

Technical Review on the Management of Eosinophilic Esophagitis: A report from the American Gastroenterological Association Institute and the Joint Task Force on Allergy-Immunology Practice Parameters

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Abbreviations used in this paper: APT, atopy patch test; CI, confidence interval; CRD, component-resolved diagnostic; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HPF, high-powered field; ITT, intention-to-treat; LR, likelihood ratio; OR, odds ratio; PICO, population, intervention, comparator, and outcome; PPI, proton pump inhibitor; RCT, randomized control trial; RR, risk ratio; sIgE, specific IgE testing in serum; SPT, skin prick testing

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 report 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 framework and 3 with a narrative summary. 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. 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 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 PPIs 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-IL-5 therapy, anti-IL-13 therapy, anti-IgE therapy, montelukast, cromolyn, and anti-TNF therapy.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic rare inflammatory condition of the esophagus that is estimated to affect 1 in every 2000 people.(1) The incidence of EoE is increasing. EoE can occur in children and adults and is more common in Whites, 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 (hpf). 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 pre-specified 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) since 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. This recommendation is supported by clinical observations that PPIs resolved EoE-related symptoms and histopathological abnormalities in over 50% of children and adults thought to have EoE. 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 Gastroenterology 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 AGA 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). **Appendix 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 **Appendix 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 eosinophils/high power field (hpf) was considered *critical* for decision-making.(10, 11) It was recognized that untreated inflammation can potentially lead to fibro-stenotic 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. (Alexander 2012,(19) Butz 2014,(20) Dellon 2017,(21) Dohil 2010,(22) Gupta 2015,(23) Konikoff 2006,(24) Miehlke 2016,(25) Straumann 2010(26))

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 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://gradepr.org/>), and were reviewed iteratively with the clinical experts (SAA, GTF, MG, JMS, and ESD), 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 **Appendix Table 3**. We conducted an electronic search using MEDLINE, EMBASE, and the Cochrane Library until May 13, 2018. A research librarian (KK) 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 non-human 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 WHO clinical trial registry to identify additional studies (<http://apps.who.int/trialsearch/>). Titles and abstracts were reviewed in duplicate by two authors (MR and RS). One methodologist (RS or MR) extracted data from eligible reports and a second methodologist (RS or MR) evaluated the accuracy of the data extraction. We contacted authors when key data were missing, first by attempting to reach the corresponding author by email and then by trying a 2nd author from the article if no response. Disagreements were resolved by discussion with a third methodologist (YFY).

Statistical Analysis

Pooled risk ratios with 95% confidence intervals (CI) were calculated when possible, using RevMan v5.3 (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 versus a comparator.

RESULTS

#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 (eosinophils <15/hpf) compared to 86.7% (unweighted) of a placebo comparison group.

Quality of Evidence: The certainty in the effect estimate was very low. 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 (e.g. pediatrics versus adult or inclusion/exclusion criteria). There were 2 RCTs identified that compared PPI to topical corticosteroid, and found similar rates of histologic remission (see **Appendix Table 4**).

PPI compared to placebo for eosinophilic esophagitis

Bibliography: Garrean 2009,(27) Peterson 2010,(28) Molina-Infante 2011,(29) Abe 2011,(30) Fujiwara 2012,(31) Francis 2012,(32) Vazquez-Elizondo 2013,(33) Moawad 2013,(34) Lee 2013(35) Dellon 2013,(36) Mangla 2014(37), Molina 2014,(38) van Rhijn 2014,(39) Gomez-Torrijos 2016,(40) Jiao 2016,(41) Savarino 2017,(42) Philpott 2016,(43) Sayej 2009,(44) Dranove 2010,(45) Schroeder 2013,(46) Rea 2013,(47) Dhaliwal 2014,(48) Gutierrez-Junquera 2016(49)

Outcomes and Follow-up	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with PPI
Not achieving histologic remission (<15 eos/hpf); follow up: mean 8 weeks	1051 (23 observational studies) ^a	⊕○○○ VERY LOW ^{b,c}	RR 0.66 (0.61 to 0.72) ^d	867 per 1,000	295 fewer per 1,000 (338 fewer to 243 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanations

- Included 2 RCTs of PPI vs topical steroids
- I-squared = 81%; very inconsistent results in absolute terms
- Patients are different than for other interventions where PPI responders were excluded
- Used historical control cohort of placebo arm of topical steroid studies

#2 Should topical glucocorticosteroids be used in patients with EoE?

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 a 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 a risk ratio 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. 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, (28, 50-53) and if they did not include budesonide or fluticasone in the treatment group (54). 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 amongst 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 prior to 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 a 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 (ITT) estimates if not reported, by examining the CONSORT 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/GI/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 al. and include local infections-candida and viral, adrenal suppression, diminished growth and fractures.(55)

Topical Glucocorticosteroids compared to placebo for eosinophilic esophagitis

Bibliography: Alexander 2012,(19) Butz 2014,(20) Dellon 2017,(21) Dohil 2010,(22) Gupta 2015,(23) Konikoff 2006,(24) Miehlke 2016,(25) Straumann 2010(26)

Outcomes and Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Topical Steroids
Not achieving histologic remission (<15 eos/hpf); follow up: mean 8 weeks	437 (8 RCTs) ^a	⊕⊕⊕○ MODERATE b,c,d,e	RR 0.39 (0.26 to 0.58)	880 per 1,000	537 fewer per 1,000 (from 369 fewer to 651 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. There 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 2010, which reported mean counts, b) Alexander 2012, which reported mean peaks (personal communication), and c) Miehlke 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]).

b. Few studies reported ITT analyses and dropout was not adequately accounted for. We accounted for this by looking at the CONSORT diagram and reporting ITT results, assuming that outcomes would favor the control.

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

d. Dellon 2017 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

e. Despite 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 down-grade for inconsistency was sufficient. We assessed clinical behavior at the extremes of the confidence interval, and judged that behavior would not change.

#3 Should systemic glucocorticosteroids be used in patients with EoE?

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 eosinophils per hpf, and adverse events, a composite endpoint defined in the footnotes. 11/40 (28%) patients in the prednisone arm vs 14/40 (35%) patients in the fluticasone arm failed to achieve histologic response, for a RR 0.79 (95% CI 0.41 to 1.52). 16/40 (40%) patients in the prednisone arm compared to 6/40 (15%) in the fluticasone arm experienced adverse events for a RR of 2.67 (1.16 to 6.11).

Quality of Evidence: The certainty in the estimates was moderate. Both outcomes were rated down for imprecision; the RR for clinical response had a confidence interval which 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 endpoint, 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, 16/40 (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, 6/40 (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.

Systemic glucocorticosteroid compared to topical glucocorticosteroid for eosinophilic esophagitis

Bibliography: Schaefer 2008(51)

Outcomes and Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with topical steroid	Risk difference with systemic steroid
Not achieving histologic remission (<15 eos/hpf); follow up: mean 8 weeks	80 (1 RCT)	⊕⊕⊕○ MODERATE a,b,c	RR 0.79 (0.41 to 1.52)	350 per 1,000 ^d	73 fewer per 1,000 (207 fewer to 182 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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- a. Despite a lack of blinding, the study was not downgraded for risk of bias.
 - b. We did not rate down for indirectness despite the fact that this trial consists of a pediatric population.
 - c. Risk Ratio crosses 1
 - d. In order to estimate an ITT 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 paper) at 4 weeks, which correlates to a cutoff of <15Eos/hpf.

#4 Should an elemental diet be used in patients with EoE?

Evidence Summary: We identified 6 observational studies which reported that 6.4% of subjects on elemental diet failed to achieve histopathologic remission (eosinophils <15/hpf) compared to 86.7% in a placebo comparison group (taken as a historical

comparison group from swallowed topical steroid data) for a RR of 0.07, (95% CI 0.05-0.12).

Quality of Evidence: The certainty in the effect estimate was moderate. 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 comprised 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 following a period of food elimination has not been described in EoE, but has been described in case reports of children with atopic dermatitis (56). Risk of prolonged peanut avoidance versus 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,(57) 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 (e.g. six 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.

Elemental Diets compared to placebo for the management of Eosinophilic Esophagitis

Bibliography: Kelly 1995^a,(58) Licarous 2005^b,(59) Henderson 2012,(60) Peterson 2013^c,(61) Leung 2015,(62) Warners 2017(63)

Outcomes and Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Elemental Diets
Not achieving histologic remission (eos<15/hpf) follow up: mean 8 weeks	431 (6 observational studies)	⊕⊕⊕○ MODERATE ^d	RR 0.07 (0.05 to 0.12)	880 per 1,000	807 fewer per 1,000 (824 fewer to 763 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanations

- 5 subjects excluded for noncompliance to diet; 2 subjects excluded for not getting follow-up endoscopy
- 8 subjects excluded for noncompliance
- Histologic remission defined as < 10 eos/hpf; 11 who started diet dropped out
- Upgraded for very large effect size

#5 Should an empiric food elimination diet be used in patients with EoE?

