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Systematic Review of Outcome Measures Used in Observational Studies of Adults with Eosinophilic Esophagitis

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Running title: Systematic review: outcome measures in adults with eosinophilic esophagitis

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Abbreviations used in this paper: A/P, absence/presence; BL, baseline; BZH, basal zone hyperplasia; COS, core outcome set; E, edema; EEsAI, eosinophilic esophagitis activity index; EA, eosinophilic microabscesses; EE, erosive esophagitis; EoE, eosinophilic esophagitis; EGD, esophagogastroduodenoscopy; EoEHSS, eosinophilic esophagitis histology scoring system EoE-QoL-A, adult eosinophilic esophagitis quality of life; EORTC-QLQOES18, Treatment of Cancer Quality of Life Questionnaire-Oesophageal Module 18; Eos, eosinophils; EOT, end of treatment; EP, epithelium; EREFS, endoscopic reference score; F, furrows; FU, follow-up; hpf, high-power field; PRO, patient-reported outcome; PPI, proton-pump inhibitors; QoL, quality of life; LP, lamina propria; MDQ, Mayo Dysphagia Questionnaire; NA, not assessed; NR, not reported; NS, not significant; PRO, patient-reported outcome; R, rings; S, stricture; SDI, Straumann Dysphagia Questionnaire; VAS, visual analogue scale; WE, white exudates.

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ABSTRACT

Background: Over the last twenty years diverse outcome measures have been used to evaluate the effectiveness of therapies for eosinophilic esophagitis (EoE). This systematic review aims to identify the readouts used in observational studies of topical corticosteroids, diet, and dilation in adult EoE patients.

Methods: We searched MEDLINE, and Embase for prospective and retrospective studies (cohorts/case series, randomized open-label, case-control) evaluating the use of diets, dilation, and topical corticosteroids in adults with EoE. Two authors independently assessed the articles and extracted information about histologic, endoscopic, and patient-reported outcomes and tools used to assess treatment effects.

Results: We included 69 studies that met inclusion criteria. EoE-associated endoscopic findings (assessed either as absence/presence or using Endoscopic Reference Score) were evaluated in 24/35, 11/17, and 9/17 studies of topical corticosteroids, diet, and dilation, respectively. Esophageal eosinophil density was recorded in 32/35, 17/17, and 11/17 studies of topical corticosteroids, diet, and dilation, respectively. Patient-reported outcomes were not uniformly used (only in 14, 8, and 3 studies of topical corticosteroids, diet, and dilation, respectively), and most tools were not validated for use in adults with EoE.

Conclusions: Despite the lack of an agreed set of core outcomes that should be recorded and reported in studies in adult EoE patients, endoscopic appearance of EoE-associated findings and esophageal eosinophil density are commonly used to assess disease activity in observational studies. Standardization of outcomes and data supporting the use of outcomes are needed to facilitate interpretation of evidence, its synthesis, and comparisons of interventions in meta-analyses of therapeutic trials in adults with EoE.

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INTRODUCTION

Eosinophilic esophagitis is characterized by presence of both symptoms related to esophageal dysfunction and esophageal eosinophilia.[1] In adults, esophageal inflammation driven by food antigens leads to the formation of fibrosis and strictures in a time dependent manner.[2,3] Dysphagia is a predominant symptom in adults with EoE. It is associated with various behavioral adaptations aimed at both avoiding and dealing with impaction episodes.[4] These adaptations include avoidance of certain foods, eating slowly, and consuming copious amounts of liquids during meal times. Therefore, capturing a full range of dysphagia experiences is a complex task. Nevertheless, in recent years, attempts have been made to assess frequency of dysphagia, albeit described using different patient language, as a patient-reported outcome (PRO) in clinical trials and observational studies.[4,5] Of various inflammation- and fibrosis-associated histologic parameters, esophageal eosinophilia is most frequently assessed in clinical practice and observational studies. Evaluating the full spectrum of EoE-associated histologic findings outside of clinical trials remains a challenge.[6] Although not pathognomonic of this condition, EoE-associated endoscopic findings are often assessed as endpoints in various studies or used to aid clinical decision-making.[7] Measuring intraluminal distensibility using Endoluminal Functional Lumen Imaging Probe, genetic profiling, assessment of various biomarkers, and immunological dissection, such as measuring of allergen specific immunoglobulin levels, T cell profiling, barrier assessment, have also been carried out over the years; however, many of these parameters are assessed as a part of the exploratory investigations.[8,9,10,11,12,13,14,15,16]

