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Technical review on the management of eosinophilic esophagitis: a report from the AGA institute and the joint task force on allergy-immunology practice parameters

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Abstract

Eosinophilic esophagitis (EoE) is a chronic inflammatory condition of the esophagus. Many new studies have been reported recently that describe EoE management. An expert panel was convened by the American Gastroenterological Association Institute and the Joint Task Force on Allergy-Immunology Practice Parameters to provide a technical review to be used as the basis for an updated clinical guideline. This technical review was developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Eighteen focused EoE management questions were considered, with 15 answered using the GRADE

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Supplementary Data

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framework and 3 with a narrative summary. There is moderate certainty in the evidence that topical glucocorticosteroids effectively reduce esophageal eosinophil counts to <15 per high-power field over a short-term treatment period of 4–12 weeks, but very low certainty about the effects of using topical glucocorticosteroids as maintenance therapy. Multiple dietary strategies may be effective in reducing esophageal eosinophil counts to <15 per high-power field over a short-term treatment period, with moderate certainty for elemental diets, low certainty for empiric 2-, 4-, and 6-food elimination diets, and very low certainty that allergy-based testing dietary eliminations have a higher failure rate compared to empiric diet elimination. There is very low certainty for the effect of proton pump inhibitors in patients with esophageal eosinophilia. Although esophageal dilation appears to be relatively safe, there is no evidence that it reduces esophageal eosinophil counts. There is very low certainty in the effects of multiple other medical treatments for EoE: anti–interleukin-5 therapy, anti–interleukin-13 therapy, anti-IgE therapy, montelukast, cromolyn, and anti-TNF therapy.

Keywords

Technical Review; Eosinophilic Esophagitis; Proton Pump Inhibitor; Swallowed Corticosteroids; Corticosteroids; Dietary Therapy; Elimination Diet; Elemental Diet; Targeted Elimination Diet; Biologic Therapy; Esophageal Dilation

Eosinophilic esophagitis (EoE) is a chronic, rare, and food antigen-driven Th2 inflammatory condition of the esophagus that is estimated to affect 1 in every 2000 people.¹ There is a large body of evidence that EoE subjects 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. The incidence of EoE is increasing. EoE can occur in children and adults and is more common in whites and males, and is associated with other atopic diseases. EoE negatively impacts the quality of life for patients and their families. Medical resource utilization costs in EoE may be significant for some.^{2,3}

EoE can be characterized by the associated symptoms, visual esophageal endoscopic findings, and histopathology. In adolescents and adults, symptoms often include dysphagia and food impaction, but can be less specific in children, and can include failure to thrive, feeding problems, vomiting, heartburn, and abdominal discomfort. Direct visual inspection of the esophagus in many but not all EoE patients can reveal rings, linear furrows, white plaques or exudates, edema or decreased vascularity, strictures, or luminal narrowing. Histopathology will reveal eosinophils in the esophageal epithelium, which can be defined as a threshold of 15 eosinophils per high-power field (eos/hpf). The primary outcome for all of the interventions for this report was achieving <15 eos/hpf except for esophageal dilation.

EoE has traditionally been distinguished from gastroesophageal reflux disease (GERD) by the failure of proton pump inhibitor (PPI) treatment to reduce esophageal eosinophilia below a prespecified threshold. Over the past 10 years, the diagnosis of EoE has been made in a patient who has symptoms of swallowing dysfunction and esophageal eosinophilia that persists despite PPI treatment, and this is the definition that is used as entry criteria for most

of the studies presented in this technical report based on previous guidelines.⁴⁻⁶ However, discerning EoE from GERD remains an area of controversy and active investigation, and the most recent diagnostic criteria for EoE leave the criterion of PPI failure to the clinician^{7,8} because PPI-responsive esophageal eosinophilia now is considered as part of the spectrum of EoE. As such, PPIs are increasingly considered as a treatment rather than as a diagnostic test for EoE, as described in a recent consensus document. In addition, the biological impact of PPIs to reduce expression of key EoE-related cytokines including eotaxin-3 in vitro and normalize the EoE transcriptome, and the multiple similarities between patients with suspected EoE who do and do not respond to a PPI, together underscore that PPI-responsive esophageal eosinophilia and EoE are potentially disorders in the same pathogenic spectrum.

The most common management approaches for EoE are topical glucocorticosteroids, dietary elimination, and esophageal dilation. Many new studies have been published recently. Therefore, the American Gastroenterological Association Institute and the Joint Task Force on Allergy-Immunology Practice Parameters (jointly sponsored by the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, and Immunology) formed a team to provide up-to-date guidance for EoE management. This technical review addresses focused clinical questions regarding different therapeutic strategies for managing children and adults with EoE. The results of this technical review were used to inform the development of an accompanying clinical guideline for EoE.

Methods

System for Rating the Quality of Evidence

This technical review and the accompanying guideline were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.⁹ The members of the technical review panel were selected by the American Gastroenterological Association Clinical Guidelines Committee and the Joint Task Force on Allergy-Immunology Practice Parameters based on their clinical content and guidelines methodological expertise. Each member underwent a thorough vetting process for potential conflicts of interest. Through an iterative process, and in conjunction with the guideline panel, the participants developed focused clinical questions on the role of specific interventions in the management of EoE. After the focused questions were approved by the organization's respective leadership groups, the technical review team identified relevant patient-important outcomes, systematically reviewed and summarized the evidence for each outcome across studies, and then rated the quality of the evidence across all outcomes for each clinical question using the GRADE framework.

Development of Focused Questions

Using the PICO format, which frames a clinical question by defining a specific Population (P), Intervention (I), Comparator (C), and Outcomes (O), the team developed clinically relevant questions. The PICOs focused on the use of therapeutics in patients with symptomatic EoE. Each of the selected PICO questions was addressed in this review using the GRADE framework except for 2 PICO questions, which were addressed using a narrative review format. Studies with children and adults were included. When possible, the

interventions were compared to placebo. When only trials compared to another intervention were available, the intervention was presented relative to another intervention (comparator). Supplementary Table 1 is a summary display of the 17 PICO questions in this technical report.

Outcomes

Potentially relevant patient-important outcomes were considered and rated in terms of importance, as summarized in Supplementary Table 2. Through consensus of the expert panel, with no voting necessary during the face-to-face review, and based on precedent literature, failing to achieve histologic remission of <15 eos/hpf was considered critical for decision-making.^{10,11} It was recognized that untreated inflammation can potentially lead to fibrostenotic disease,^{12–15} but also that symptoms do not always correspond with histology.^{16–18} Symptoms, changes in peak tissue eosinophil levels, and adverse effects were considered important for decision-making. If data on certain outcomes were not available, the a priori plan was to use indirect evidence to guide decision making if additional data were not provided after contacting the investigators.

Outcomes that are reported in the evidence profiles are those that were found in the literature. Several outcomes that were rated as important by the expert panel are not reported in the evidence profiles because they were not assessed in the included literature. Symptoms were reported using many different scales. Validated EoE symptom questionnaires were not available when most of the studies were performed. Therefore, symptom severity was an outcome that could not be synthesized in a summary estimate due to this heterogeneity in reporting. Similarly, not all studies utilized a validated endoscopy score, and endoscopic outcomes could not be synthesized. Finally, a key decision in forming the estimate of the effect for observational studies lacking a contemporaneous control group was to use the placebo control arm rate for failing to achieve histologic remission from topical corticosteroid studies. The expert panel was in consensus, with no voting needed, that the 86.7% estimate for failing to achieve histologic remission (≥ 15 eosinophils/hpf) in the placebo arm during a study period of 8 weeks was reasonable based on the overall information available in the literature.^{19–25}

Systematic Review Process

A common approach to study selection was used for each question. For all PICOs, we first considered high-quality systematic reviews for evidence synthesis, particularly those that synthesized data from randomized controlled trials (RCTs). If systematic reviews of RCTs were not available, we then looked to individual RCTs and generated summary estimates as needed. Systematic reviews of observational studies, and in particular, single-arm cohort/observational studies, were considered as the least-preferred option to inform the evidence, with rates pooled when possible. Case series with <5 cases and case reports were excluded, unless no other evidence for the question was available. Systematic reviews that were missing recent trial data were updated and re-analyzed rather than creating a de novo systematic review. When well-done systematic reviews were unavailable, we searched for primary articles using a preliminary search strategy. Next, preliminary evidence profiles were constructed using GRADEPRO (<https://gradeepro.org/>), and were reviewed iteratively

with the clinical experts (S.A.A., G.T.F., M.G., J.M.S., and E.S.D.), where feedback was provided about missing studies, missing data, and preliminary evidence ratings.