A. Should an empiric 6 food elimination diet be used in patients with EoE?

Evidence Summary: We identified 10 single armed observational studies which reported that 32.1% (unweighted) of subjects on an empiric elimination diet failed to achieve histopathologic remission (eosinophils <15/hpf) compared to 86.7% of a

placebo comparison group (taken as a historical comparison group from swallowed topical steroid data), for a 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.

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. 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.

SFED compared to placebo for the management of Eosinophilic Esophagitis

Bibliography: Kagalwalla 2006^a,⁽⁶⁴⁾ Gonsalves 2012^b,⁽⁶⁵⁾ Henderson 2012^c,⁽⁶⁶⁾ Lucendo 2013^d,⁽⁶⁷⁾ Colson 2014^e,⁽⁶⁸⁾ Rodriguez-Sanchez 2014^f,⁽⁶⁹⁾ Philpott 2016^g,⁽⁷⁰⁾ Molina-Infante 2018^h,⁽⁷¹⁾ Reed 2017ⁱ,⁽⁷²⁾ Homan 2015⁽⁷³⁾

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with SFED
Failure to achieve histologic remission (Proportion) assessed with: Esophageal eosinophils < 15/hpf follow up: mean 6 weeks	633 (9 observational studies)	⊕⊕○○ LOW ^j	RR 0.38 (0.32 to 0.43)	880 per 1000	550 fewer per 1000 (600 fewer to 500 fewer)

SFED compared to placebo for the management of Eosinophilic Esophagitis

Bibliography: Kagalwalla 2006^a,(64) Gonsalves 2012^b,(65) Henderson 2012^c,(66) Lucendo 2013^d,(67) Colson 2014^e,(68) Rodriguez-Sanchez 2014^f,(69) Philpott 2016^g,(70) Molina-Infante 2018^h,(71) Reed 2017ⁱ,(72) Homan 2015(73)

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE) CI	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with SFED

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. Used < 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.
- b. Measured SF-36
- c. 15/26 subjects did SFED + foods with + SPT/APT
- d. Also eliminated rice + corn
- e. Also eliminated foods with + SPT/APT
- f. Excluded subjects with + IgE tests prior to enrollment. The response rate is lower and therefore likely underestimates the effect estimate in the pooled results.
- g. Only subjects with < 5 eos/hpf ("complete" remission)
- h. Combined clinical and histopathological remission; estimated for SFED based on 2-4-6 FED step-up protocol
- i. Did not include Wolf 2014 in analysis to avoid duplicate subjects
- j. When 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.

B. Should an empiric 4 food elimination diet be used in patients with EoE?

Evidence Summary: We identified 3 single armed studies which reported that 43.1% (unweighted) of subjects on an empiric elimination diet failed to achieve histopathologic remission (eosinophils <15/hpf) compared to 86.7% (unweighted) of a placebo

comparison group (taken as a historical comparison group from swallowed topical steroid data), for a 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.

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.

4 Food empiric elimination diet compared to placebo for eosinophilic esophagitis

Bibliography: Molina-Infante 2014,(38) Kagalwalla 2017,(74) Molina-Infante 2017^a (71)

Outcomes and Follow-up	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with 4 Food empiric elimination diet
Not achieving histologic remission (No remission) assessed with: eos < 15/hpf follow up: 6 weeks	426 (3 observational studies)	⊕⊕○○ LOW	RR 0.49 (0.42 to 0.57)	880 per 1,000 ^b	449 fewer per 1,000 (510 fewer to 378 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. Pediatric study
- b. Placebo group responses from topical steroid trials

C. Should an empiric 2 food elimination diet be used in patients with EoE?

Evidence Summary: We identified 2 single armed studies which reported that 57.9% (unweighted) of subjects on an empiric elimination diet failed to achieve histopathologic remission (eosinophils <15/hpf) compared to 86.7% (unweighted) of a placebo comparison group (taken as a historical comparison group from swallowed topical steroid data) for a 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.

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 Molina-Infante study, the 2 foods eliminated were milk and wheat. In the Reed study, 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.

2 food elimination diet compared to placebo for eosinophilic esophagitis

Bibliography: Molina-Infante 2017^a,(71) Reed 2018^b (75)

Outcomes and Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with 2 food elimination diet
Not achieving histologic remission (Remission) assessed with: Eos < 15/hpf follow up: 6 weeks	311 (2 observational studies)	⊕○○○ VERY LOW	RR 0.66 (0.57 to 0.77)	880 per 1,000 ^c	299 fewer per 1,000 (378 fewer to 202 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

- 2FED=milk + wheat
- 2FED=milk + soy
- Placebo group is from topical steroid trials

D. Should an empiric single food elimination diet be used in patients with EoE?

Evidence Summary: We identified 2 single armed studies which reported that 45.9% (unweighted) of subjects on a single food empiric elimination diet failed to achieve histopathologic remission (eosinophils <15/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.

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) 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 endoscopy because only 1 food 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.

Single food elimination compared to placebo for eosinophilic esophagitis

Bibliography: Kagalwalla 2012^a,(76) Kruszewski 2016^b (77)

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Single food elimination
Not achieving histologic remission (Remission) assessed with: eos < 15/hpf follow up: 6 weeks	203 (2 observational studies)	⊕○○○ VERY LOW ^c	RR 0.52 (0.37 to 0.74)	880 per 1,000 ^d	422 fewer per 1,000 (554 fewer to 229 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. Milk
- b. Milk, 6 dropped out and were considered treatment failures for this analysis
- c. Low information size
- d. Placebo data are from topical steroid studies

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

Evidence Summary: We identified 12 single armed studies which reported that 49.2% (unweighted) of subjects on a testing-based elimination diet failed to achieve histopathologic remission (eosinophils <15/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.

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% to 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 weren't 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. There is emerging evidence that aeroallergens may be important triggers for EoE. There are currently only very small case series reporting aeroallergen immunotherapy in patients with EoE.

Allergy-Based Elimination Diets compared to placebo for management of EoE

Bibliography: Licarous 2005^a,(59) Qaugletta 2007^b,(78) Rizo Pascual 2011^b,(79) Henderson 2012,(66) Molina-Infante 2012^c,(80) Spergel 2012,(81) Al-Hussaini 2013,(82) Rodriguez-Sanchez 2014,(69) Homan 2015,(73) Syrigou 2015^d,(83) Van Rhijn 2015^e,(84) Constatine 2017,(85) Reed 2017(72)

Outcomes and Follow-up	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (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 weeks	830 (11 observational studies)	⊕○○○ VERY LOW ^f	RR 0.57 (0.33 to 0.73)	880 per 1,000 ^g	373 fewer per 1,000 (581 fewer to 234 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanations

- Skin prick test (SPT) + atopy patch test (APT), some had previously failed pharmacologic therapy
- Remission defined as < 10 eos/hpf
- SPT + APT + PPT
- SPT + specific IgE testing (sIgE) + APT
- Component-resolved diagnostics (CRD)
- Very inconsistent results
- Placebo group responses from topical steroid trials

#7 Should maintenance therapy be recommended in patients with EoE?

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 eosinophils < 20/hpf.

Quality of Evidence: The certainty in the effect estimate was very low. 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 one year (<5 eos) compared to 36% of the active arm, which was a strong trend (p=0.06). Similarly, the absolute eosinophil counts were significantly lower in the treatment arm compared to placebo (32 eos/hpf vs 65 eos/hpf; p=0.02). 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 which provide some additional evidence.

We found 6 single-armed observational cohorts for topical glucocorticosteroids. Butz et al 2014(20) reported that 11 out of 15 were able to maintain remission on a lower dose of topical glucocorticosteroid (fluticasone 0.88 mg) over 3 months. Andreae et al 2016 (86) 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 al 2016 (87) reported in an abstract that 42% of their cohort were able to maintain remission on budesonide 2 mg/day. Greuter et al 2017(88) reported that out of 33 people who had achieved clinical and histological remission for 6 months, 27 experienced relapse with an average time-to-relapse of 22 weeks after stopping topical glucocorticosteroids. Eluri et al 2017 (89) reported that 20 out of 33 adults who were using topical glucocorticosteroids experienced a relapse when followed over a 12 month period. Rubenstein et al 2018 ***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 al 2017 (90) 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 2015(91) reported that 55 of 75 remained in remission on PPI with a mean follow-up length of 26 months. Gomez-Torrijos 2016(40) 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 2016(49) 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-armed cohorts of long term dietary treatment. Lucendo 2013 (92) 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 2015 (93) reported that 10 of 10 who maintained dietary therapy remained in remission with a mean follow-up length of 36 weeks. Reed 2017 (72) 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.