EoE-associated endoscopic findings and esophageal eosinophilia represent the most common outcomes for the purposes of monitoring treatment efficacy/effectiveness in adults with EoE. Nevertheless, standardizing outcome assessment, whether in the context of randomized controlled trials (RCTs) or observational studies, remains a challenge. For example, Ma *et al.* have recently demonstrated that certain heterogeneity in use of clinical, endoscopic, and histologic outcome measures in RCTs in adults with EoE can be observed, and concluded that this may pose challenges for drug development.[17] Further refinement of

tools used to assess outcomes in adults with EoE, use of data- and patient-driven approaches to define the response and remission for these tools, and development of the core outcome set (COS) to be reported in all clinical trials and observational studies are important steps towards improving and standardizing outcome assessment in this condition. Although uptake of COS may take a few years, adapting COS will pave the way for improved quality of evidence synthesis and will facilitate RCT design. In adults with EoE, assessment of symptoms using electronic daily diaries, histologic findings using eosinophilic esophagitis histology scoring system (EoE HSS), and other state-of-the-art outcomes, such as esophageal distensibility, is mostly carried out in the context of industry-sponsored registration trials. [18,19,20] Whether these same outcomes should be recommended for use in observational studies as part of COS remains to be determined. A substantial proportion of EoE research on response to various therapies during the past two decades has been reported in observational studies and non-controlled trials. In this systematic review, we evaluated outcomes used in the observational studies of swallowed topical corticosteroids, diets, and dilation to inform outcome selection for the COS exercise in adults with EoE.

METHODS

Search strategy

A systematic literature search was conducted in MEDLINE (Ovid, inception to January 1st, 2021) and Embase for observational studies without language restriction. Citations and abstracts were screened for potentially eligible studies, and complete manuscripts were retrieved for full-text review. The search strategy is outlined in Supplementary File 1. Data from studies that met inclusion criteria were independently extracted by two investigators (ES, CS); discrepancies were resolved by consensus or in cases of discrepancy, review with a third author (AMS). The study was conducted in accordance with the PRISMA guidelines.

Study Selection

Included studies were prospective or retrospective case series, case-control, cohort, or quasi-experimental studies of EoE adult patients (>18 years of age) that underwent treatment with one of the following therapies: corticosteroid, diet or dilation. Although trials are not the focus of this overview, we nevertheless also considered randomized open-label trials for completeness. Placebo-controlled clinical trials of children and adults, studies that included children and adolescents, and studies evaluating the use of therapies other than a corticosteroid, diet or dilation were excluded as these were the focus of previous systematic reviews.[17,21]

Data extraction

The following covariates were extracted: 1) study-related variables (study design, type of intervention, publication year, country/region of origin, calendar period, single- or multi-centered, total participants, inclusion and exclusion criteria, number of treatment arms, duration of follow-up); 2) patient-related variables (demographic characteristics, presence of associated atopic conditions, age at diagnosis or enrollment, gender); and 3) outcome-related variables (description of quality of life, symptom-based, endoscopic, and histological outcomes; esophageal eosinophil count before and after treatment; definitions of response and remission if applicable; and use of measurement tools, scores, or validated instruments). Furthermore, we extracted information on whether blood markers were assessed or other

experimental techniques were performed. Given that the focus of this review was on outcomes assessed in different studies (as opposed to the meta-analysis of changes in various outcomes in response to therapies), we did not exclude any studies with overlapping patient population.

Data Synthesis and Analysis

Standard descriptive statistics were used to summarize study characteristics. A list of outcomes and definitions produced by a qualitative review were summarized into the following categories: histologic outcomes, baseline and end-of-treatment esophageal eosinophil counts, endoscopic outcomes, quality of life and symptom-based outcomes, biomarkers/results of immunological dissection.

This systematic review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

RESULTS

The flow diagram of the studies that were identified, screened, and included for purposes of this review is shown in **Supplementary Figure 1**. Of the 69 studies extracted for the purposes of this review, 58 studies were case series/cohorts, four were randomized open-label, and seven were case-control studies. A total of 35 studies examined the use of corticosteroids (swallowed topical fluticasone or budesonide or oral prednisolone), 17 studies examined the dietary therapy, and 17 studies examined the use of dilation in adults with EoE. The baseline study characteristics are shown in **Table 1**.