An additional, final systematic literature search was performed after the preliminary evidence profiles were constructed and reviewed with the expert panel to ensure completeness. Details of the search strategy are reported in the Supplementary Table 3. We conducted an electronic search using MEDLINE, EMBASE, and the Cochrane Library until May 13, 2018. A research librarian (K.K.) developed a single search strategy for MEDLINE and then adapted to EMBASE and Cochrane. The search strategy was iteratively refined to maximize sensitivity, working directly with the clinical experts. The search excluded letters, commentaries, editorials, notes, conference abstracts, and nonhuman studies. We only searched for clinical trials in the electronic literature search for all PICO questions except for the dietary interventions where observational studies were considered, a decision made by the expert panel after considering the preliminary evidence profiles. We searched the World Health Organization clinical trial registry to identify additional studies (<http://apps.who.int/trialsearch/>). An additional search to identify health disparities or other equity issues associated with the selected PICOs was carried out using the MEDLINE Health Disparities and Minority Health Search Strategy filter (https://www.nlm.nih.gov/services/queries/health_disparities_details.html).

Titles and abstracts were reviewed in duplicate by 2 authors (M.R. and R.S.). One methodologist (R.S. or M.R.) extracted data from eligible reports and a second methodologist (R.S. or M.R.) evaluated the accuracy of the data extraction. We contacted authors when key data were missing, first by attempting to reach the corresponding author by e-mail and then by trying a second author from the article if no response was received from the corresponding author. Disagreements were resolved by discussion with a third methodologist (Y.F.Y.). A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram was constructed (see Supplementary Figure 1).

Statistical Analysis

Pooled risk ratios with 95% confidence intervals (CI) were calculated when possible, using RevMan, version 5.3 (Cochrane Collaboration, Copenhagen, Denmark), or Open Meta[analyst] (Brown University, Providence, RI), particularly when single-arm rates were pooled. In RevMan, analyses were performed using a random-effects model. In OpenMeta[analyst], we used binary random effects using the DerSimonian-Laird method. Statistical heterogeneity was assessed using the I^2 statistic. Publication bias was assessed using funnel plots when possible. GRADEpro software was used to construct the evidence profiles and calculate the absolute effects. When historical controls were used, risk ratios (RRs) were presented and the resulting absolute effects were informed by applying the baseline risk from the untreated control arms from steroid RCTs to the RR. It is important to note that RR refers, in this technical report, to the risk of not achieving histologic remission in the treatment vs a comparator.

Results

PICO Question 1: *Should Proton Pump Inhibitors Be Used in Patients With Esophageal Eosinophilia?*

Evidence summary—We identified 23 observational studies, which reported that 58.3% (unweighted) of subjects on PPI failed to achieve histopathologic remission (<15 eos/hpf) compared to 86.7% (unweighted) of a placebo comparison group.

Quality of evidence—The certainty in the effect estimate was very low (see Table 1 and Supplementary Figure 2, PICO Question 1). The certainty in the estimate was downgraded for inconsistency.

Discussion—This question is related to patients with esophageal eosinophilia, who, depending on the study and inclusion criteria, may be different than patients with EoE. It is important to note that this is an indirect comparison because participants in the topical corticosteroid studies had failed PPI treatment. Understanding PPI response in EoE remains an active area of investigation. The inconsistency seen in the point estimates for histologic response was not clearly explained by any specific criteria (eg, pediatrics vs adult or inclusion/exclusion criteria). There were 2 RCTs identified that compared PPI to topical corticosteroid, and found similar rates of histologic remission (see Supplementary Table 4).

PICO Question 2: *Should Topical Glucocorticosteroids Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary—Eight double-blind placebo-controlled RCTs were identified. Summary estimates indicate that 35.1% of patients treated with glucocorticosteroids failed to achieve histologic remission compared to 86.7% of patients treated with placebo, leading to an RR of 0.39 (95% CI, 0.26–0.58). Adverse events were experienced by 43% of patients in the topical glucocorticosteroid group compared to 36% of those exposed to placebo, with an RR of 1 (95% CI, 0.85–1.19).

Quality of evidence—The certainty in the effect estimates was moderate for the outcome of histologic response (see Table 2 and Supplementary Figure 2, PICO Question 2). We downgraded for inconsistency due to heterogeneity ($I^2 = 77\%$). The certainty in the effect estimates was low for the outcome of adverse events. We rated down for indirectness given heterogeneity in how adverse events were defined and for imprecision given that the risk ratio crossed 1.

Discussion—RCTs were excluded if they did not have an explicit glucocorticosteroid vs placebo comparison,^{27,49–51} and if they did not include budesonide or fluticasone in the treatment group.⁵² Six meta-analyses were reviewed and excluded because they did not include the most recent RCTs published in the field, or included studies in addition to a placebo/glucocorticosteroid comparison.

After discussion among the expert panel, the following decisions were made regarding how to pool the data: a single pooled estimate is presented despite differences in type of glucocorticosteroid, delivery mechanism, dosages, patient population (adult/pediatric), and

manner of outcome reporting (peak vs mean counts). Notably, sensitivity analyses isolating these individual groups did not alter findings significantly, lending credence to the decision to pool topical glucocorticosteroid data. Most trials required a failed PPI treatment trial before enrolling subjects, or excluded patients with GERD.

Similar categories of data were reported across the 8 included RCTs on 3 outcomes: Histologic response (defined as any eosinophils <15/hpf), symptomatic response, and adverse events. For histologic response: (a) data are presented as failure to achieve histologic response, so RR of <1 means that patients in a given arm are less likely to fail to achieve histologic response, and (b) we approximated intention-to-treat estimates if not reported, by examining the CONSORT (Consolidated Standards of Reporting Trial) diagram and accounting for dropout. All participants who dropped out in any study arm were categorized as failing to achieve histologic remission.

For adverse events, there was a variable definition of adverse events (ranging from general (fever/fatigue) to skin/respiratory/gastrointestinal/endocrine disorders/infections, to those that needed drug discontinuation). Numbers for adverse events were taken from per protocol analyses (when possible). Potential adverse events have been summarized by Philpott et al⁵³ and include local infections, such as candida and viral, adrenal suppression, diminished growth, and fractures.

PICO Question 3: *Should Systemic Glucocorticosteroids Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary—We identified 1 RCT that compared prednisone to fluticasone in the treatment of EoE in children. We reported outcomes of “lack of histologic response” defined as failure to achieve <15 eos/hpf, and adverse events, a composite end point defined in the footnotes. Eleven of 40 patients (28%) in the prednisone arm vs 14 of 40 patients (35%) in the fluticasone arm failed to achieve histologic response (RR, 0.79; 95% CI, 0.41–1.52). Sixteen of 40 patients (40%) in the prednisone arm compared to 6 of 40 patients (15%) in the fluticasone arm experienced adverse events (RR, 2.67; 95% CI, 1.16–6.11).

Quality of evidence—The certainty in the estimates was moderate (see Table 3). Both outcomes were rated down for imprecision; the RR for clinical response had a CI that crossed 1 and adverse events had few events.

Discussion—A single RCT comparing systemic and topical glucocorticosteroids suggests similar efficacy but a higher rate of adverse events for patients receiving systemic glucocorticosteroid. Systemic adverse events were reported as a composite end point, defined in the study as hyperphagia, weight gain, and/or cushingoid features. Other potential adverse effects that have a longer potential time frame to develop, such as effects on bone health, immunity, cataract formation, glucose levels, and blood pressure were not measured. In the prednisone group, 16 of 40 patients (40%) experienced systemic adverse events; 3 of these 16 exited the study before week 4 and were transitioned to the fluticasone group (outside the protocol). In the fluticasone group, 6 of 40 patients (15%) patients experienced esophageal candida overgrowth, though none did in the prednisone arm; all of these candida

esophageal patients were free of the presenting symptoms by week 4. This single study was conducted in children and may not be applicable to adults.

PICO Question 4: *Should an Elemental Diet Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary—We identified 6 observational studies reporting that 6.4% of subjects on elemental diet failed to achieve histopathologic remission (<15 eos/hpf) compared to 86.7% in a placebo comparison group (taken as a historical comparison group from swallowed topical steroid data) (RR, 0.07; 95% CI, 0.05–0.12).