Maintenance Therapy compared to placebo for eosinophilic esophagitis

Bibliography: Straumann 2011^a (50)

Outcomes and Follow up	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Maintenance Therapy
Not achieving histologic remission (Eos < 20/hpf) (Hist remission) assessed with: Eos < 20/hpf follow up: mean 50 weeks	28 (1 RCT)	⊕○○○ VERY LOW ^{b,c}	RR 0.70 (0.38 to 1.30)	714 per 1,000	214 fewer per 1,000 (443 fewer to 214 more)

Maintenance Therapy compared to placebo for eosinophilic esophagitis

Bibliography: Straumann 2011^a (50)

Outcomes and Follow up	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Maintenance Therapy

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanations

- To be eligible had to be in remission eos < 5 /hpf on high dose budesonide 2 mg/day and low symptom score (< 2 on their scale); budesonide given via TIA nebulizer (does not exist in US) at dose 0.5 mg (low); partial remission < 20 rather than < 15 which is used for most other intervention outcomes; not all patients completed 50 weeks---if clinical symptoms and relapse confirmed they stopped (9 completed 50 weeks in BUD group and 5 in PLAC)
- Used low dose of budesonide delivered through a device not available in the US
- Very low information size and CI crosses 1.

#8 Should esophageal dilation be used in patients with EoE?

Evidence Summary: Histologic remission was not assessed for this intervention. Estimates were taken from the Dougherty 2017 meta-analysis(94) 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 greater 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 nor adverse events would reasonably occur if dilation was not performed. 87% 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 GI hemorrhage was reported in 0.1% of dilations.

Quality of Evidence: The certainty in the effect estimate was very low across all outcomes. 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 though it was noted that patients who need dilation have fibro-stenotic 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 symptomatic improvement.

Discussion: There are 3 meta-analyses from 2017 that investigated the use of dilation in patients with EoE (94-96). We compared them, found the Dougherty 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.

Esophageal dilation compared to no dilatation for Eosinophilic Esophagitis

Bibliography: Dougherty 2017(94)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no dilatation	Risk difference with Esophageal dilation
Clinical Improvement (not defined) ^{a,b}	1928 dilations (14 observational studies) ^c	⊕○○○ VERY LOW ^{d,e,f}	not estimable	0 per 100 ^g	0 fewer per 100 (0 fewer to 0 fewer)
Mortality ^h	2772 dilations (20 observational studies) ⁱ	⊕○○○ VERY LOW ^{d,f}	not estimable	-- per -- ^g	-- per -- (-- to --)
Perforation ^h	2772 dilations (20 observational studies) ⁱ	⊕○○○ VERY LOW ^{d,f}	not estimable	0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 0 fewer)
Hospitalization ^h	2466 dilations (12 observational studies) ^j	⊕○○○ VERY LOW ^{d,f}	not estimable	0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 0 fewer)

Esophageal dilation compared to no dilatation for Eosinophilic Esophagitis

Bibliography: Dougherty 2017(94)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no dilatation	Risk difference with Esophageal dilation
Hemorrhage ^{h,k}	2588 dilations (12 observational studies)	⊕○○○ VERY LOW ^{d,f}	not estimable	0 per 1,000 ^g	0 fewer per 1,000 (0 fewer to 0 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanations

- Follow up Median of 12 months and a range from 1 week to 36 months
- Clinical improvement expressed per patient. Heterogeneous definition of "clinical improvement".
- 37 studies were included in meta-analysis, though only 14 studies were included for this outcome. There was one randomized trial (Kavitt) and there rest were observational studies with greater 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.
- Absolute 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 with <5 patients were excluded. Only absolute rates provided because there was no control group.
- Despite heterogeneity of pooled estimate, assumption is that dilation does cause symptomatic improvement.

f. 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, we did not rate down for indirectness.

g. Assumption was that no clinical improvement nor adverse events could occur if dilation not performed.

h. Expressed as number per dilation

i. 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 greater 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.

j. 37 studies were included in meta-analysis, though only 12 studies were included for this outcome. There was one randomized trial (Kavitt) and there rest were observational studies with greater 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.

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

#9 Should anti-IL-5 therapy be used in patients with EoE?

Evidence Summary: There are 3 RCTs of anti-IL-5 therapy compared to placebo. Anti-IL-5 treatment had little or no effect, with 94.4% of patients assigned to anti-IL-5 therapy failed to achieve histologic remission compared to 93.9% of the placebo group, for a RR of 0.92, 0.84, 1.00.

Quality of Evidence: The certainty in the effect estimate was low. 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 prior to entering the trials. The certainty was also downgraded for imprecision because the confidence interval included 1.

Discussion: Very few individuals in the intervention or placebo arms achieved the pre-specified histologic remission rate of < 15 eosinophils/hpf. We grouped 2 different drugs with similar mechanisms of action-mepolizumab and reslizumab-for the effect size estimate. One of the studies (Assa'ad 2011) 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 (Spergel 2012), and there were no major signals of harms reported in the 3 studies.

Anti-IL-5 monoclonal antibodies compared to placebo for eosinophilic esophagitis

Bibliography: Straumann 2010^a,(97) Assa'ad 2011^b,(98) Spergel 2012^c (99)

Outcomes and Follow-up	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (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 weeks to 16 weeks	286 (3 RCTs)	⊕⊕○○ LOW ^{e,f}	RR 0.92 (0.84 to 1.00)	902 per 1,000	72 fewer per 1,000 (144 fewer to 0 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. Mepolizumab in adults (escalating mepolizumab doses)
- b. Mepolizumab 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
- c. Reslizumab in children; grouped 3 doses of reslizumab together in intervention group (no obvious dose response)
- d. Participant selection for these studies are different than for other interventions—have failed many other interventions prior to enrolling in this study
- e. CI crosses 1
- f. CI touches 1 (upper boundary of CI is 1.0—no effect—which could lead to a different recommendation and therefore represents imprecision.

#10 Should anti-IL-13 therapy be used in patients with EoE?

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. 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. In Hirano et al, 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/hpf compared to 24 out of 24 in the placebo arm (risk ratio=0.17, 0.07-0.42). In Dellon et al, two 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<0.0001).

a.

QAX-576 compared to placebo for eosinophilic esophagitis

Bibliography: Rothenberg 2015 (100)

Outcomes and Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with QAX-576
Not achieving histologic remission < 15 eos/hpf (hist remission) assessed with: < 15 eos/hpf follow up: mean 12 weeks	25 (1 RCT)	⊕⊕○○ LOW ^{a,b}	RR 0.94 (0.67 to 1.30)	875 per 1,000	53 fewer per 1,000 (289 fewer to 263 more)

QAX-576 compared to placebo for eosinophilic esophagitis

Bibliography: Rothenberg 2015 (100)

Outcomes and Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with QAX-576

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanation

- a. Very low information size
- b. Patients with higher baseline esophageal eosinophilia and more likely to have failed other treatments

#11 Should anti-IgE therapy be used in patients with EoE?

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. 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 (Loizou 2015) (101) 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.

Omalizumab compared to placebo for eosinophilic esophagitis

Bibliography: Clayton 2014 (102)

Outcomes and Follow-up	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Omalizumab
Change in peak eosinophil counts/hpf (Peak eosinophils) assessed with: eos/hpf follow up: mean 16 weeks	30 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	-	The mean change in peak eosinophil counts/hpf was 0 eos/hpf ^c	MD 6 eos/hpf more (4 fewer to 16 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

-
- a. Selected 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.
- b. Very low information size
- c. Personal communication with Dr. Fred Clayton that no subject in either arm achieved histologic remission < 15 eos/hpf.

#12 Should montelukast be used in patients with EoE?

Evidence Summary: There is 1 RCT that compares montelukast with placebo for maintenance therapy after subjects had achieved symptomatic and histologic remission(90), and 4 observational studies that report outcomes after montelukast use [Atwood 2003 (n=8)(103); Vanderhoof 2003 (n=8)(104); Lucendo 2011 (n=11)(105); Stumphy 2011 (n=8)(106)]. Based on the RCT, the RR for the recurrence of solid food dysphagia was 0.79 (95% CI 0.51 to 1.21). Failing to achieve histologic remission of < 15 eosinophils/high power field was not measured in this trial.

Quality of Evidence: The certainty in the effect estimate was very low. 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 histological 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.

Montelukast compared to placebo for management of Eosinophilic esophagitis

Bibliography: Alexander 2017 (90)

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

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanations

- The abridged dysphagia questionnaire used the questions on dysphagia frequency, severity, and food impaction from the Mayo Dysphagia Questionnaire, 2-week version
- All 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.
- Large confidence interval that crosses 1; estimate based on a single RCT

#13 Should cromolyn be used in patients with EoE?

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

Quality of Evidence: The certainty in the effect estimate was low. The certainty in the estimate was downgraded twice for very serious imprecision given the very low number of study participants and because the 95% confidence interval 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. (59)

Cromolyn compared to placebo for eosinophilic esophagitis

Bibliography: Lieberman 2018(107)

Outcomes and Follow-up	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with cromolyn
Not achieving histologic remission (Histologic remission) assessed with: Eos < 5/hpf follow up: mean 8 weeks	16 (1 RCT)	⊕⊕○○ LOW ^a	RR 0.89 (0.71 to 1.12)	1,000 per 1,000	110 fewer per 1,000 (290 fewer to 120 more)

Cromolyn compared to placebo for eosinophilic esophagitis

Bibliography: Lieberman 2018(107)

Outcomes and Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with cromolyn

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

Explanation
a. Very serious imprecision
#14 Should anti-TNFs be used in pts with EoE?

Evidence Summary: There is one 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.(108) 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 greater than 24 eosinophils/ high-power field (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.