Outcome reporting in studies of corticosteroid therapy

Outcomes assessed in the studies of corticosteroid therapy are summarized in **Tables 2** and **5**. Esophageal eosinophil density is the most frequently reported outcome assessed in studies of corticosteroid therapies. On its own, it has been reported in 20 studies. In another 12 studies, other histologic parameters, including presence of eosinophil abscesses, basal zone hyperplasia, spongiosis, mast cells, basophils, subepithelial fibrosis, were assessed. Definitions of response/remission included < 15 eosinophils per hpf (n=10), < 7 or ≤ 7 eosinophils per hpf (n=2), and < 5 or ≤ 5 eosinophils per hpf (n=3).

At least four EoE-associated endoscopic features, including exudates, rings, edema, furrows, and strictures, were assessed in 23 studies of corticosteroids therapies. Of the 23 studies, seven studies (published in 2014 or later) reported endoscopic outcomes based on the EoE Endoscopic Reference Score (EREFS) developed by Hirano *et al*.[7] Of those, scoring algorithm/grading was reported in 5 studies.

EoE-specific symptoms were assessed in 31 studies. Dysphagia, either as absence/presence, frequency or severity, was the most commonly assessed EoE-associated symptom (assessed in 22 studies). In 14 studies, PRO tools were used. Other than the Mayo Dysphagia Questionnaire and Watson Dysphagia Scale, the remaining tools and the complementary scoring systems have not been previously validated.

Outcome reporting in studies of dietary therapy

Outcomes assessed in the studies of diet therapy are summarized in **Tables 3** and **5**. Esophageal density was assessed in all studies of dietary therapy, and additional histologic parameters (eosinophil abscesses, basal zone hyperplasia, spongiosis, mast cells) in six studies. Definitions of remission included < 15 eosinophils per hpf (n=8), ≤ 10 eosinophils per hpf (n=2), and < 5 or ≤ 5 eosinophils per hpf (n=4). In four studies, multiple remission definitions were used. At least four EoE-associated endoscopic features, including exudates, rings, edema, furrows, and strictures, were assessed in 11 studies, of which six used EREFS. Of the six studies using EREFS, the scoring algorithm was reported in 4 studies. Various characteristics of dysphagia (frequency, severity, duration) or else presence of dysphagia were assessed in 13 studies using primarily non-validated instruments; in eight studies, patients reported their symptom severity. General patient-reported quality of life was assessed using The Short Form-36 in three studies.

Outcome reporting in studies of dilation

Outcomes assessed in the studies of dilation are summarized in **Tables 4** and **6**. Esophageal eosinophil density at the time of dilation was assessed in 11 studies of dilation. Presence of at least four EoE-associated endoscopic features was assessed in 7/17 studies of dilation, and EREFS was assessed in 2/17 studies. Only three studies examined baseline dysphagia characteristics and the improvement in these characteristics following the dilation using non-validated patient-reported outcomes measures.

DISCUSSION

In this systematic review, we assessed outcomes used in observational studies in adults with EoE. We found that there was a considerable heterogeneity in outcome assessment in observational studies of adults with EoE, and our results are congruent with those obtained in systematic reviews of the outcomes used in pediatric and adult trials.[17,21]

We found that esophageal eosinophil count is the most reported outcome in studies evaluating the use of various EoE-specific treatments, but there was a lack of agreement on remission definitions and most remission definitions do not conform to the cutoff of ≤ 6 eosinophils per hpf recently proposed by United States Food and Drug Administration (US FDA).[22] The remission definitions reported in observational studies are mostly comparable with those used in trials of adults.17 For example, the histologic cut-off of < 5 eosinophils per hpf has been used in both trials and observational studies; however, a more stringent definition of ≤ 1 eosinophil per hpf has been used in trials only. All these definitions are empirically chosen and likely do not define clinically relevant populations, but there are emerging data to support certain response thresholds.[23,24,25] In addition, adapting any one of them will not eliminate variability stemming from the differences in the cross-sectional hpf areas of various microscope manufacturer and normalizing density to eosinophils per mm2 should still be encouraged.26 EoEHSS proposed by Collins *et al* assesses grade (severity) and stage (extent) of eight histologic features including esophageal eosinophil density.6 Although this scoring system has been used in a number of clinical trials in adults and have shown to be valid, there is limited evidence that assessment of EoEHSS /additional features histologic features of EoE outperforms simple esophageal eosinophil count in pediatric and adult populations; therefore, these data are urgently needed.[6,18,19,20,27,28,29] Although not assessed using EoEHSS, the presence of basal zone hyperplasia, frequently encountered in patients with EoE, was associated with presence of symptoms and endoscopic findings in the absence of esophageal eosinophilia and hence might be suggestive of ongoing disease activity despite the lack of eosinophilia.[29] There are methodological challenges of addressing multicollinearity arising from associations between various histologic alterations, and

elucidating the importance of assessing EoEHSS alterations other than esophageal eosinophil density and basal zone hyperplasia might further be hampered by the low prevalence of some of these findings in EoE patients and inability to consistently sample the lamina propria with mucosal biopsies. In summary, seeking community-wide consensus on the uniform esophageal eosinophilia remission definition and generating data supporting the assessment of additional histologic features other than esophageal eosinophil density are of particular priority for purposes of outcome reporting in observational studies and trials.

