate this concern. Hence, elimination diets of any type should be used in discretion and for as short a period that 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 EoE?**

<table>
<thead>
<tr>
<th>In patient with EoE the AGA/JTF suggests using an empiric six-food elimination diet over no treatment (conditional recommendation, low quality evidence).</th>
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Ten studies reported the effectiveness of an empiric, six-food elimination diet (SFED) with an overall, unweighted histologic response rate of 68%, though 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 (0.32 to 0.43). 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 “six-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 on account of the multiple different types of tree nuts, fin fish and shellfish. In addition, two studies eliminated foods to which patients had abnormal skin testing and one 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 following 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.

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 SFED was associated with low rates of disease recurrence, and that not all major allergens needed to be removed initially. While this approach potentially reduces the burden of repeated endoscopies during the reintroduction process and may improve lifestyle and adherence, the effectiveness appears to be lower. Less invasive procedures such as transnasal endoscopy (which does not require sedation) as well as non-endoscopic, 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 reintroduction process, thereby increasing the practical application of elimination diet for EoE.\textsuperscript{12}

**Question 6. Should allergy-based testing be used for the purpose of identifying food triggers in patients with EoE?**

<table>
<thead>
<tr>
<th>6. In patients with EoE, the AGA/JTF suggests allergy testing-based elimination diet over no treatment (Conditional recommendation, very low quality evidence)</th>
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</thead>
<tbody>
<tr>
<td><em>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</em></td>
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</table>

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-armed, observational studies that have non-comparative study designs. Testing based diets involve the scientific rational 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 trigger without identifying their direct role in the pathogenesis of the disease process. Twelve single armed studies reported that 49.2\% of subjects on an allergy-testing based elimination diet failed to achieve histologic remission (defined as <15 eosinophils/hpf). The estimated RR for failure to achieve histologic remission relative to placebo based on historical controls was 0.57 (0.33 to 0.73).\textsuperscript{2} An important limitation in pooling these studies involves the degree of inconsistency due to different testing techniques (e.g., 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 EoE?

Recommendation: In patient with EoE in remission following 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 (i.e. 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 randomized controlled trials, and observational cohort studies support the likely chronic nature of symptoms and histopathology of EoE if it either is untreated, or if 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.\textsuperscript{1,19}

At this time, there are a paucity of studies, and therefore very limited evidence, to define what constitutes effective maintenance therapy in EoE.\textsuperscript{2} Only one very small trial randomized patients to a year of low dose budesonide (0.25 mg bid) 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 one year, and no dose finding study supported the choice of the 0.25mg BID as appropriate or sufficient versus other amounts. The use of a low maintenance dose of budesonide compared to the induction dose of 1 mg BID likely reduced the efficacy, although development of steroid-tolerance or selection of steroid-refractory patients is plausible. Additional single-armed 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, three, single-armed 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 either PPI, 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 only include topical glucocorticosteroids. 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 EoE?

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.)

A recent meta-analysis of 1607 patients in 39 publications who underwent esophageal dilatation found symptom relief in 85% in patients with dysphagia and EoE, although this evidence was considered low quality due to the retrospective, single arm design of these reports and the lack of a standard definition for what constitutes clinical improvement.2,13 There is no associated benefit in terms of histological improvement in eosinophilia with dilation, and dilation is considered a point of care option for the endoscopist. Of importance, despite the initial case reports of increased complications from dilation in EoE, large series using a more conservative dilatation approach in experienced centers found that complications were not increased over rates expected from dilation of non-EoE, benign esophageal strictures.2

A systematic review and meta-analysis of 977 patients who underwent 2034 dilatations for EoE found that the rate of perforation was 0.033% (95% CI 0-0.226%) with none of the perforations requiring surgical intervention nor related to subsequent patient mortality.2,14 Most of the perforations were prior to 2009 with subsequent improvement in perforation rate after this time period which was speculated to be the result of more conservative techniques. The use of balloon or bougies did not significantly increase rate of perforation though numerically balloons had a perforation rate of 0.06% (95% CI 0 – 0.37%) versus 0.02% (95% CI 0-0.34%) with bougies. Larger dilators (>17 mm diameter) were associated with an increased rate of perforation though this was not statistically significant since only 9 perforations were reported in these studies. The most common adverse event reported was chest discomfort in 24% (95% CI 5.9-41%) and GI hemorrhage occurring in 0.03% (95% CI 0-0.217%).
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 prior to using dilation. Though fibrostenotic disease may be present in many of these patients, it has not been demonstrated that these patients will respond better to dilation as opposed to alternative medical or diet therapies. Retrospective case series have identified a lower utilization of esophageal dilation among patients effectively treated with medical therapy. Esophageal dilatation alone as a treatment modality for patients with EoE and daily dysphagia has only been reported in a small retrospective series and required maintenance dilatation on average every two years. 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-IL-5 therapy be used in patients with EoE?**

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

Given the role of 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). 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 though formal non-inferiority between the drugs has not been studied. While a reduction in tissue eosinophilia was observed, very few participants achieved prespecified histologic remission with < 15 eosinophils/hpf.
Greater than 90% of patients in treatment groups failed to achieve histologic remission, for a RR of 0.92 (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-IL-13 therapy be used in patients with EoE?**

| In patients with EoE the AGA/JTF recommends using anti-IL-13 or anti-IL4 receptor alpha 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 Th-2 inflammatory conditions by directing eosinophil production, prolonged survival, and trafficking into tissues. Anti-IL-4 and anti-IL-13 therapy has shown benefit in Th-2 associated conditions such as atopic dermatitis and asthma, thus 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. This study did not meet its primary endpoint of > 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 manuscripts 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. The second study using dupilumab, a monoclonal antibody against the IL-4α receptor inhibiting the signaling of both IL-13 and IL-4, demonstrated symptom, histologic and endoscopic efficacy compared to placebo in 47 adults with EoE. 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 EoE?

In patients with EoE the AGA/JTF suggests against the use of anti-IgE therapy for EoE (conditional recommendation; very low-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. This study did not demonstrate any change in esophageal eosinophilia or reduction in symptoms. Based upon 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 endpoint evaluated in this guideline (eosinophils < 15/hpf). Other interventions, such as montelukast (did not include eosinophils/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 EoE?

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. These therapeutic agents have been grouped together for the purposes of this guideline based upon limited evidence for a mechanistic role of their biological 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 EGD be used to assess patients with EoE 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 endpoints 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
following treatment will reduce long-term disease complications is limited. On the other hand, the use of symptom-based therapeutic assessment without EGD and biopsy is limited and often misleading due to the ability of patients to modify dietary intake (i.e. avoidance of hard texture foods, excessive mastication, prolonged meal times) to overcome objective histologic and endoscopic disease manifestations. 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. 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 GERD 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 following therapy are being actively investigated to identify core outcome metrics for both clinical trials and clinical practice. 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. The recommended frequency for EGD with biopsy during clinical follow-up is identified as a knowledge gap and may vary depending upon the severity of initial clinical presentation.

**Question 17. What is the management of patients who become asymptomatic after initial PPI treatment?**

The recently published European and International consensus statements have removed the PPI trial from the diagnostic criteria for EoE. 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**

Over 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. While swallowed, topical glucocorticosteroids were the only therapy to receive a strong recommendation, the evidence supported conditional recommendations for proton pump inhibition 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 endpoints 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.
REFERENCES