Quality of evidence—The certainty in the effect estimate was moderate (see Table 4 and Supplementary Figure 2, PICO Question 4). The certainty in the estimate was rated up for anticipated large effect.

Discussion—There were differences in the effect estimates when grouping children and adult studies, with adult studies having a lower proportion of study participants achieving histologic remission. This comparison is limited by use of a historical comparison group composed of placebo-treated patients in topical steroid studies, which is an indirect but permissible method under GRADE to handle such situations where only single-arm observational studies exist. Symptom response was reported for 4 studies, but could not be synthesized due to considerable differences in the way symptoms were reported. Of the 6 studies used for the efficacy assessment, 3 specifically measured nutritional status and 1 measured overall quality of life. Difficulty adhering to an elemental diet was raised as an important consideration for this intervention. Potential harms of this intervention were raised by the expert panel and include the interruption of developmental progress of eating for children, the potential need for gastrostomy tube placement, and the risks associated with repeated endoscopies needed when food is ultimately re-introduced. Risk of developing IgE-mediated food allergy after a period of food elimination has not been described in EoE, but has been described in case reports of children with atopic dermatitis.⁵⁴ Risk of prolonged peanut avoidance vs early introduction of peanut in the first year of life has been shown as a factor influencing peanut allergy development in children with either severe eczema and/or known egg allergy,⁵⁵ but has not been described in EoE and it is unclear how such data would therefore apply. Consultation with an allergist would be recommended in this situation to manage potential competing risks and harms with avoidance diets that would prolong introduction of foods such as peanut (and possibly egg) in children in their first year of life, and potentially place them at risk for developing IgE mediated food allergy. Finally, the expert panel noted that the consideration of an elemental diet would be made in the context of other management options, including other dietary management options, such as empiric food elimination (eg, 6-food elimination diet) or testing-based elimination diet and with careful consideration for the age of the patient, potential detrimental effects of widespread food elimination, and patient preferences. The elemental diet intervention has the highest response rate compared to the other dietary interventions.

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

PICO Question 5a: *Should an Empiric 6-Food Elimination Diet Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary: We identified 10 single-arm observational studies that reported that 32.1% (unweighted) of subjects on an empiric elimination diet failed to achieve histopathologic remission (<15 eos/hpf) compared to 86.7% of a placebo comparison group (taken as a historical comparison group from swallowed topical steroid data) (RR, 0.38; 95% CI, 0.32–0.43).

Quality of evidence: The certainty in the effect estimate was low due to non-comparative single-arm study designs (see Table 5 and Supplementary Figure 2, PICO Question 5a).

Discussion: Symptom response was reported for 3 studies but could not be synthesized due to considerable differences in the way symptoms were reported. Of the 10 studies used for the efficacy assessment, 2 specifically measured nutritional status and 1 formally measured overall quality of life. Difficulty adhering to an empiric diet where 6 foods were eliminated was raised as an important consideration for this intervention. Empiric diet approaches with fewer foods may improve adherence to dietary avoidance and be associated with fewer endoscopies required to identify food triggers. The 6 foods eliminated in these studies were not all the same 6 foods. Potential harms of this intervention were raised by the expert panel and include the effect on nutrition and the risks associated with repeated endoscopies needed when food is ultimately re-introduced. Finally, the expert panel noted that the consideration of an empiric diet would be made in the context of other management options, including other dietary management options, such as elemental or testing-based elimination diets.

PICO Question 5b: *Should an Empiric 4-Food Elimination Diet Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary: We identified 3 single-arm studies reporting that 43.1% (unweighted) of subjects on an empiric elimination diet failed to achieve histopathologic remission (<15 eos/hpf) compared to 86.7% (unweighted) of a placebo comparison group (taken as a historical comparison group from swallowed topical steroid data) (RR, 0.46; 95% CI, 0.42–0.57).

Quality of evidence: The certainty in the effect estimate was low due to non-comparative single-arm study designs (see Table 6 and Supplementary Figure 2, PICO Question 5b).

Discussion: The 6-food elimination diet estimate for not achieving histologic remission was slightly lower but similar (32% compared to 43%) than for 4-food elimination diet. Similar to the 6-food elimination diet, potential harms of this intervention were raised by the expert panel and include the effect on nutrition and the risks associated with repeated endoscopies needed when food is ultimately re-introduced.

PICO Question 5c: *Should an Empiric 2-Food Elimination Diet Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary: We identified 2 single-arm studies reporting that 57.9% (unweighted) of subjects on an empiric elimination diet failed to achieve histopathologic remission (<15 eos/hpf) compared to 86.7% (unweighted) of a placebo comparison group (taken as a historical comparison group from swallowed topical steroid data) (RR, 0.66; 95% CI, 0.57–0.77).

Quality of evidence: The certainty in the effect estimate was very low due to non-comparative single-arm study designs and was further rated down for imprecision due to low information size (see Table 7 and Supplementary Figure 2, PICO Question 5c).

Discussion: The 6- and 4-food elimination diet estimates for not achieving histologic remission were slightly lower than for 2-food elimination (32% and 43% compared to 58%). In the study by Molina-Infante et al,⁶⁷ the 2 foods eliminated were milk and wheat. In the study by Reed et al,⁷¹ the 2 foods were milk and soy, and the participants had previously been treated with a combination of topical steroids and 2-food elimination in the prior 3 months. Potential harms of this intervention were raised by the expert panel and include the effect on nutrition and the risks associated with repeated endoscopies needed when food is ultimately re-introduced, although fewer for an empiric 2-food elimination diet than a 4- or 6-food elimination diet. Finally, the expert panel noted that the consideration of an empiric diet would be made in the context of other management options, including other dietary management options, such as elemental, other empiric elimination strategies, and testing-based dietary elimination.

PICO Question 5d: *Should an Empiric Single-Food Elimination Diet Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary: We identified 2 single-arm studies which reported that 45.9% (unweighted) of subjects on a single food empiric elimination diet failed to achieve histopathologic remission (<15 eos/hpf) compared to 86.7% (unweighted) of a placebo comparison group (taken as a historical comparison group from swallowed topical steroid data).

Quality of evidence: The certainty in the effect estimate was very low due to non-comparative single-arm study designs and was further rated down for imprecision due to low information size (see Table 8 and Supplementary Figure 2, PICO Question 5d).

Discussion: The 6- and 4-food elimination diet estimates for not achieving histologic remission were slightly lower than for single-food elimination for 2-food elimination (32% and 43% compared to 46%) but was lower than for 2-food elimination (58%). The higher rates of remission with single food (milk) compared to 2-food (both of which included milk) elimination are not easily explained based on study design or patient characteristics and are very uncertain based on the assessment of quality of the evidence. While the risks with a single-food elimination strategy are lower compared to 2-, 4-, or 6-food elimination, similar potential harms of this intervention were raised by the expert panel, which include the effect

on nutrition and the risk associated with endoscopy (though only 1 follow-up endoscopy because only 1 food was eliminated). Finally, the expert panel noted that the consideration of an empiric diet would be made in the context of other management options, including other dietary management options, such as elemental, other empiric elimination strategies, and testing-based dietary elimination.

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

Evidence summary—We identified 12 single-arm studies reporting that 49.2% (unweighted) of subjects on a testing-based elimination diet failed to achieve histopathologic remission (<15 eos/hpf) compared to 86.7% (unweighted) of a placebo comparison group (taken as a historical comparison group from swallowed topical steroid data).

Quality of evidence—The certainty in the effect estimate was very low due to non-comparative single-arm study designs (see Table 9 and Supplementary Figure 2, PICO Question 6).

Discussion—Inconsistency was noted and thought to be most likely related to the different testing approaches that were used to inform the dietary elimination. Different studies used different testing techniques, or combinations of techniques, including skin-prick testing, serum IgE testing, or patch testing. Some studies used all 3 methods to select the dietary intervention. We performed a sensitivity analysis that found 41% (95% CI, 18%–64%) failed to achieve remission in studies in which patch testing was used and 61% (95% CI, 38%–83%) in studies not using patch testing. Thus, there were more favorable outcomes in studies in which patch testing was performed, but the outcomes were not clearly better (considerable CI overlap) and there is very low certainty in this comparative effect estimate. Symptom response was reported for 4 studies but could not be synthesized due to considerable differences in the way symptoms were reported. Of the 10 studies used for the efficacy assessment, 1 specifically measured nutritional status and none formally measured overall quality of life. Difficulty adhering to an elimination diet was raised as an important consideration for this intervention. Potential harms of this intervention were raised by the expert panel and include the effect on nutrition and the risks associated with repeated endoscopies needed when food is ultimately re-introduced. The expert panel noted that the consideration of a testing based diet would be made in the context of other management options, including other dietary management options, such as elemental or empiric dietary elimination. Finally, the expert panel discussed the potential role of aeroallergen testing and treatment in EoE.