The EREFS grading and classification system by Hirano *et al* has been used in most recent clinical trials of anti-inflammatory therapies for purposes of regulatory approval, and its uptake for use in observational studies has been relatively swift.[7,18,19,20,24,30] Most studies report esophageal EoE-associated endoscopic findings in proximal and distal esophagus, which mirrors the histologic findings from these segments. However, we have recently shown that the score that takes into account the findings in both proximal and distal esophagus explained 95% of variation (coefficient of determination) in endoscopist global assessment when compared to 90% of that captured by the score simply taking into account the most severe grade of all the features in the esophagus overall.[31] Therefore, it appears that the gain in separately scoring endoscopic features in proximal and distal esophagus is relatively small. Further studies are needed to examine the extent to which different EREFS-based scores explain variation in biologic disease severity assessed by means other than endoscopy. Unifying scoring recommendations may also aid in deriving EREFS-based remission and response definitions. Ideally, these outcome definitions should be derived from data-driven approaches rather than “expert opinion” alone. For example, anchor-based methods used for developing patient-reported outcome measure-based response definitions may be applied to establish meaningful within-patient change in EREFS based on expert endoscopists’ impression of change.[32] In summary, given that EREFS continues to undergo further refinement, it is likely that a certain degree of heterogeneity in endoscopic outcome assessment will persist at least in the near future. Nevertheless, EREFS in its current state will be recommended as part of COS for use in observational studies, and agreement on a unified

scoring algorithm of EoE-associated endoscopic findings will undoubtedly lead to less heterogeneity in the outcome assessment in adults with EoE. These efforts will in turn facilitate the derivations of EREFS-based remission and response definitions.

In most observational studies examined in this review, the symptoms were assessed using non-validated tools; in the few remaining studies, PRO instruments not specifically validated for adult EoE patients (such as the Mayo Dysphagia Questionnaire and Watson Dysphagia Scale) were used. For example, although dysphagia improvement following dilation has been reported in multiple studies, patient-reported improvement in dysphagia characteristics following dilation requires evaluation using newly developed validated measures over a defined time period.[33] Although one could argue that the uptake of the validated tools for use in observational studies has been slow, it is also worth noting that the first study on validation of a PRO instrument was only published in 2013, and this PRO was copyrighted for use in a single RCT for the purpose of regulatory approval.[5] Despite existing issues with current symptom-based PRO tools, as no tool currently covers the entire spectrum of language used by patients to describe dysphagia, the assessment of patient-reported symptom- and quality of life-based outcomes in the context of observational studies should be carried out using validated instruments. Whilst tools with daily recall (such as Dysphagia Symptom Questionnaire/Dysphagia Symptom Diary) are most frequently used in RCTs aimed at drug approval, the use of a tool with a longer recall period (such as symptom-based eosinophilic esophagitis activity index, EEsAI, 7-day recall period) may be better logistically suited for adult EoE patients enrolled into observational studies or for non-registration trials.[4,5,18] As electronic data capture platforms continue to improve and creating secure medical mobile apps become less expensive, we postulate that daily electronic diaries will eventually transition from the realm of RCTs to being widely available in observational studies. Deriving response and remission definitions for daily and weekly symptom-based PRO tools remains a priority. For example, EEsAI PRO-based remission definition (score of ≤ 20 points) has been derived based on defining histologic and endoscopic remission in an observational study and successfully used in trials.[34,30] No remission definitions currently exist for other PRO tools. Although the

US FDA has emphasized the use of anchor-based methods for deriving response definitions, these are yet to be published for any of the validated PRO instruments used in adults with EoE. Field-wide consensus on the use of the PRO tools in observational studies will undoubtedly reduce heterogeneity in outcome assessment in adults with EoE, and, hence, is urgently needed.