#15 Should immunomodulators be used in the treatment of EoE?

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 the 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 papers with a total included population of 4 people; therefore the evidence base for immunodulator treatment in patients with EoE is very small.(109, 110) In these case series, it is not clear if 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 was not available.

#16 Should repeat EGD be used to assess patients with EoE 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 EREFS 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”(111). Further, a set of four studies from different centers in the U.S. and Europe independently show that the longer the duration of disease prior to diagnosis (as a proxy for time prior to treatment), the higher the proportion of patients who have a stricture or fibrostenotic phenotype at the time of diagnosis (12-15). For example, in one study, more than 80% of patients had strictures if the diagnostic delay was >20 years. Other studies document progression in distinct patients (112). 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, 75, 113). There are several reasons for this. Patients can avoid foods that cause dysphagia or other symptoms, or modify the way they eat (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 two 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)(114). 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 suggests 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, financial and time burden. These considerations need to be accounted for when balancing the risks and benefits of performing surveillance endoscopies especially in children.

#17 What is the management of patients who become asymptomatic after initial PPI 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 eosinophilic esophagitis 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 gastroesophageal reflux is more probable and similarly will have a high likelihood of response to PPI. Endoscopic features and associated histological 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 a poor correlation between symptoms and inflammation. Recent data from Aceves et al has recently showed that proximal eosinophilia associates with self-reported symptoms in a sample of children from CeGIR consortium centers, which may hold potential promise as a marker to monitor disease progression.(115)

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 above and in Question #16. Clinical observation for side effects of PPIs is warranted. While a degree of overlap exists between EoE and GERD (116, 117), 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 gastro-esophageal junction.

There are multiple unresolved additional issues, including establishing the optimal minimal duration of PPI treatment prior to 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.

APPENDIX

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Appendix Table 1. PICO Questions

#	Question	PICO Question				Method
		Population	Intervention(s)	Comparator	Outcome	
1	Should PPIs be used in patients with symptomatic esophageal eosinophilia?	Esophageal eosinophilia, not necessarily meeting EoE criteria	PPI	Placebo	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE

2	Should topical glucocorticosteroids be used in patients with EoE?	Patients with EoE	Topical Steroids	Placebo	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE
3	Should systemic glucocorticosteroids be used in patients with EoE?	Patients with EoE	Systemic steroids	Placebo or topical steroids	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE
4	Should an elemental diet be used in patients with EoE?	Patients with EoE	Elemental diet	No diet change	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE
5	Should an empiric elimination diet be used in patients with EoE?	Patients with EoE	-6 food elimination diet -4 food elimination diet -2 food elimination diet -Single food elimination diet	No elimination diet	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE

6	Should allergy-based testing be used for the purpose of identifying food triggers in patients with EoE?	Patients with EoE	-SPT, sIGE, APT, and/or CRD to direct an elimination diet	No elimination diet	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE
7	Is maintenance therapy recommended in patients with EoE?	Patients with EoE who are in clinical and histologic remission	Maintaining therapy	Discontinuing therapy	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE
8	Should esophageal dilation be used in patients with EoE?	Patients with EoE	Dilation	No dilation	-Adverse events	GRADE
9	Should anti-IL-5 therapy be used in patients with EoE?	Patients with EoE	Anti-IL-5 therapy	Placebo	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE
10	Should anti-IL-13 therapy be used in patients with EoE?	Patients with EoE	Anti-IL-13 therapy	Placebo	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE

1 1	Should anti-IgE therapy be used in patients with EoE?	Patients with EoE	Anti-IgE therapy	Placebo	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE
1 2	Should montelukast be used in patients with EoE?	Patients with EoE	Montelukast	Placebo	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE
1 3	Should cromolyn be used in patients with EoE?	Patients with EoE	Cromolyn	Placebo	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE
1 4	Should anti-TNFs be used in patients with EoE?	Patients with EoE	Anti-TNF	Placebo	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE
1 5	Should Immunomodulators be used in patients with EoE?	Patients with EoE	Azathioprine or 6-MP	Placebo	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	GRADE

1 6	Should repeat EGD be used to assess patients with EoE after a change in treatment?	Patients with EoE	EGD with Esophageal biopsy	N/A	N/A	Narrative
1 7	Management of patients who become asymptomatic on initial PPI treatment	Patients with esophageal eosinophilia and/or EoE	Repeat EGD, followed by additional therapy if eosinophils still elevated	No EGD, no change in treatment	-Failing to achieve histologic remission (eosinophils<15/hpf) -Symptoms -Adverse events	Narrative

Appendix Table 2. Summary of EoE outcomes considered

Name of Outcome	Definition	Minimally Important Difference	Rating (1-9)	Critical vs Important vs Non-important
Histology	eosinophil counts <15/hpf in esophagus	Not known	8	Critical
Symptoms	DSQ, MDQ, EEsAI, PEES	Response: 30-50% improvement Remission: Absence of symptoms. For EEsAI, score <30 may indicate inactive disease/remission	6	Important
Endoscopic Findings	(EREFS)	Response: 30-50% improvement	6	Important

		Remission: normalization		
Complications of EoE	Stricture Food impaction Malnutrition psychiatric	N/A	8	Critical
Quality of Life	Peds EoE QL Adult Eoe QL	Response: 30-50% improvement as response Remission: Baseline for healthy people	6	Important
Biomarkers	Peripheral Eos Progenitor Eos Gene Expression Cytosponge EST readout Tissue cytokines eosinophil granules	N/A	4	Non- important
Adverse Events of Medication Treatment	Allergy Weight gain Anaphylaxis Infections	N/A	6	Important
Complications of endoscopy	Perforation Anesthesia complications	N/A	8	Critical
Costs		N/A	6	Important

Appendix Table 3. Electronic Search Strategies

Search Strategy

EoE – Final Search

Search date: May 13, 2018

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2018 May 11; Wiley Cochrane. Individual systematic review

searches were not registered in Prospero, as this technical report represents an umbrella evidence review.

Ovid MEDLINE(R), Embase

#	Searches	Results
1	exp Eosinophilic Esophagitis/	5991
2	(eosinophilic adj2 (esophagitis or oesophagitis)).ti,ab.	6556
3	1 or 2	7480
4	exp EOSINOPHILIA/	62171
5	exp ESOPHAGITIS/	45445
6	exp ESOPHAGUS/	133201
7	4 and (5 or 6)	2855
8	eo.e.ti,ab.	3588
9	3 and (7 or 8)	4580
10	exp Adrenal Cortex Hormones/ use ppez	376133
11	exp corticosteroid/ use emczd	935731
12	(corticosteroid* or steroid* or prednisone or budesonide or fluticasone).ti,	786701
13	exp Leukotriene Antagonists/ use ppez	2974
14	exp leukotriene receptor blocking agent/ use emczd	18407
15	exp montelukast/ use emczd	8443
16	(montelukast or singulair).mp.	10840
17	exp Proton Pump Inhibitors/ use ppez	16773
18	exp proton pump inhibitor/ use emczd	68622
19	(proton pump inhibitor* or PPI* or omeprazole or Prilosec or Yosprala or lansoprazole or Prevacid or dexlansoprazole or Dexilent or rabeprazole (Aciphex or pantoprazole or Protonix or esomeprazole or Nexium or Vimc or Zegerid).ti,ab.	88470
20	exp monoclonal antibody/ use emczd	480638
21	exp Antibodies, Monoclonal, Humanized/ use ppez	39896
22	exp Interleukin-5/ai [Antagonists & Inhibitors]	293
23	exp Receptors, Interleukin-5/ai [Antagonists & Inhibitors]	31

24	exp interleukin 5/ use emczd	25332
25	(anti-il-5* or Interleukin-5 or Mepolizumab or nucala or Reslizumab or Cir6850 or Benralizumab or fasenra).ti,ab.	
26	exp Interleukin-13/ai [Antagonists & Inhibitors]	219
27	interleukin 13/ use emczd	20432
28	exp Interleukin-4/ai [Antagonists & Inhibitors]	501
29	exp interleukin 4/ use emczd	71100
30	(Dupilumab or Dupixent or anti-il-13* or anti-il-4* or Interleukin-13 or Interleukin-4).ti,ab.	26804
31	exp Immunoglobulin E/ai [Antagonists & Inhibitors]	20
32	immunoglobulin e/ use emczd or immunoglobulin e antibody/ use emczd	80681
33	(anti-IgE or Omalizumab or Xolair).mp.	14248
34	exp Dilatation/ use ppez	10447
35	exp esophagus dilatation/ use emczd	3265
36	(dilation or dilatation).ti,ab.	210743
37	exp Immunologic Factors/ use ppez	127460 5
38	exp immunomodulating agent/ use emczd	104544 0
39	immunomodulator*.ti,ab.	93101
40	exp Mercaptopurine/	46362
41	(6-Mercaptopurine or 6-MP or Purinethol or Purixan or azothioprine or Azathioprine or Azasan or Imuran).ti,ab.	46642
42	exp Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]	14168
43	tumor necrosis factor inhibitor/ use emczd	10354
44	(Infliximab or remicade or adalimumab or humira or golimumab or simpo vedolizumab or entyvio or tofacitinib or Xeljanz or Jakvinus).ti,ab.	45437
45	exp Cromolyn Sodium/ use ppez	4044
46	exp cromoglycate disodium/ use emczd	15471
47	cromolyn.ti,ab.	2968
48	Food Hypersensitivity/di [Diagnosis]	6271
49	exp Protein Array Analysis/ use ppez	7467