Allergy testing–based avoidance for aeroallergens was not the subject of this PICO question, but is included here in the allergy testing discussion due to growing evidence that EoE subjects have aeroallergen sensitization and concurrent atopic diseases, including asthma, allergic rhinitis, and eczema. There is evidence that aeroallergens may be important triggers for EoE. There are currently only very small case series reporting interventions with aeroallergen avoidance or aeroallergen immunotherapy in patients with EoE.

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

Evidence summary—There is 1 RCT of continuing therapy compared to placebo for patients who had achieved clinical and histologic remission. The risk ratio was 0.70 (95% CI, 0.38–1.30) for failing to maintain histologic remission, defined for that study as <20 eos/hpf.

Quality of evidence—The certainty in the effect estimate was very low (see Table 10 and Supplementary Figure 2, PICO Question 7). The certainty in the estimate was rated down for indirectness as the intervention used a delivery mechanism and dose of topical corticosteroid that is different than most previously reported corticosteroid studies. The certainty was also downgraded twice for very serious imprecision due to very low information size.

Discussion—A single very small RCT of low-dose topical glucocorticosteroid (0.25 mg budesonide twice daily) failed to show or to exclude a beneficial effect on maintaining remission in patient who had previously achieved it, using an absolute threshold of <20 eos/hpf. However, no patient in the placebo group met the definition of complete response at 1 year (<5 eos) compared to 36% of the active arm, which was a strong trend ($P = .06$). Similarly, the absolute eosinophil counts were significantly lower in the treatment arm compared to placebo (32 eos/hpf vs 65 eos/hpf; $P = .02$). Quality of life was not described and no significant harms were identified. There are observational cohort studies of topical glucocorticosteroids and other maintenance treatment options that provide some additional evidence.

We found 6 single-arm observational cohorts for topical glucocorticosteroids. Butz et al²⁰ reported that 11 of 15 were able to maintain remission on a lower dose of topical glucocorticosteroid (fluticasone 0.88 mg) over 3 months. Andreae et al⁸² reported on 54 pediatric patients treated long term with swallowed fluticasone and with mean follow-up of 20 months found 63% remained in histologic remission. Dellon et al⁸³ reported in an abstract that 42% of their cohort were able to maintain remission on budesonide 2 mg/d. Greuter et al⁸⁴ reported that of 33 people who had achieved clinical and histologic remission for 6 months, 27 experienced relapse with an average time-to-relapse of 22 weeks after stopping topical glucocorticosteroids. Eluri et al⁸⁵ reported that 20 of 33 adults who were using topical glucocorticosteroids experienced a relapse when followed over a 12-month period. Rubinstein et al⁸⁶ reported that 7 of 8 children who attempted to reduce budesonide to a 3-times per week dosing schedule from a daily schedule experienced a relapse.

Alexander et al⁸⁷ was profiled earlier in this technical report, and is listed here because the subjects were in remission when they were randomized to montelukast or placebo.

We identified 3 long-term PPI studies that reported remission/relapse rates over extended time periods. Molina-Infante et al⁸⁸ reported that 55 of 75 remained in remission on PPI with a mean follow-up length of 26 months. Gomez-Torrijos et al³⁹ reported that 31 of 38 remained in remission when dose of PPI reduced to once daily, and 15 of 18 remained in remission when daily high-dose PPI was reduced to regular dose PPI. Gutierrez-Junquera et

al⁴⁸ reported that 17 of 57 failed to maintain remission over a 1-year period on 1 mg/kg per dose twice daily of PPI.

We identified 3 single-arm cohorts of long-term dietary treatment. Lucendo et al⁸⁹ reported that 25 of 42 who had initially achieved remission with dietary therapy remained in remission 52 weeks later, with many patients dropping out of the study. Philpott et al⁹⁰ reported that 10 of 10 who maintained dietary therapy remained in remission with a mean follow-up length of 36 weeks. Reed et al⁶⁸ reported that 10 of 10 who maintained dietary therapy remained in remission over a mean follow-up length of 25 weeks.

Overall, it appears clear from the placebo arms of randomized trials, natural history studies, and cohort studies that if treatments in EoE are stopped, then disease activity (including symptomatic, endoscopic, and histologic) has a high chance of recurring. The difficulty is that there are few data to guide either treatment or surveillance of long-term treatment in EoE. A general approach is to repeat an endoscopy for monitoring after treatment changes, which is discussed in a later question in this document. For dietary treatment, continuing to avoid confirmed food triggers should be effective, but may have significant nutritional and/or quality of life deficits, depending on the nature and duration of prolonged avoidance. However, the details of dosing, treatment intensity, and endoscopic surveillance frequency remain areas that need to be studied.

PICO Question 8: *Should Esophageal Dilation Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary—Histologic remission was not assessed for this intervention. Dilation should be considered an acute and adjuvant rather than an isolated chronic management strategy. Estimates were taken from the Dougherty et al⁸⁹ meta-analysis that investigated the use of dilation in patients with EoE. Data for outcomes of interest were extracted and pooled from studies included in the Dougherty meta-analysis that explicitly noted that they were performed with more than 5 participants. We summarized outcomes on clinical improvement as well as adverse events (mortality, perforation, hospitalization, and hemorrhage). Rates for each outcome are presented. The assumption was that no clinical improvement or adverse events would reasonably occur if dilation was not performed. Eighty-seven percent of patients experienced clinical improvement with esophageal dilation in symptoms (but not esophageal eosinophil counts). There was no mortality associated with dilation. The pooled perforation rate was 0.4%, hospitalization was reported after 1.2% of dilations, and significant gastrointestinal hemorrhage was reported in 0.1% of dilations.

Quality of evidence—The certainty in the effect estimate was very low across all outcomes (see Table 11 and Supplementary Figure 2, PICO Question 8). We rated down for risk of bias given that there was no control group. This, combined with the fact that we started with a majority of observational data, yielded very low certainty in the effect. It is also important to note that the assessment of clinical improvement does not account for concomitant use of medication or diet. We did not rate down for indirectness, although it was noted that patients who need dilation have fibrostenotic disease. Though this population may be distinct from those included in studies where therapeutic management with

medications was investigated, for “clinical improvement,” we did not rate down for inconsistency despite heterogeneity of the pooled estimate (I^2); our assumption was that dilation does indeed result in symptomatic improvement.

Discussion—There are 3 meta-analyses from 2017 that investigated the use of dilation in patients with EoE.^{89–91} We compared them, found Dougherty et al⁸⁹ to be the most inclusive after discussion with the expert panel, and used that study as the basis for our evidence profile. Use of dilation in this patient population was not associated with any noted safety risks. Clinicians should recognize that dilation is not a treatment for the inflammation associated with EoE per se, but rather a treatment directed at the dysphagia symptoms associated with EoE. Histologic outcomes are not routinely reported in dilation studies, nor are biopsies taken during dilation, and this measure is not being discussed in the context of a management strategy that would decrease esophageal eosinophilia. We recognized that there was significant variability in how several outcomes were measured in the constituent studies. Rates and absolute effects were presented because the majority of the included studies had no control group. There were 3 studies of children and 2 studies of children and adults mixed together of the 37 studies included; therefore, the evidence for use of dilation for dysphagia from a stricture associated with EoE is primarily derived from adult populations.

PICO Question 9: *Should Anti-Interleukin-5 Therapy Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary—There are 3 RCTs of anti-IL-5 therapy compared to placebo. Anti-IL-5 treatment had little or no effect; 94.4% of patients assigned to anti-IL-5 therapy failed to achieve histologic remission compared to 93.9% of the placebo group (RR, 0.92; 95% CI, 0.84–1.00).

Quality of evidence—The certainty in the effect estimate was low (see Table 12 and Supplementary Figure 2, PICO Question 9). The certainty in the estimate was downgraded for indirectness because the participants in this study were different than other interventions in that many had failed the other interventions before entering the trials. The certainty was also downgraded for imprecision because the CI included 1.