This review highlights several challenges that need to be overcome for standardization of outcome assessment. In this systematic review, we found many histologic remission definitions were used in observational studies of adults with EoE. The uptake of the EREFS has been the quickest, whilst uptake of the validated symptom-based PRO measures and EoEHSS has been slower to come. Although we evaluated the use of other more advanced molecular and genetic endpoints, these remain largely experimental. Measuring intraluminal distensibility using the Endoluminal Functional Lumen Imaging Probe shows a great promise although adoption in routine clinical practice remains limited. While the present study has strengths such as rigorous methodology and a comprehensive literature search, there are some limitations. These include the possibility that some pertinent studies may have been missed, as well as a lack of formal meta-analysis. We believe the search strategy minimized the chanced of missed data, and we do not feel that the data extracted were appropriate for pooled analysis techniques given the heterogeneity of the studies included and data assessed.

Given that many instruments for EoE outcome assessment in adults with EoE have been developed relatively recently, further refinement tools and use of data- and patient-driven approaches to define the response and remission thresholds are merited for improving outcome assessment in this condition. Further studies for informing the choice of outcomes assessed in various observational studies and clinical trials of adults with EoE are urgently needed. Although outcomes based on many of the state-of-the-art instruments are being used in trials designed to obtain regulatory approval for anti-inflammatory therapies for EoE, adapting these outcomes for purposes of observational studies may not always be feasible. For example, whilst the use of blinded central reading to reduce observation bias for endoscopy and histology in trials is being examined, this strategy is unlikely to be implemented

in most observational studies. Despite these many challenges, standardization of outcome reporting is needed to facilitate validity of evidence synthesis and comparisons of interventions in meta-analyses in therapeutic trials in adults with EoE. This emphasizes the need for a community-wide exercise to seek agreement on COS to be reported in all observational studies and trials in adult EoE patients.

329 **Table 1.** Characteristics of included studies describing outcome of treatment in adult patients
330 with eosinophilic esophagitis.
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Characteristic	Studies (n=69)	Proportion of studies (%)
Publication period		
2003 - 2006	6	9
2007 - 2010	8	12
2011 - 2014	23	33
2015 - 2018	28	40
2019 - 2020	4	6
Number of centers		
Single-center	56	81
Multicenter	13	19
Type of study		
Cohort/Case series	58	84
Randomized open-label	4	6
Case-control	7	10
Study design		
Retrospective	44	64
Prospective	25	36
Study size		
≤ 30 patients	36 (6)[a]	52
31 – 60 patients	18 (4)[a]	26
61 – 100 patients	9 (1)[a]	13
> 100 patients	6	9
Study region		
Asia	2	3
Australia	4	6
Europe	21	30
North America	41	59
Mixed	1	2

332 [a] Number of studies, into which higher than indicated overall patient number was enrolled;
333 however, these studies were categorized into a given category based on number of patients
334 that underwent intervention of interest.

Table 2. Histologic, endoscopic, symptom-based, and quality of life outcomes as well as biomarkers used in adult EoE patients treated with corticosteroids (swallowed topical fluticasone or budesonide or oral prednisolone).

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
1	Arora 2003[35] Case series Retrospective (n = 21) Incl: ≥ 20 eos/hpf	Fluticasone, 0.22mg puffs 2x/d for 6 weeks Exact FU time	Eos, BZH	≥ 20	NR	NR	Dysphagia frequency and foods causing dysphagia (questionnaire not further described), duration of relief (subjective), and food impactions (symptoms assessed 6 months after fluticasone therapy by telephone interview) PRO: no	NA
2	Lucendo 2005[36] Case series Retrospective (n = 9) Incl: >24eos/hpf	Fluticasone 0.5mg 2x/d (5/6 patients) for 12 weeks and Methylprednisolone (1/6 patient, 0.5mg/kg/d, weaned over 24 weeks) Exact FU time	Eos, BZH, papillary elongation	>24	Normal (not otherwise defined)	R, S (A/P)	Subjective symptom improvement PRO: no	IgE
3	Kumar 2005[37] Case series Retrospective (n = 8) Incl: >20 eos/hpf	Fluticasone n= 5/8) Median FU: 7 months (range 2-20)	Eos Remission not defined	25 - ≥ 80		F, R	Dysphagia, food impaction No score used PRO: no	Peripheral eosinophilia, serum IgE levels