50	exp IMMUNOASSAY/ use ppez	475054
51	exp allergy test/ use emezd or exp food allergy/ use emezd	35286
52	(Component Resolved Diagnostic Testing or crd).ti,ab.	6533
53	(test* adj2 (allerg* or hypersensitivit*)).ti,ab.	17189
54	or/10-53	463182 7
55	9 and 54	2875
56	(Randomized Controlled Trial or Pragmatic Clinical Trial or meta-analysis	550035
57	exp Randomized Controlled Trials as Topic/	263799
58	"Randomized Controlled Trial (topic)"/	145282
59	Randomized Controlled Trial/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double Blind Procedure/ or Double-Blind Studie Single-Blind Method/ or Single Blind Procedure/ or Single-Blind Studies/ Placebos/ or Placebo/	142074
60	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/	416180
61	(random* or sham or placebo*).ti,ab,hw,kf,kw.	310035 7
62	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	491550
63	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	1696
64	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review overview*))).ti,ab,kf,kw.	303565
65	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.	19173
66	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* o overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	49299
67	(data synthes* or data extraction* or data abstraction* or handsearch* or hand search or mantel haenszel or peto or der simonian or dersimonian fixed effect* or latin square* or met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal* or meta regression* or metaregression* or outcomes research relative effectiveness).ti,ab,kf,kw.	151747
68	(cochrane or (health adj2 technology assessment) or evidence report).jw	44072
69	(meta-analy* or metaanaly* or systematic review* or biomedical technolc assessment* or bio-medical technology assessment*).mp,hw.	594805

70	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,h	387579
71	(meta-analysis or systematic review).md.	0
72	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.	27349
73	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.	4938
74	or/56-73	374998 1
75	55 and 74	420
76	exp diet therapy/	380595
77	(diet* adj2 (6 food or six food or elimination or elemental)).ti,ab.	5676
78	76 or 77	385128
79	9 and 78	875
80	75 or 79	1166
81	animals/ not (humans/ and animals/)	576852 0
82	80 not 81	1163
83	limit 82 to (case reports or comment or editorial or letter or conference abstract or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,Embase; records were retained]	418
84	case report/	421168 7
85	82 not (83 or 84)	722
86	remove duplicates from 85	496

Wiley Cochrane

ID	Search Hits	
#1	MeSH descriptor: [Eosinophilic Esophagitis] explode all trees	26
#2	(eosinophilic near/2 (esophagitis or oesophagitis)):ti,ab	126
#3	#1 or #2	128
#4	MeSH descriptor: [Eosinophilia] explode all trees	240
#5	MeSH descriptor: [Esophagitis] explode all trees	680
#6	MeSH descriptor: [Esophagus] explode all trees	1282
#7	#4 and (#5 or #6)	36
#8	eo:ti,ab	86
#9	#3 or #7 or #8	131
#10	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees	13563

- #11 (corticosteroid* or steroid* or prednisone or budesonide or fluticasone):ti,ab 35079
- #12 MeSH descriptor: [Leukotriene Antagonists] explode all trees 439
- #13 (montelukast or singulair):ti,ab 1269
- #14 MeSH descriptor: [Proton Pump Inhibitors] explode all trees 1302
- #15 (proton pump inhibitor* or PPI* or omeprazole or Prilosec or Yosprala or lansoprazole or Prevacid or dexlansoprazole or Dexilent or rabeprazole or Aciphex or pantoprazole or Protonix or esomeprazole or Nexium or Vimovo or Zegerid):ti,ab 6841
- #16 MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees 3971
- #17 MeSH descriptor: [Interleukin-5] explode all trees 159
- #18 MeSH descriptor: [Receptors, Interleukin-5] explode all trees 9
- #19 (anti-il-5* or Interleukin-5 or Mepolizumab or nucala or Reslizumab or Cinqair or Benralizumab or fasenra):ti,ab 806
- #20 MeSH descriptor: [Interleukin-13] explode all trees 81
- #21 MeSH descriptor: [Interleukin-4] explode all trees 332
- #22 (Dupilumab or Dupixent or anti-il-13* or anti-il-4* or Interleukin-13 or Interleukin-4):ti,ab 873
- #23 MeSH descriptor: [Immunoglobulin E] explode all trees 1287
- #24 (anti-IgE or Omalizumab or Xolair):ti,ab 704
- #25 MeSH descriptor: [Dilatation] explode all trees 420
- #26 (dilation or dilatation):ti,ab 6065
- #27 MeSH descriptor: [Immunologic Factors] explode all trees 8197
- #28 immunomodulator*:ti,ab 2491
- #29 MeSH descriptor: [Mercaptopurine] explode all trees 1304
- #30 (6-Mercaptopurine or 6-MP or Purinethol or Purixan or azothioprine or Azathioprine or Azasan or Imuran):ti,ab 2101
- #31 MeSH descriptor: [Tumor Necrosis Factor-alpha] explode all trees 3094
- #32 (Infliximab or remicade or adalimumab or humira or golimumab or simponi or vedolizumab or entyvio or tofacitinib or Xeljanz or Jakvinus):ti,ab 3531
- #33 MeSH descriptor: [Cromolyn Sodium] explode all trees 705
- #34 cromolyn:ti,ab 332
- #35 MeSH descriptor: [Food Hypersensitivity] explode all trees 731
- #36 MeSH descriptor: [Protein Array Analysis] explode all trees 34
- #37 MeSH descriptor: [Immunoassay] explode all trees 4804
- #38 (Component Resolved Diagnostic Testing or crd):ti,ab 166
- #39 (test* near/2 (allerg* or hypersensitivit*)):ti,ab 756
- #40 MeSH descriptor: [Diet Therapy] explode all trees 5354
- #41 (diet* near/2 (6 food or six food or elimination or elemental)):ti,ab 306
- #42 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 86910
- #43 #9 and #42 103

Appendix Table 4. Additional Evidence Profile

Bibliography: Peterson 2010, Moawad 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical Steroids	PPI	Relative (95% CI)	Absolute (95% CI)		
Failure to achieve histologic response (assessed with: < 15 Eos/hpf)												
2	randomised trials	not serious	not serious	serious ^a	serious ^b	none	53/88 (60.2%)	55/88 (62.5%)	RR 0.96 (0.76 to 1.22)	25 fewer per 1,000 (from 137 more to 150 fewer)	⊕⊕○ ○ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. No PPI trial before steroids (so GERD is possible confounder)
- b. Clinical management would vary at ends of CI