Discussion—Very few individuals in the intervention or placebo arms achieved the prespecified histologic remission rate of <15 eos/hpf. We grouped 2 different drugs with similar mechanisms of action—mepolizumab and reslizumab—for the effect size estimate. One of the studies⁹³ did not have a true placebo group, but instead used a low dose of mepolizumab as a comparator. The participants in these studies frequently failed other treatments and had higher levels of esophageal eosinophilia upon entry into the study than in studies for other interventions. Symptom outcomes were reported differently in the 3 studies and therefore were not grouped to create an effect estimate. Quality of life was reported in 1 study,⁹⁴ and there were no major signals of harms reported in the 3 studies.

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

Evidence summary—There is 1 published RCT of anti-IL-13 therapy compared to placebo. The RR was 1.08 (95% CI, 0.81–1.40) for participants in the anti-IL-13 arm failing to achieve histologic remission compared to placebo.

Quality of evidence—The certainty in the effect estimate was low (see Table 13). The certainty in the estimate was downgraded for imprecision due to very low information size and for indirectness as patients who entered the study were more likely to have failed other treatments and have very high baseline esophageal eosinophilia.

Discussion—A single small RCT failed to show or exclude an effect of anti-IL-13 in EoE. Quality of life was not described and no significant harms were reported. The expert panel identified 2 additional RCTs, which are reported as abstracts but not yet published as full manuscripts. These 2 studies each included interventions that are somewhat different than in Rothenberg et al.⁹⁵ In Hirano et al,⁹⁶ dupilumab, an IL-13/IL-4 receptor blocker, was compared with placebo. In the dupilumab arm, 4 of 23 failed to achieve histologic remission <15 eos/hpf compared to 24 of 24 in the placebo arm (RR, 0.17; 95% CI, 0.07–0.42). In Hirano et al,⁹⁷ 2 doses of an anti-IL-13Ra1/Ra2 blocker, was compared to placebo in 99 subjects. The mean eosinophil counts were significant reduced from baseline for both doses levels compared to placebo (–99.9 eos/hpf for high dose, –94.8 eos/hpf for low dose, and –4.4 eos/hpf for placebo; all comparisons $P < .0001$).

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

Evidence summary—There is 1 RCT of anti-IgE therapy compared to placebo. The RR was not estimable because no subjects in either trial arm achieved histologic remission.

Quality of evidence—The certainty in the effect estimate was very low (see Table 14). The certainty in the estimate was downgraded for imprecision due to very low information size and for indirectness because subjects were selected who failed topical steroid.

Discussion—A single very small RCT showed no effect of omalizumab in EoE. We identified an observational cohort,⁹⁸ but elected to only consider the RCT, given the stronger study design and larger overall number of subjects. Quality of life or harms were not described in the RCT.

PICO Question 12: Should Montelukast Be Used in Patients With Eosinophilic Esophagitis?

Evidence summary—There is 1 RCT that compares montelukast with placebo for maintenance therapy after subjects had achieved symptomatic and histologic remission,⁸⁷ and 4 observational studies that report outcomes after montelukast use (Attwood et al,¹⁰⁰ n = 8; Vanderhoof et al,¹⁰¹ n = 8; Lucendo et al,¹⁰² n = 11; Stumphy et al,¹⁰³ n = 8). Based on the RCT, the RR for the recurrence of solid food dysphagia was 0.79 (95% CI, 0.51–1.21). Failing to achieve histologic remission of <15 eos/hpf was not measured in this trial.

Quality of evidence—The certainty in the effect estimate was very low (see Table 15). The certainty was downgraded for serious indirectness because subjects in the study had already achieved remission with topical glucocorticosteroid and for very serious imprecision due to very low information size. The observational data were not summarized in an evidence profile.

Discussion—The findings from the RCT are most relevant to patients who had already achieved remission after taking topical glucocorticosteroids. However, the certainty about the efficacy of montelukast for EoE after patients achieved remission with topical glucocorticosteroid is very low. The findings are not informative for the outcome of histologic remission because this outcome was not measured in the single clinical trial of montelukast for EoE. The trial was performed in adults and therefore the data may not be applicable to children. The findings are not directly relevant for patients who are newly diagnosed with EoE and have not started any previous treatments.

PICO Question 13: *Should Cromolyn Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary—There is 1 RCT of cromolyn compared to placebo. Based on the trial, 89% of subjects (8 of 9) treated with cromolyn failed to achieve histologic remission compared to 100% (7 of 7) in the placebo arm.

Quality of evidence—The certainty in the effect estimate was low (see Table 16). The certainty in the estimate was downgraded twice for very serious imprecision given the very low number of study participants and because the 95% CI crosses 1.

Discussion—Mast cells are implicated in EoE pathogenesis. Therefore, targeting mast cells with cromolyn has biological plausibility. The single, small study performed with cromolyn does not exclude the possibility of a benefit for cromolyn in patients with EoE. An observational study of 14 children with EoE treated with cromolyn found that none of the children had improvement in histology or symptoms.⁵⁷

PICO Question 14: *Should Anti-TNFs Be Used in Patients With Eosinophilic Esophagitis?*

Evidence summary—There is 1 observational study, a case series described as an open-label, nonrandomized pilot T1 translational trial that investigated the use of infliximab as acute therapy in 3 adults with EoE who were steroid-resistant and included patients had active EoE.¹⁰⁵ Three outcomes were measured: response as inferred by study report of esophageal eosinophilic infiltration, response as inferred by symptom score (Straumann's Criteria), and endoscopic alterations (Straumann's Criteria). Results are described narratively because quantitative summary estimates were not presented in the included study.

Quality of evidence—The overall certainty in the effects was very low. The certainty was rated down due to risk of bias (no control population, the possibility of selection bias, and that fact outcome measures may not be well-validated). We could not assess publication bias, effect size, or confounding. It is a relevant patient population, though one that is refractory to standard therapy. We did rate down for indirectness given that it was a population that was refractory to standard therapy.

Discussion—Active EoE was defined clinically as dysphagia (when not on anti-inflammatory therapy) and histologically by a peak cell density of >24 eos/hpf (is this also on anti-inflammatory therapy?). Included patients had “inadequate response to prior treatment.” This was explained by the authors as patients 1 and 3 were almost free of symptoms during maintenance therapy with topical fluticasone, but immediately after cessation of the medication, symptoms reappeared. Patient 2 had been receiving systemic corticosteroid treatment for the past 8 years and needed at least 10 mg of prednisone per day for symptom control. Patients 2 and 3 had previously undergone repeated dilations for the treatment of strictures. No adverse events were reported.

PICO Question 15: *Should Immunomodulators Be Used in the Treatment of Eosinophilic Esophagitis?*

Evidence summary—Two observational studies were included identified that investigated the use of immunomodulators in EoE. The outcome listed in the evidence profile was response, though it was variably defined in the included studies as “symptomatic remission” or “clinical remission.” Results are described narratively because quantitative summary estimates were not presented in the included study.

Quality of evidence—The certainty in the effect estimate was very low. The quality of the evidence was rated down for the lack of control populations, suspected selection bias, possible confounding, and outcomes that were not well-defined. There was also concern regarding indirectness of the included patient population as a more severe disease phenotype, given that included patients were steroid-dependent. We did rate down for indirectness given that it was a population that was refractory to standard therapy.

Discussion—The evidence was derived from 2 articles with a total included population of 4 people, therefore, the evidence base for immunodulator treatment in patients with EoE is very small.^{106,107} In these case series, it is not clear whether the histologic changes were related to starting the immunomodulator or other factors, such as the attempts with withdraw systemic steroid. Therefore, it is difficult to draw any conclusions about how immunomodulators work for EoE.

Narrative Summaries

The following 2 PICO questions are addressed as narrative summaries based on the consensus of the expert panel that data in format amenable to GRADE analysis were not available.

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

The role of performing upper endoscopy and biopsy for monitoring EoE biologic disease activity (endoscopic severity assessed visually with the eosinophilic esophagitis endoscopic reference score classification and esophageal eosinophilia assessed histologically) has not been formally studied in higher-quality trials. However, there are numerous studies that support performing endoscopy to survey disease activity. This is based on several concepts.