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
4	Remedios 2006[38] Cohort Prospective (n = 19/26 treated with steroids) Incl: ≥ 15 eos/hpf	Fluticasone, 0.25mg 4x/d (2x2), 4 weeks Exact FU time	Eos	25 in proximal, 39.4 in distal esophagus	4.5 in proximal, 3.8 in distal esophagus	WE, R, F, S, EE, narrowing (A/P)	Based on DeMeester scores[39,40] for heartburn, regurgitation, and dysphagia; chest pain, vomiting, abdominal pain and history of impaction. Symptom score for dysphagia, chest pain, heartburn, regurgitation, vomiting, and abdominal pain (each scored 0 to 3, total of 18). (For dysphagia specifically, score of 0=none; score of 1=occasional transient sensation of food sticking, score of 2=episode of dysphagia requiring liquids to clear, score of 3= progressive dysphagia for solids requiring medical attention, need for dilation and bolus obstruction requiring hospital admission). BL: 5.42 and EOT: 0.68 ($p<0.001$) PRO: no	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
5	Lucendo 2007[41] Case series Prospective (n = 30) Incl: >24eos/hpf	Fluticasone, 0.5mg 2x/d for 12 weeks Exact FU time	Eos, BZH, papillary elongation, spongiosis, erosions, ulcerations, anti-MBP staining	>24	0	WE, R, E, F, S, narrowing (A/P)	Dysphagia, food impaction, epigastric oppression, heartburn, retrosternal pain, non-specific dyspeptic-type manifestations (A/P) Improvement in number of choking episodes, volume of liquid needed to drink with meals, time needed to eat lunch or dinner (minutes), capacity to swallow foods of different consistencies (each scored from 1 to 5 for a total of 25) PRO: yes	NA
6	Helou 2008[42] Case series Retrospective (n = 32/51 treated replied) Incl: >20eos/hpf	Fluticasone 0.22mg 4puffs/d for 6 weeks Mean FU: 3.3 years	NR	>20	NR	No EGD performed	Dysphagia (difficulty swallowing) frequency, food causing dysphagia, symptom recurrence, and food impactions (food sticking) Part of the questionnaire comes from Mayo Dysphagia Questionnaire (MDQ)[43] Score NR PRO: yes	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
7	Enns 2010[44] Cohort Retrospective (n = 54) Incl: > 20 eos/hpf	Fluticasone 0.25mg 4puffs/d (2x2) for 6 weeks Exact FU time	Eos	>20	NR	NR	Subjective symptom improvement (A/P) PRO: no	NA
8	Peterson 2010[45] Randomized open-label prospective (n = 15/30 treated with steroids) Incl: ≥ 15 eos/hpf	Fluticasone 0.44mg 2x/d for 8 weeks Exact FU	Eos Remission defined as partial if ≤ 15 eos/hpf and complete if ≤ 5 eos/hpf reached	92	48	WE, R, F (A/P)	Dysphagia frequency scale[46], reflux disease scale (heartburn, regurgitation, dyspepsia)[47] Improvement in dysphagia (8-point) scale (scoring from 0 to 7; score of 0=no dysphagia; 1=solid food dysphagia once in 3–12 months; 2=solid food dysphagia once in 1–3 months; 3=solid food dysphagia once every 2–4 weeks; 4=solid food dysphagia once every 1–2 weeks;5=solid food dysphagia once every 1–7 days; 6=solid food dysphagia with every meal; 7=dysphagia to solid and liquid food) BL: 3.7 and EOT: 1.7 PRO: yes	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
9	Bergquist 2011[48] Case series Prospective (n = 31) Incl: >20eos/hpf	Mometasone furoate 0.2mg 4x/d for 8 weeks Exact FU time	Eos	≥ 20	NR	NR	Dysphagia frequency, quality of life Watson Dysphagia Score[49] ranging from 0 to 45 (the presence of dysphagia for each liquid/solid substance scored on a 3-point Likert scale - 1=always, 0.5=sometimes, and 0=never) BL: 21.2 and EOT: 8.9 Treatment of Cancer Quality of Life Questionnaire-Oesophageal Module 18 (EORTC-QLQOES18)[50], scored from 0 to 100, where a high score represents a high level of symptoms/problems. Consists of 4 scales: the dysphagia, eating, reflux, and local pain each scored on 4-point Likert scale (not at all, sometimes, most of the time, and always) QoL: The Short Form-36[51] PRO: yes	NA
10	Lucendo 2011[52] Case-control Prospective (n = 10) Incl: ≥ 15eos/hpf	Fluticasone 0.4mg/d for 12 months Exact FU time	Eos in EP and LP, LPF (Massen-Trichrome coloration)	EP upper: 58.8 EP lower: 71.8 LP upper: 14.4 LP lower: 13.7	EP upper: 0.7, EP lower: 1.6; LP upper: 0.4, LP lower: 2.7	WE, R, F, S, crêpe-paper, Schatzki rings (A/P)	Subjective symptom improvement, food impactions(A/P) PRO: no	PCR from esophageal biopsies for IL5, TGFbeta1, FGF-9, CCL18