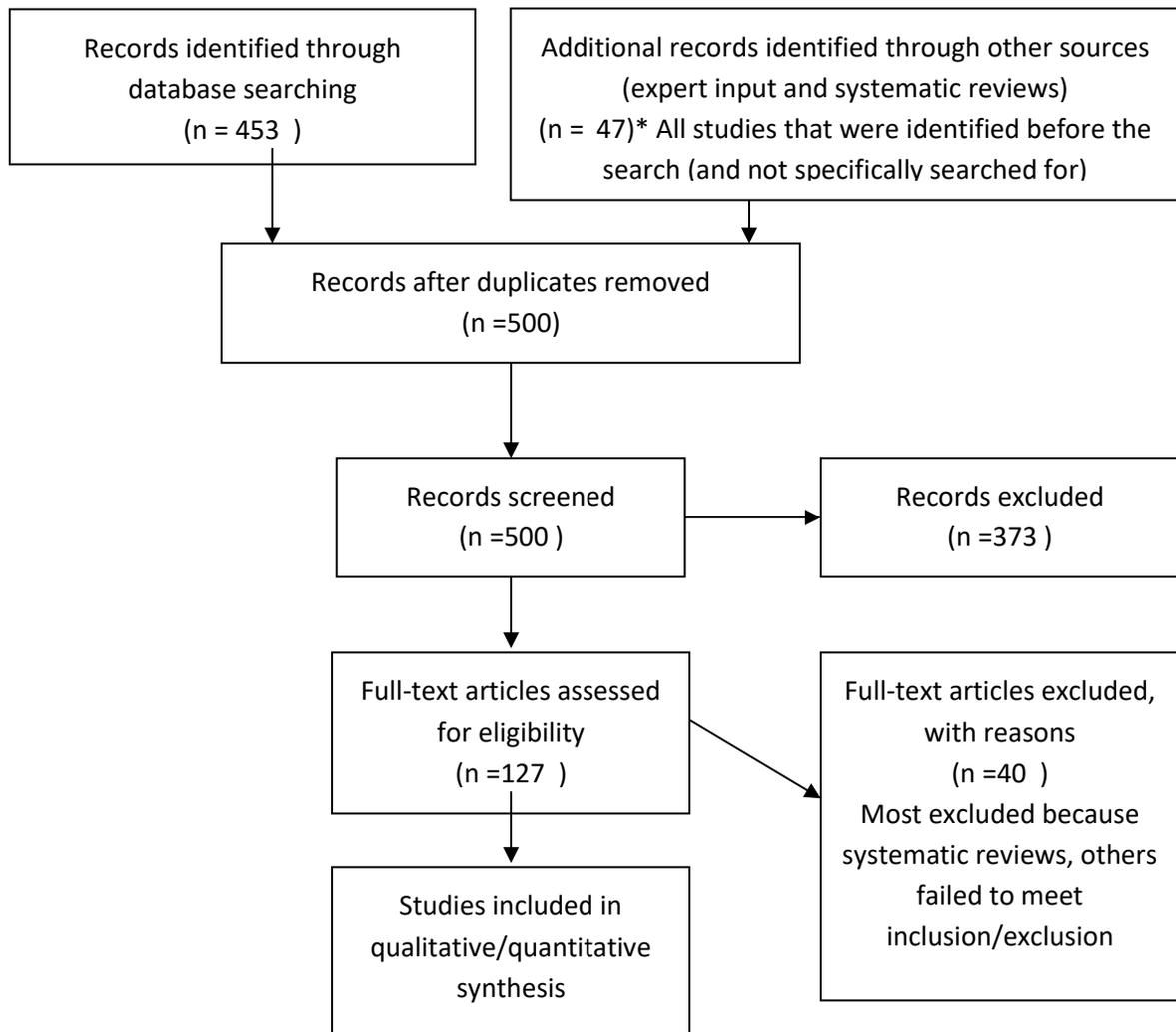
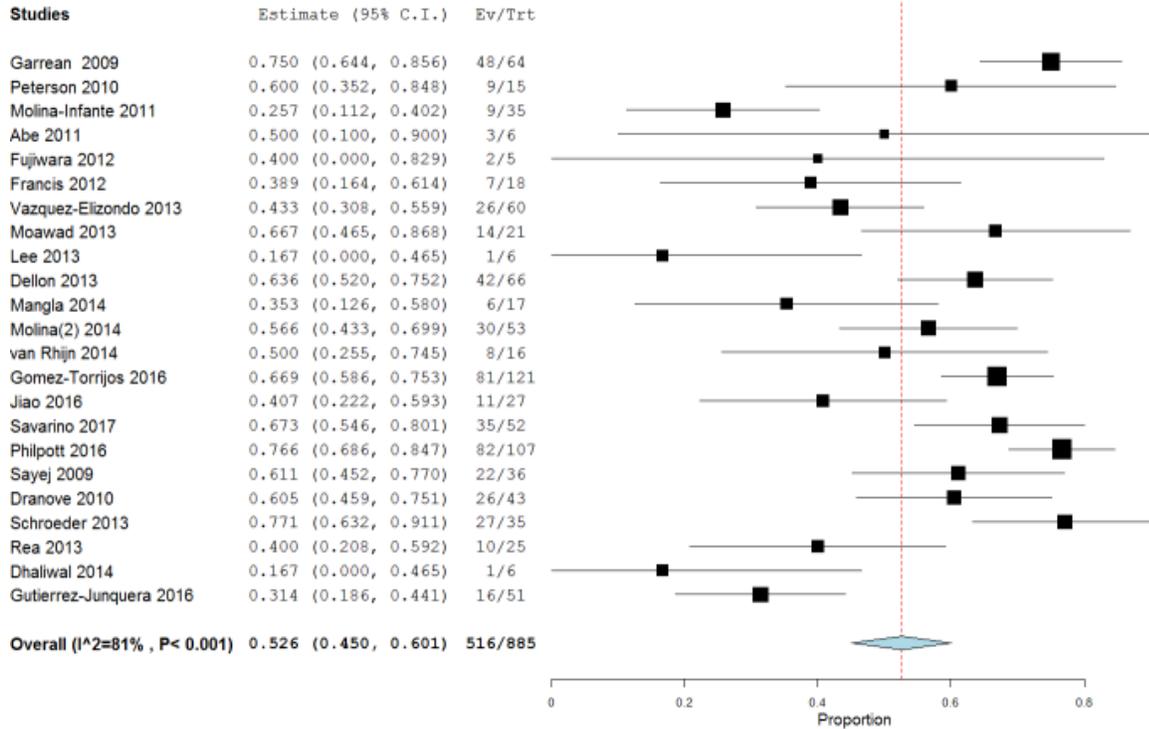
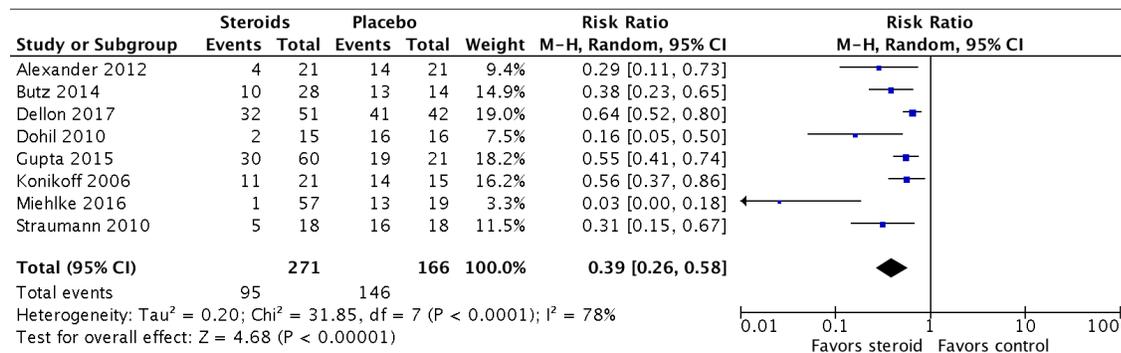
Figure 1. PRISMA Flow Diagram

Figure 2. Forest Plots for each PICO question

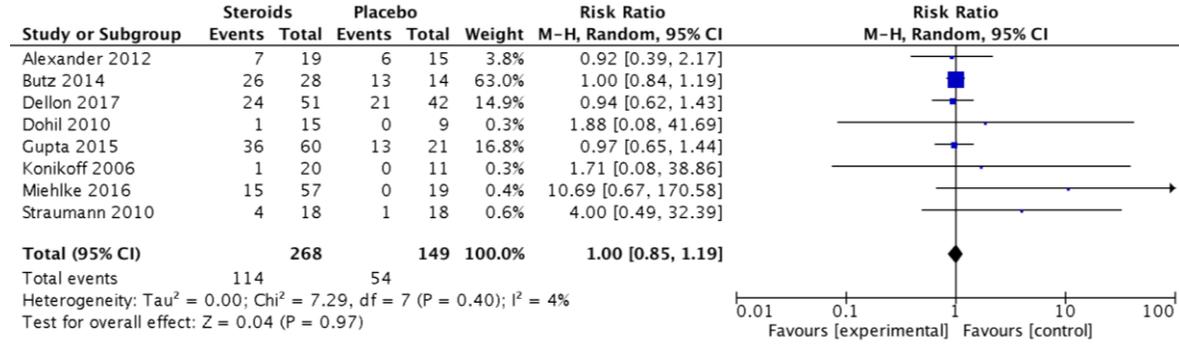
#1 Should proton pump inhibitors be used in patients with esophageal eosinophilia?



#2 Should topical glucocorticosteroids be used in patients with EoE?



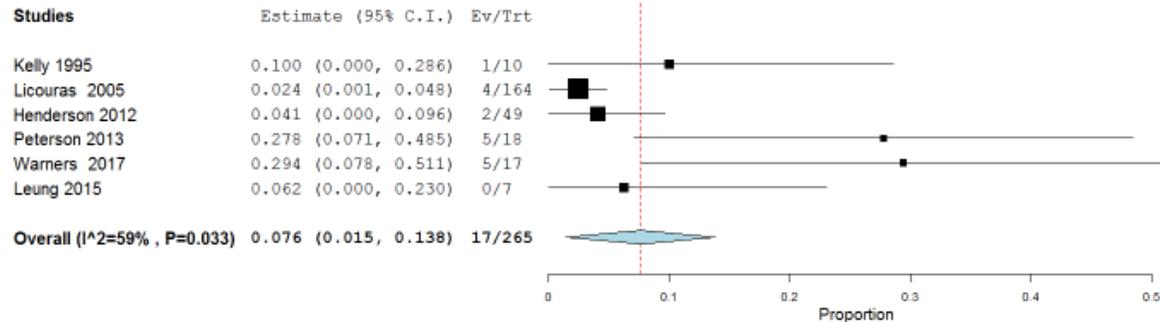
Adverse events in topical steroids compared to placebo



#3 Should systemic glucocorticosteroids be used in patients with EoE?