The first is an understanding that for many patients, the natural history of untreated esophageal eosinophilia is a progression from an inflammatory to a fibrostenotic phenotype.¹ Cohort studies of untreated patients and placebo groups of RCTs repeatedly demonstrate that esophageal eosinophilia does not resolve over time and that patients with EoE do not “grow out of it.”¹⁰⁸ Furthermore, a set of 4 studies from different centers in the United States and Europe independently show that the longer the duration of disease before diagnosis (as a proxy for time before treatment), the higher the proportion of patients who have a stricture or fibrostenotic phenotype at the time of diagnosis.^{12–15} For example, in 1 study, >80% of patients had strictures if the diagnostic delay was >20 years. Other studies document progression in distinct patients.¹⁰⁹ Therefore, because there is a consequence to persistent eosinophilic inflammation in the esophagus (fibrosis leading to strictures), it is important to survey to confirm that esophageal eosinophilia has been corrected. Second, symptoms only modestly correlate with disease activity. Numerous studies have shown discordance between symptoms of esophageal dysfunction and endoscopic and histologic disease activity.^{18,71,110} There are several reasons for this. Patients can avoid foods that cause dysphagia or other symptoms, or modify the way they eat (eg, chewing carefully, eating slowly, lubricating foods, drinking copious fluids) to minimize symptom regardless of the level of biologic disease activity. Additionally, symptoms and biologic activity do not have a linear relationship, and symptoms may remain quite mild until a certain threshold of endoscopic severity is reached. If patients have previously had an esophageal stricture and have undergone esophageal dilation, then symptoms of dysphagia will be improved regardless of underlying biologic activity. The third concept is specific for PPIs. Reflux and EoE can have a complicated relationship. In particular, the 2 conditions may overlap, and EoE may predispose to secondary reflux or less effective clearance of physiologic reflux (due to decreased esophageal compliance and/or the mild dysmotility).¹¹¹ In this situation, PPIs may help to treat reflux and thus improve some symptoms, but might not be effective for the underlying EoE. In sum, the chronic nature of EoE where esophageal eosinophilia can lead to progressive fibrosis, the potential discordance between symptoms and underlying biologic disease activity of EoE, and a possible non-EoE-related mechanism of potential symptom response to PPI, all suggest that endoscopy for surveillance may be effective, even in patients who have a symptom response to PPI. Reasons for not performing follow-up endoscopies include potential risks of sedation impacting development in younger children, risks of repeated endoscopy, and financial and time burdens. These considerations need to be accounted for when balancing the risks and benefits of performing surveillance endoscopies, especially in children.

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

The significance of esophageal eosinophilia is not a pathognomonic finding and has to be carefully considered within the appropriate clinical context. For instance, if an otherwise healthy atopic adult patient undergoes endoscopy for food impaction or dysphagia and is found to have esophageal eosinophilia, both the literature and clinical experience support a probable diagnosis of EoE and high likelihood of some response to PPIs (see Question 1). If a young child with chronic vomiting, abdominal pain, and weight loss is found to have esophageal eosinophilia, a diagnosis of GERD is more probable and similarly will have a

high likelihood of response to PPI. Endoscopic features and associated histologic findings beyond eosinophil counts should be considered supplementary to helping establish diagnostic clarity. A friable mucosa is an unusual finding in EoE, whereas extensive eosinophilic degranulation would be a much more common finding.

In either situation, an argument can be made for the value of a post-PPI treatment follow-up endoscopy. For either diagnostic situation detailed above, resolution of eosinophilia would need to be documented to ensure healing has occurred that may potentially alter the long-term outcome. Historically, children with EoE have demonstrated poor correlation between symptoms and inflammation. Recent data from Aceves et al¹¹² has found that proximal eosinophilia associates with self-reported symptoms in a sample of children from Consortium for Gastrointestinal Eosinophilic Researches centers, which may hold potential promise as a marker to monitor disease progression.

The long-term management of children and adults with esophageal eosinophilia who are treated with PPIs remains an evolving concept. If a patient is thought to have EoE, long-term treatment would be indicated with appropriate follow-up as described here and in Question 16. Clinical observation for side effects of PPIs is warranted. While a degree of overlap exists between EoE and GERD,¹¹³ performance of a fundoplication for PPI-responsive EoE is not currently recommended because of the potential anti-inflammatory properties of PPIs, the theoretical concern for retention of offending food antigens in the esophagus, and worsening dysmotility due to a tight gastroesophageal junction.

There are multiple unresolved additional issues, including establishing the optimal minimal duration of PPI treatment before repeat endoscopy, optimal dose and duration of PPI use as a primary EoE treatment, optimal duration of long-term PPI treatment if a PPI response is observed, and determining the next best treatment if inflammation persists despite PPI therapy.

Summary and Conclusions

In evaluating the efficacy of multiple treatments for EoE to achieve a primary outcome of reducing esophageal eosinophil counts to <15 eos/hpf, few treatments have moderate certainty of evidence for such an effect, and most have low to very low certainty of evidence for such an effect. There is moderate certainty in the evidence that topical glucocorticosteroids effectively reduce esophageal eosinophil counts to <15/hpf over a short-term treatment period of 4–12 weeks, but very low certainty about the effects of using topical glucocorticosteroids as maintenance therapy given the lack of studies on this topic. Moderately certain evidence suggests that systemic glucocorticosteroids have similar efficacy rates as topical glucocorticosteroids, but at a cost of higher rates of adverse effects. Multiple dietary strategies may be effective in reducing esophageal eosinophil counts to <15/hpf over a short-term treatment period, with moderate certainty for elemental diets, low certainty for empiric 4- and 6-food elimination diets, and very low certainty for allergy-based testing dietary eliminations and empiric 1- and 2-food elimination diets. We report very low certainty for the effect of PPIs in patients with esophageal eosinophilia and for the effects of esophageal dilation in patients with EoE, although it appears to be relatively safe.

We found low or very low certainty in the effects of multiple other medical treatments for EoE: anti-IL-5 therapy, anti-IL-13 therapy, anti-IgE therapy, montelukast, cromolyn, and anti-TNF therapy, many of which failed to exclude or confirm a benefit. Current research should focus on directly comparing available treatments with more reliable study designs, testing new treatments, using validated symptom questionnaires, and consistently measuring quality of life and nutritional status (see Table 17 for list of knowledge gaps).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper:

CI	confidence interval
EoE	eosinophilic esophagitis
GERD	gastroesophageal reflux disease
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
eos/hpf	eosinophils per high-power field
IL	interleukin
PICO	population, intervention, comparator, and outcome
PPI	proton pump inhibitor
RCT	randomized control trial
RR	risk ratio

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Table 1

Summary of Findings for PICO Question 1^a

PPI compared to placebo for EoE				
Outcomes and follow-up	No. of participants (studies) ²⁶⁻⁴⁸	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects Risk with placebo Risk difference with PPI
Not achieving histologic remission (<15 eos/hpf); follow-up: mean 8 wk	1051 (23 observational studies) ^b	⊕○○○ VERY LOW ^{c,d}	0.66 (0.61-0.72) ^e	867 per 1000 295 fewer per 1000 (338 fewer to 243 fewer)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bIncluded 2 RCTs of PPI vs topical steroids.

^c $I^2 = 81\%$; very inconsistent results in absolute terms.

^dPatients are different than for other interventions where PPI responders were excluded.

^eUsed historical control cohort of placebo arm of topical steroid studies.

Table 2

Summary of Findings for PICO Question 2^a

Topical glucocorticosteroids compared to placebo for EoE					
Outcomes and follow-up	No. of participants (studies) ¹⁹⁻²⁵	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)		
			<table border="0"> <tr> <td>Risk with placebo</td> <td>Risk difference with topical steroids</td> </tr> </table>	Risk with placebo	Risk difference with topical steroids
Risk with placebo	Risk difference with topical steroids				
Not achieving histologic remission (<15 eos/hpf); follow-up: mean 8 wk	437 (8 RCTs) ^b	⊕⊕⊕ MODERATE ^{c,d,e,f}	<table border="0"> <tr> <td>880 per 1000</td> <td>537 fewer per 1000 (from 369 fewer to 651 fewer)</td> </tr> </table>	880 per 1000	537 fewer per 1000 (from 369 fewer to 651 fewer)
880 per 1000	537 fewer per 1000 (from 369 fewer to 651 fewer)				

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bThere was variability in whether histologic response was reported as mean vs peak eosinophil levels. All included trials reported Peaks with the exception of (a) Straumann et al,²⁵ which reported mean counts, (b) Alexander et al,¹⁹ which reported mean peaks (personal communication), and (c) Miehlke et al²⁴ reported eosinophil density, which we correlated to eosinophil counts. Removing these individual trials in a sensitivity analysis did not significantly alter the summary estimates (0.59 [0.46-0.76]).

^cFew studies reported intention-to-treat analyses and dropout was not adequately accounted for. We accounted for this by looking at the CONSORT diagram and reporting intention-to-treat results, assuming that outcomes would favor the control.