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
11	Francis 2012[53] Cohort Prospective (n = 28/51 treated) Incl: ≥ 15eos/hpf	Budesonide 2mg/d (viscous solution) for 6 weeks Exact FU time	Eos Remission defined as eosinophils of <5 eos/hpf	46.7	NR, 57% in histologic remission	R, F, EE felinization (A/P), hiatal hernia	Dysphagia severity using MDQ 30-day version[39] Change in subjective patient-reported symptom improvement with the MDQ-30-day version[39] Score: NR PRO: yes	NA
12	Lee 2012[54] Case-control Prospective (n = 11) Incl: ≥ 15eos/hpf	Budesonide 3mg 2x/d for 1wk followed by 3mg/d for 5wks, or fluticasone 0.88mg 2x/d for 6 weeks Exact FU time	NR	Median 60 (range: 18-100)	NR	Esophageal diameter (assessed by barium esophagrams)	Dysphagia frequency and severity, food avoidance, foods causing dysphagia, impaction, heartburn, and acid regurgitation evaluated using MDQ 30-day version[39] and MDQ 2-week version questionnaires Score: NR PRO: yes	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
13	Leung 2012[55] Case series Prospective (n = 11, of which 10 adults) Incl: ≥ 15eos/hpf	Fluticasone 0.44mg 2x/d for 6 weeks Exact FU time	Eos Remission defined as ≤7 eos/hpf	Median: 36	Median: 23	NA	Based on DeMeester scores [38,39,40] for heartburn, regurgitation, and dysphagia; chest pain, vomiting, abdominal pain and history of impaction. Symptom score for dysphagia, chest pain, heartburn, regurgitation, vomiting, and abdominal pain (each scored 0 to 3, total of 18). (For dysphagia specifically, score of 0=none; score of 1=occasional transient sensation of food sticking, score of 2=episode of dysphagia requiring liquids to clear, score of 3= progressive dysphagia for solids requiring medical attention, need for dilation and bolus obstruction requiring hospital admission). BL: 3 and EOT: 1 (both median) PRO: yes	FeNO (exhaled nitric oxide in non-asthma EoE patients)

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
14	Moawad 2013[56] Randomized open-label Prospective (n = 21/42 treated with steroids) Incl: ≥ 15eos/hpf	Fluticasone 0.44mg 2x/d for 8 weeks Exact FU time	Eos, Remission defined as <7 eos/hpf	55.9	39.2	WE, R, F, S, crêpe-paper, Schatzki ring, EE (A/P)	Dysphagia frequency and severity, food avoidance, foods causing dysphagia, impaction MDQ 2-week version[39] For study group treated with steroids: BL: 17 and EOT: 12 (NS) PRO: yes	NA
15	Tomomatsu 2013[57] Case-control Retrospective (n = 3/10 treated with steroids) Incl: ≥ 15eos/hpf	Prednisolone 20mg/d FU time NR	Eos, EA	≥ 15	NR	WE, R, E, F, S, crêpe-paper (A/P)	Subjective symptom improvement (A/P) PRO: no	NA
16	Katzka 2014[58] Case-control Prospective (n = 10) Incl: ≥ 15eos/hpf	Fluticasone 0.88mg/2x for 8 weeks Exact FU time	Eos, spongiosis	37	NR	NR	NR	Esophageal biopsy staining for filaggrin, zonula occludens-1/-2/-3, and claudin-1