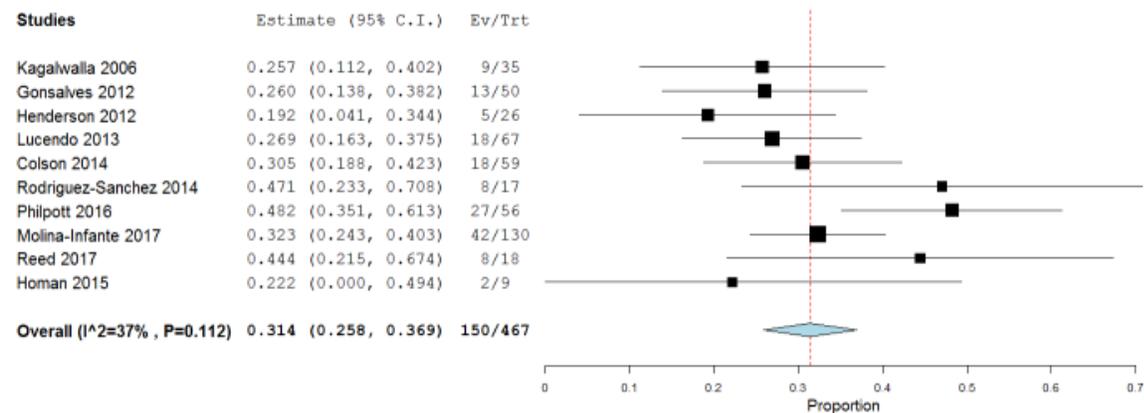
Forest plot not shown (only 1 study)

#4 Should an elemental diet be used in patients with EoE?



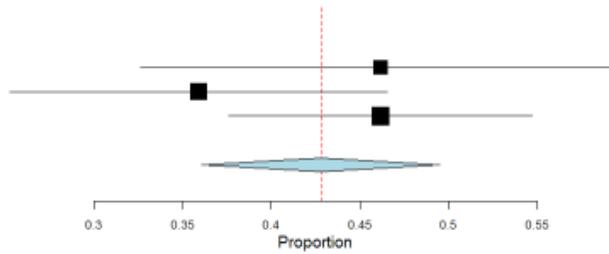
#5 Should an empiric food elimination diet be used in patients with EoE?

6 food elimination



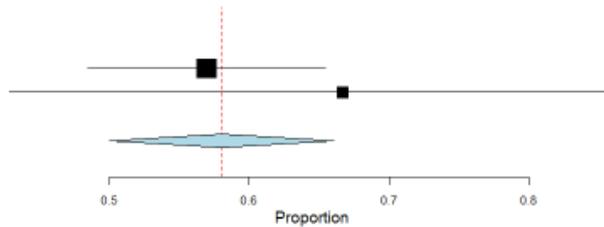
4 food elimination

Studies	Estimate (95% C.I.)	Ev/Trt
Molina-Infante 2014	0.462 (0.326, 0.597)	24/52
Kagalwalla 2017	0.359 (0.253, 0.465)	28/78
Molina-Infante(2) 2017	0.462 (0.376, 0.547)	60/130
Overall (I²=18% , P=0.296)	0.428 (0.361, 0.495)	112/260



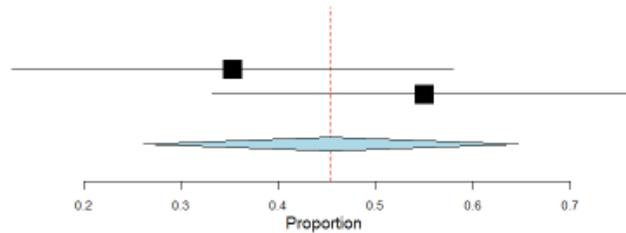
2 food elimination

Studies	Estimate (95% C.I.)	Ev/Trt
Molina-Infante 2017	0.569 (0.484, 0.654)	74/130
Reed 2018	0.667 (0.428, 0.905)	10/15
Overall (I²=0% , P=0.451)	0.580 (0.500, 0.660)	84/145



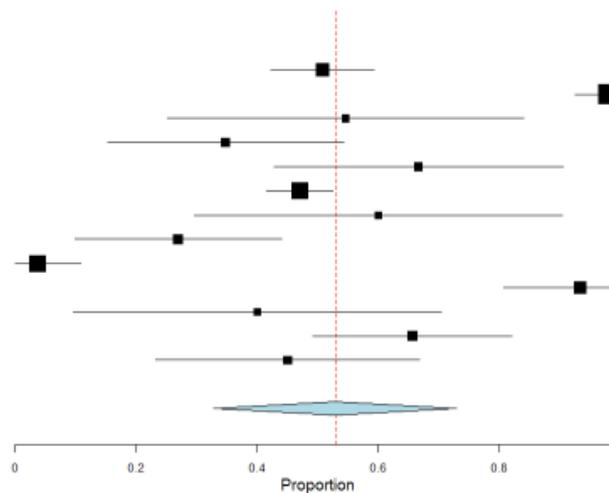
Single food elimination

Studies	Estimate (95% C.I.)	Ev/Trt
Kagalwalla 2012	0.353 (0.126, 0.580)	6/17
Kruszewski 2016	0.550 (0.332, 0.768)	11/20
Overall (I²=34% , P=0.220)	0.454 (0.261, 0.647)	17/37



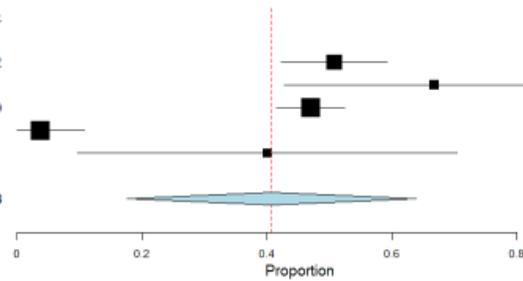
#6 Should allergy-based testing be used for the purpose of identifying food triggers in patients with EoE?

Studies	Estimate (95% C.I.)	Ev/Trt
Licarous 2005	0.508 (0.422, 0.593)	67/132
Quagletta 2007	0.980 (0.925, 1.000)	24/24
Rizo Pascual 2011	0.545 (0.251, 0.840)	6/11
Henderson 2012	0.348 (0.153, 0.542)	8/23
Molina-Infante 2012	0.667 (0.428, 0.905)	10/15
Spergel 2012	0.470 (0.415, 0.525)	150/319
Al-Hussaini 2013	0.600 (0.296, 0.904)	6/10
Rodriguez-Sanchez 2014	0.269 (0.099, 0.440)	7/26
Syrigou 2015	0.037 (0.000, 0.108)	1/27
Van Rhijn 2015	0.933 (0.807, 1.000)	14/15
Constatine 2017	0.400 (0.096, 0.704)	4/10
Reed 2017	0.656 (0.492, 0.821)	21/32
Homan 2015	0.450 (0.232, 0.668)	9/20
Overall (I²=98% , P< 0.001)	0.529 (0.328, 0.729)	327/664



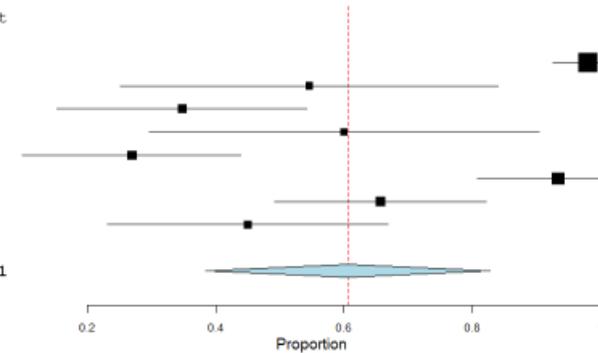
Studies including patch testing

Studies	Estimate (95% C.I.)	Ev/Trt
Licarus 2005	0.508 (0.422, 0.593)	67/132
Molina-Infante 2012	0.667 (0.428, 0.905)	10/15
Spiegel 2012	0.470 (0.415, 0.525)	150/319
Syrigou 2015	0.037 (0.000, 0.108)	1/27
Constatine 2017	0.400 (0.096, 0.704)	4/10
Overall (I²=96% , P< 0.001)	0.408 (0.176, 0.639)	232/503



Studies not using patch testing

Studies	Estimate (95% C.I.)	Ev/Trt
Quagletta 2007	0.980 (0.925, 1.000)	24/24
Rizo Pascual 2011	0.545 (0.251, 0.840)	6/11
Henderson 2012	0.348 (0.153, 0.542)	8/23
Al-Hussaini 2013	0.600 (0.296, 0.904)	6/10
Rodriguez-Sanchez 2014	0.269 (0.099, 0.440)	7/26
Van Rhijn 2015	0.933 (0.807, 1.000)	14/15
Reed 2017	0.656 (0.492, 0.821)	21/32
Homan 2015	0.450 (0.232, 0.668)	9/20
Overall (I²=94% , P< 0.001)	0.605 (0.384, 0.827)	95/161



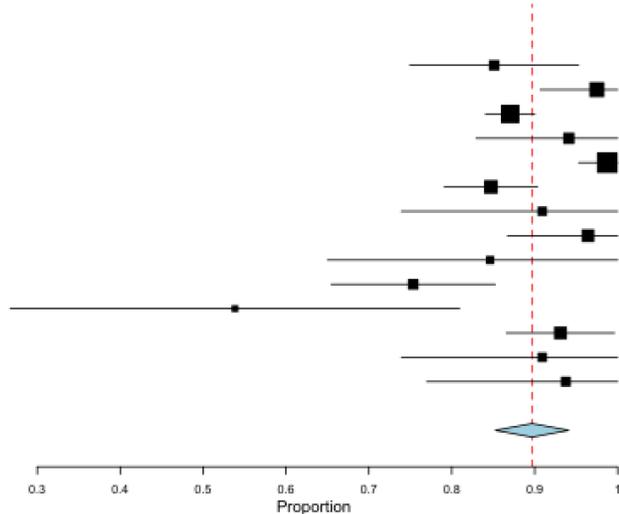
#7 Should maintenance therapy be recommended in patients with EoE?