^d $I^2 = 77\%$.

^eDellon et al²¹ might have had a more severe baseline patient population, accounting for decreased response to glucocorticosteroids when compared to other studies. We did not however rate down for indirectness

^fDespite the fact that there are <300 events (which can indicate suboptimal information size), we did not rate down for imprecision. We also felt that because inconsistency and imprecision are related concepts, a single downgrade for inconsistency was sufficient. We assessed clinical behavior at the extremes of the CI, and judged that behavior would not change.

Table 3

Summary of Findings for PICO Question 3^a

Systemic glucocorticosteroid compared to topical glucocorticosteroid for EoE					
Outcomes and follow-up	No. of participants (studies) ⁵⁰	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects	Risk difference with systemic steroid
				Risk with topical steroid	
Not achieving histologic remission (<15 eos/hpf); follow-up: mean 8 wk	80 (1 RCT)	⊕⊕⊕○ MODERATE ^{b,c,d}	RR 0.79 (0.41–1.52)	350 per 1000 ^e	73 fewer per 1000 (207 fewer to 182 more)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bDespite a lack of blinding, the study was not downgraded for risk of bias.

^cWe did not rate down for indirectness despite the fact that this trial consists of a pediatric population.

^dRR crosses 1.

^eIn order to estimate an intention-to-treat analysis, we changed the denominator to the number of subjects who were originally randomized to each group (40 per group). The numerator denotes the number of individuals who achieved at “mild” or normal histologic grade (per Schaefer et al⁵⁰) at 4 wk, which correlates to a cutoff of <15 eos/hpf.

Table 4

Summary of Findings for PICO Question 4^a

Elemental diets compared to placebo for the management of EoE		No. of participants (studies) ⁵⁶⁻⁶¹	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects	
Outcomes and follow-up	Risk with placebo				Risk difference with elemental diets	
Not achieving histologic remission (eos <15/hpf) follow-up: mean 8 wk	431 (6 observational studies) ^{b,c,d}	⊕⊕⊕○ MODERATE ^e	0.07 (0.05–0.12)	880 per 1000	807 fewer per 1000 (824 fewer to 763 fewer)	

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bFive subjects excluded for noncompliance to diet; 2 subjects excluded for not getting follow-up endoscopy (Kelly et al⁵⁶).

^cEight subjects excluded for noncompliance (Licarous et al⁵⁷).

^dHistologic remission defined as <10 eos/hpf; 11 who started diet dropped out (Peterson et al⁵⁹).

^eUpgraded for very large effect size.

Table 5

Summary of Findings for PICO Question 5^a

SFED compared to placebo for the management of EoE				
Outcomes	No. of participants up ⁶²⁻⁶⁹	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects Risk with placebo Risk difference with SFED
Failure to achieve histologic remission (proportion) assessed with: esophageal eosinophils <5/hpf follow-up: mean 6 wk	633 (9 observational studies) ^{b,c,d,e,f,g,h,i,j}	⊕⊕○○ LOW ^k	0.38 (0.32-0.43)	880 per 1000 550 fewer per 1000 (600 fewer to 500 fewer)

Abbreviation: SFED, 6-food elimination diet.

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bUsed <10 eos/hpf for definition of remission. Studies with a cutoff of <15 eos/hpf will likely underestimate the response rate within the pooled results and therefore strengthen the assumed estimate of effect (Kagalwalla et al⁶²).

^cMeasured SF-36 (Gonsalves et al⁶³).

^d15 of 26 subjects did SFED + foods with + SPT/APT (Henderson et al⁶⁴).

^eAlso eliminated rice + corn (Lucendo et al⁶⁴).

^fAlso eliminated foods with + SPT/APT (Colson et al⁶⁵).

^gExcluded subjects with + IgE tests before enrollment. The response rate is lower and therefore likely underestimates the effect estimate in the pooled results (Rodriguez-Sanchez et al⁶⁶).

^hOnly subjects with <5 eos/hpf (“complete” remission) (Philpott et al⁶⁷).

ⁱCombined clinical and histopathologic remission; estimated for SFED based on 2-, 4-, 6-FED step-up protocol (Molina-Infante et al⁶⁷).

^jDid not include Wolf 2014 in analysis to avoid duplicate subjects (Reed et al⁶⁸).

^kWhen compared to historical controls, a very large effect estimate is likely. However, the evidence certainty was not rated up due to concerns of possible residual confounding and/or indirectness.

Table 6

Summary of Findings for PICO Question 5^a

4-Food empiric elimination diet compared to placebo for EoE					
Outcomes and follow-up	No. of participants (studies) ^{37,67,70}	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects	Risk difference with 4-food empiric elimination diet
Not achieving histologic remission (no remission) assessed with: <15 eos/hpf follow-up: 6 wk	426 (3 observational studies) ^b	⊕⊕○○ LOW	0.49 (0.42–0.57)	Risk with placebo 880 per 1000 ^c	449 fewer per 1000 (510 fewer to 378 fewer)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bPediatric study (Molina-Infante et al⁶⁷).

^cPlacebo group responses from topical steroid trials.

Table 7

Summary of Findings for PICO Question 5^d

2-Food elimination diet compared to placebo for EoE				
Outcomes and follow-up	No. of participants (studies) ^{6,7,1}	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	
			Anticipated absolute effects	
			Risk with placebo	
			Risk difference with 2-food elimination diet	
Not achieving histologic remission (remission) assessed with <15 eos/hpf, follow-up: 6 wk	311 (2 observational studies) ^{b,c}	⊕○○○ VERY LOW	880 per 1000 ^d	299 fewer per 1000 (378 fewer to 202 fewer)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^b2-Food elimination diet = milk + wheat (Molina-Infante et al⁶).

^c2-Food elimination diet = milk + soy (Reed et al⁷).

^dPlacebo group is from topical steroid trials.

Table 8

Summary of Findings for PICO Question 5^d

Single-food elimination compared to placebo for EoE					
Outcomes	No. of participants (studies), follow-up ^{7,73}	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects	Risk difference with single-food elimination
Not achieving histologic remission (remission) assessed with <15 eos/hpf, follow-up: 6 wk	203 (2 observational studies) ^{b,c}	⊕○○○ VERY LOW ^d	0.52 (0.37–0.74)	Risk with placebo 880 per 1000 ^e	Risk difference with single-food elimination 422 fewer per 1000 (554 fewer to 229 fewer)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bMilk (Kagalwalla et al⁷²).

^cMilk, 6 dropped out and were considered treatment failures for this analysis (Kruszewski et al⁷³).

^dLow information size.

^ePlacebo data are from topical steroid studies.

Table 9

Summary of Findings for PICO Question 6^a

Allergy-based elimination diets compared to placebo for management of EoE.				
Outcomes and follow-up	No. of participants (studies) ^{57,64,66,68,69,74-81}	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects
				Risk with placebo
				Risk difference with allergy-based elimination diets
Not achieving histologic response assessed with: <15 eos/hpf, follow-up: 8 wk	830 (11 observational studies) ^{b,c,d,e,f}	⊕○○○ VERY LOW ^g	0.57 (0.33-0.73)	880 per 1000 ^h 373 fewer per 1000 (581 fewer to 234 fewer)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bSkin-prick test (SPT) + atopy patch test (APT), some had previously failed pharmacologic therapy (Licarous et al⁵⁷).

^cRemission defined as <10 eos/hpf (Quaglietta et al,⁷⁴ Rizo Pascual et al⁷⁵).

^dSPT + APT + PPT (Molina-Infante et al⁷⁶).

^eSPT + specific IgE testing (sIgE) + APT (Syriou et al⁷⁹).

^fComponent-resolved diagnostics (Van Rhiijn et al⁸⁰).

^gVery inconsistent results.

^hPlacebo group responses from topical steroid trials.

Table 10

Summary of Findings for PICO Question 7^a

Maintenance therapy compared to placebo for EoE				
Outcomes and follow-up	No. of participants (studies) ⁴⁹	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	
			Anticipated absolute effects	
			Risk with placebo	
			Risk difference with maintenance Therapy	
Not achieving histologic remission (eos <20/hpf) (histologic remission) assessed with: eos <20/hpf, follow-up: mean 50 wk	28 (1 RCT) ^b	⊕○○○ VERY LOW ^{c,d}	714 per 1000	214 fewer per 1000 (443 fewer to 214 more)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bTo be eligible had to be in remission <5 eos/hpf on high-dose budesonide 2 mg/d and low symptom score (<2 on their scale); budesonide given via TIA nebulizer (does not exist in United States) at dose 0.5 mg (low); partial remission <20 rather than <15 eos/hpf, which is used for most other intervention outcomes; not all patients completed 50 wk—if clinical symptoms and relapse confirmed they stopped (9 completed 50 wk in budesonide group and 5 in placebo) (Straumann et al⁴⁹).