Forest Plot not shown (only 1 study)

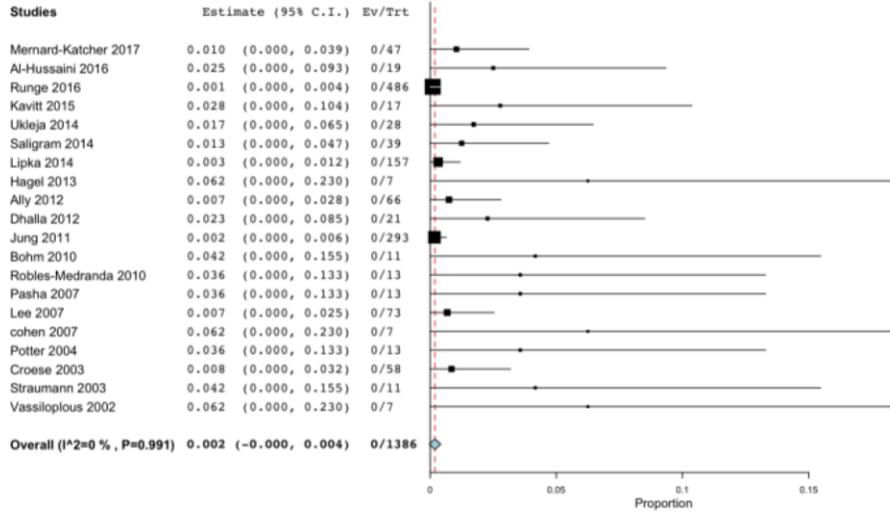
#8 Should esophageal dilation be used in patients with EoE?

Clinical Improvement:

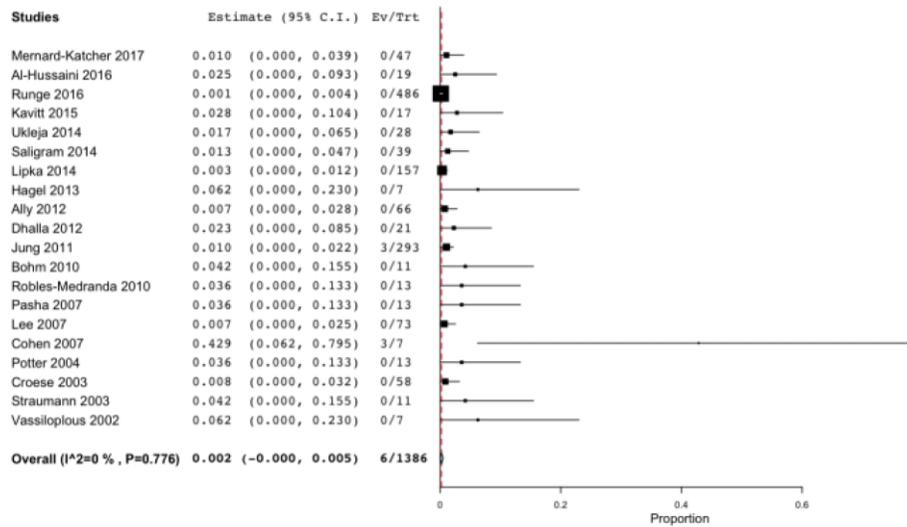
Studies	Estimate (95% C.I.)	Ev/Trt
Mernard-Katcher 2017	0.851 (0.749, 0.953)	40/47
Al-Hussaini 2016	0.975 (0.907, 1.000)	19/19
Runge 2016	0.870 (0.841, 0.900)	423/486
Kavitt 2015	0.941 (0.829, 1.000)	16/17
Saligram 2014	0.988 (0.953, 1.000)	39/39
Lipka 2014	0.847 (0.791, 0.903)	133/157
Bohm 2010	0.909 (0.739, 1.000)	10/11
Robles-Medrandra 2010	0.964 (0.867, 1.000)	13/13
Pasha 2007	0.846 (0.650, 1.000)	11/13
Lee 2007	0.753 (0.655, 0.852)	55/73
Potter 2004	0.538 (0.267, 0.809)	7/13
Croese 2003	0.931 (0.866, 0.996)	54/58
Straumann 2003	0.909 (0.739, 1.000)	10/11
Vassilopoulos 2002	0.938 (0.770, 1.000)	7/7
Overall (I²=7638 % , P< 0.001)	0.897 (0.852, 0.941)	837/964



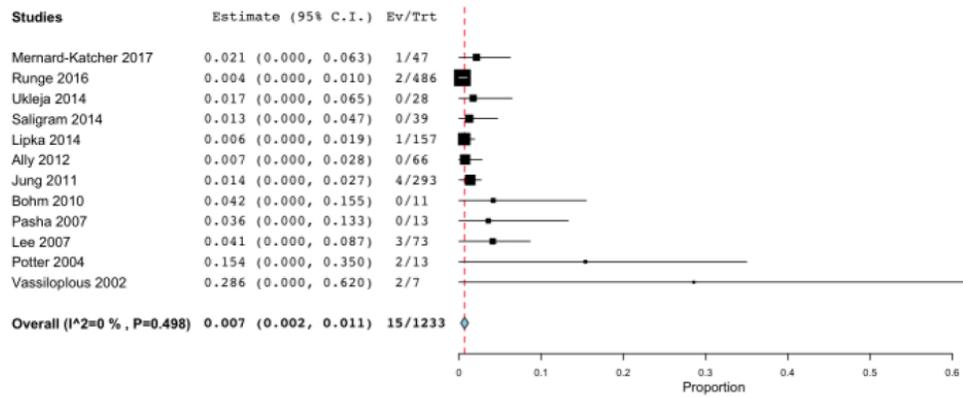
Mortality



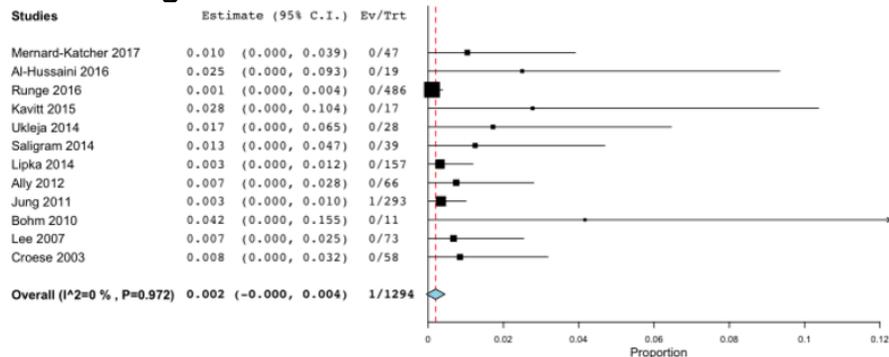
Perforation



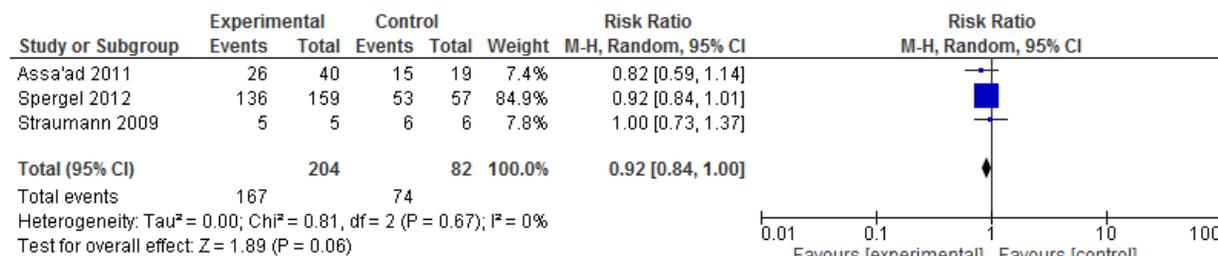
Hospitalizations



Hemorrhage



#9 Should anti-IL-5 therapy be used in patients with EoE?



#10 Should anti-IL-13 therapy be used in patients with EoE?

Forest plot not shown (only 1 study)

#11 Should anti-IgE therapy be used in patients with EoE?

Forest plot not shown (only 1 study)

#12 Should montelukast be used in patients with EoE?

Forest plot not shown (only 1 study)

#13 Should cromolyn be used in patients with EoE?

Forest plot not shown (only 1 study)

#14 Should anti-TNFs be used in pts with EoE?

Forest plot not shown (only 1 study)

#15 Should immunomodulators be used in the treatment of EoE?

Forest plot not shown (only 1 study)

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