^cUsed low dose of budesonide delivered through a device not available in the United States.

^dVery low information size and CI crosses 1.

Table 11

Summary of Findings for PICO Question 8^a

Esophageal dilation compared to no dilatation for EoE					
Outcomes	No. of participants (studies), follow-up ^{8,9}	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects Risk with no dilatation	Risk difference with esophageal dilatation
Clinical improvement (not defined) ^{b,c}	1928 dilations (14 observational studies) ^d	⊕○○○ VERY LOW ^{e,f,g}	Not estimable	0 per 1000 ^h	0 fewer per 1000 (0 fewer to 0 fewer)
Mortality ⁱ	2772 dilations (20 observational studies) ^j	⊕○○○ VERY LOW ^{e,g}	Not estimable	— ^h	—
Perforation ⁱ	2772 dilations (20 observational studies) ^j	⊕○○○ VERY LOW ^{e,g}	Not estimable	0 per 1000 ^h	0 fewer per 1000 (0 fewer to 0 fewer)
Hospitalization ⁱ	2466 dilations (12 observational studies) ^k	⊕○○○ VERY LOW ^{e,g}	Not estimable	0 per 1000 ^h	0 fewer per 1000 (0 fewer to 0 fewer)
Hemorrhage ^{i,l}	2588 dilations (12 observational studies)	⊕○○○ VERY LOW ^{e,g}	Not estimable	0 per 1000 ^h	0 fewer per 1000 (0 fewer to 0 fewer)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bFollow-up median of 12 mo and a range from 1 wk to 36 mo.

^cClinical improvement expressed per patient. Heterogeneous definition of “clinical improvement.”

^d57 studies were included in meta-analysis, though only 14 studies were included for this outcome. There was 1 randomized trial (Kavitt) and the rest were observational studies with more than 5 participants. Some studies did not specify the number of participants and were excluded. The included case-control (Cohen et al) study in the Dougherty meta-analysis was also excluded in this analysis.

^eAbsolute rate calculated from data provided in Dougherty et al meta-analysis, pooling data from cohort/RCT studies where “n” was available for outcome of interest. Case-control and observational studies will <5 patients were excluded. Only absolute rates provided because there was no control group.

^fDespite heterogeneity of pooled estimate, assumption is that dilation does cause symptomatic improvement.

^gIt was noted that patients who need dilation have fibrostenotic disease. Though this population may be distinct from those included in studies where therapeutic management with medications was investigated, we did not rate down for indirectness.

^hAssumption was that no clinical improvement or adverse events could occur if dilation not performed.

ⁱExpressed as number per dilation.

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37 studies were included in meta-analysis, though only 20 studies were included for this outcome. There was one randomized trial (Kavitt) and there rest were observational studies with more than 5 participants. Some studies did not specify the number of participants, and as such, were excluded. The included case-control (Cohen et al) study in the Dougherty meta-analysis was also excluded in this analysis.

37 studies were included in meta-analysis, though only 12 studies were included for this outcome. There was one randomized trial (Kavitt) and the rest were observational studies with more than 5 participants. Some studies did not specify the number of participants, and as such, were excluded. The included case-control (Cohen et al) study in the Dougherty meta analysis was also excluded in this analysis.

Significant gastrointestinal bleeds were those defined as needing additional clinical intervention, usually re-endoscopy, and did not include mucosal tears seen immediately after dilation.

Table 12

Summary of Findings for PICO Question 9^a

Anti-IL-5 monoclonal antibodies compared to placebo for EoE				
Outcomes and follow-up	No. of participants (studies) ^{9,2,94}	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects Risk with placebo Risk difference with anti-IL-5 monoclonal antibodies
Not achieving histologic remission (<15 eos/hpf) (remission, partial) assessed with: <15/hpf, follow-up: range 9 wk to 16 wk	286 (3 RCTs) ^{b,c,d,e}	⊕⊕○○ LOW ^{f,g}	0.92 (0.84 to 1.00)	902 per 1000 72 fewer per 1000 (144 fewer to 0 fewer)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bMepolizumab in adults (escalating mepolizumab doses) (Straumann et al⁹²).

^cMepolizumab in children, used very low dose mepolizumab as placebo or “comparator” group as suggested by authors in the Methods section; grouped other 2 doses of mepolizumab together (no obvious dose response); missing description of blinding and allocation concealment (Assa’ad et al⁹³).

^dReslizumab in children; grouped 3 doses of reslizumab together in intervention group (no obvious dose response) (Spergel et al⁹⁴).

^eParticipant selection for these studies are different than for other interventions—have failed many other interventions before enrolling in this study.

^fCI crosses 1.

^gCI touches 1 (upper boundary of CI is 1.0—no effect—which could lead to a different recommendation and therefore represents imprecision).

Table 13

Summary of Findings for PICO Question 10^a

QAX-576 compared to placebo for EoE		No. of participants (studies) ⁹⁵	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects	
Outcomes and follow-up	Risk with placebo				Risk difference with QAX-576	
Not achieving histologic remission <15 eos/hpf (histologic remission) assessed with: <15 eos/hpf follow-up: mean 12 wk		25 (1 RCT)	⊕⊕○○ LOW ^{b,c}	0.94 (0.67–1.30)	875 per 1000	53 fewer per 1000 (289 fewer to 263 more)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bVery low information size.

^cPatients with higher baseline esophageal eosinophilia and more likely to have failed other treatments.

Table 14

Summary of Findings for PICO Question 11^a

Omalizumab compared to placebo for EoE					
Outcomes and follow-up	No. of participants (studies) ⁹⁹	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects	Risk difference with omalizumab
				Risk with placebo	
Change in peak eosinophil counts/hpf (peak eosinophils) assessed with: eos/hpf follow-up: mean 16 wk	30 (1 RCT)	⊕○○○ VERY LOW ^{b,c}	—	Mean change in peak eosinophil counts/hpf was 0 eos/hpf ^d	MD 6 eos/hpf more (4 fewer to 16 more)

Abbreviation: MD, mean difference.

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bSelected subjects who failed topical steroid; some had trialed PPI before and some were on PPI during trial, outcome is change in mean eosinophils, which may be a less direct outcome to consider.

^cVery low information size.

^dPersonal communication with Fred Clayton that no subject in either arm achieved histologic remission <15 eos/hpf.

Table 15

Summary of Findings for PICO Question 12^a

Montelukast compared to placebo for management of EoE					
Outcomes and follow-up	No. of participants (studies) ^{b7}	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects	Risk difference with montelukast
				Risk with placebo	Risk difference with montelukast
Solid food dysphagia (improvement) (telephone symptom questionnaire) ^b follow-up: 26 wk	41 (1 RCT)	⊕○○○ VERY LOW ^{c,d}	0.79 (0.51–1.21)	760 per 1000	160 fewer per 1000 (370 fewer to 160 more)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bThe abridged dysphagia questionnaire used the questions on dysphagia frequency, severity, and food impaction from the Mayo Dysphagia Questionnaire, 2-week version.

^cAll patients had first achieved remission with topical glucocorticosteroid treatment. Therefore, this is indirect to our PICO question of should we use montelukast for EoE as the question is very specific to should we use montelukast to maintain remission.

^dLarge CI that crosses 1; estimate based on a single RCT.

Table 16

Summary of Findings for PICO Question 13^a

Cromolyn compared to placebo for EoE		No. of participants (studies) ¹⁰⁴	Certainty of the evidence (GRADE)	Anticipated absolute effects	
Outcomes and follow-up	Relative effect, RR (95% CI)			Risk with placebo	Risk difference with cromolyn
Not achieving histologic remission (histologic remission) assessed with: eos <5/hpf, follow-up: mean 8 wk	0.89 (0.71 to 1.12)	16 (1 RCT)	⊕⊕○○ LOW ^b	1000 per 1000	110 fewer per 1000 (290 fewer to 120 more)

^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bVery serious imprecision.

Table 17**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 in spite of 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)
Using clinical history of symptoms with food exposure to guide therapy in EoE
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