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
17	Schlag 2014[59] Case series Prospective (n = 15) Incl: ≥ 15eos/hpf	Fluticasone 0.5mg 2x/d for 12 weeks Exact FU time	Eos, mast cells (BL 13.9/hpf, EOT 5.1/hpf)	68.1	30.1	WE, R, F, S (A/P)	Severity of dysphagia, heartburn, retrosternal pain, regurgitation and globus sensation assessed using Visual Analog Scale (VAS) each ranging from 0 to 10, 0= free of symptom, 10= unbearable symptom, total of 50) BL: 34.5 and EOT: 19.9 ($p<0.001$) PRO: yes	Serum levels of eosinophil cationic protein and serum levels of mast cell tryptase
18	Kuchen 2014[60] Cohort Retrospective (n = 206) Incl: ≥ 15eos/hpf	Budesonide or fluticasone, no exact dosage reported Median FU time: 5 years	Eos, BZH, papillary elongation	NR	NR	EREFS	Occurrence of food bolus impactions necessitating endoscopic removal (A/P) PRO: no	NA
19	Iwakura 2015[61] Case-control Retrospective (n = 12/43 EoE patients) Incl: ≥ 15eos/hpf	Fluticasone 0.4mg 2x/d for 8 weeks Exact FU time	Eos, basophils (BL: 2.6/hpf, EOT 0.1/hpf)	46	0	WE, R, F, S, EE, Barrett's esophagus (A/P), hiatal hernia	Subjective improvement in dysphagia and occurrence of food impactions (A/P) PRO: no	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
20	Dellon 2015[62] Cohort Prospective (n = 61/148 treated) Incl: ≥ 15eos/hpf	Oral viscous budesonide 1mg 2x/d or fluticasone 0.88mg 2x/d for 8 weeks Exact FU time	Eos	146	54.5	WE, R, F, S, EE, narrowing, crêpe-paper, Schatzki ring, hiatal hernia (A/P)	NR	Serum levels of interleukin (IL)-4, IL-5, IL-6, IL-9, IL-13, TGF-α, TGF-β, TNF-α, eotaxin-1, -2, -3, thymic stromal lymphopoietin, major basic protein, eosinophil-derived neurotoxin

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
21	Van Rhijn 2015[63] Case series Prospective (n = 15) Incl: >15eos/hpf	Fluticasone 0.5mg 2x/d for 8 weeks Exact FU time	Eos, EA, mast cells, BZH, spongiosis Remission defined as <15 eos/hpf	70	<15 in 10/15 (67%)	EREFS BL: 4 and EOT: 3	Frequency and severity of dysphagia assessed using 6-point Likert scale, where 0 represents “no dysphagia” and 5 “daily/severe” dysphagia in analogy to reflux disease questionnaire[64] BL: 4 and EOT: 0 Reflux disease questionnaire[64] PRO: yes	Esophageal electrical tissue impedance in vivo during endoscopy, transepithelial electrical resistance and transepithelial molecule flux in Ussing chambers using esophageal biopsies. Gene expression (qPCR) of IL-5, IL-13, CCL26, periostin, thymic stromal lymphopoietin, filaggrin, desmoglein-1 in esophageal biopsies

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
22	Larsson 2015[65] Case series Prospective (n = 47/51 completed the questionnaire) Incl: >15eos/hpf	Mometasone furoate 0.2mg 4x/d for 8 weeks Median time between diagnosis and FU: 23 months	NA	NA	NA	NA	Dysphagia frequency, quality of life Watson Dysphagia Scale[49], EORTC-QLQOES18[50], and The Short Form-36[51] NR PRO: yes Assessment at month 2 (after 2 months treatment with mometasone) and at least 12 months after EoE diagnosis	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
23	Nennstiel 2016[66] Cohort Prospective (n = 20) Incl: ≥ 15eos/hpf	Budesonide 1mg 2x/d for 8 weeks Exact FU time	Eos	56.6	6.6	WE, R, E, F, S, crêpe-paper, short-segment and long-distance stenosis classified as either absent (0), mild (1), moderate (2) or severe (3) for a total score of 21; a global assessment of endoscopic appearance on a 10-cm VAS High resolution manometry: mean reduction in intra-bolus pressure under therapy, motility disorders observed before and after therapy	Frequency and severity of dysphagia Straumann Dysphagia Index (SDI)[67] score: BL: 4 and EOT: 0.7 ($p<0.001$) PRO: no	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
24	Albert 2016[68] Cohort Retrospective (n = 56/75 adults treated) Incl: ≥ 15eos/hpf	Budesonide 1mg 2x/d or fluticasone 0.44mg 2x/d for 8 weeks Exact FU time	Eos Remission defined as <15 eos/hpf	72	44% achieved histologic response	WE, R, E, F, S (A/P)	Subjective symptom improvement (A/P) PRO: no	NA
25	Dellon 2016[69] Cohort Prospective (n = 48/61 EoE cases with measured periostin levels) Incl: ≥ 15eos/hpf	Budesonide 1mg 2x/d or fluticasone 0.88mg 2x/d for 8 weeks Exact FU time	Eos	1st group (low periostin): 133.4 2nd group (high periostin): 172.7	1st group (low periostin): 23.8 2nd group (high periostin): 36.4	WE, R, E, F, S, crêpe-paper, narrowing (A/P)	NR	Serum IL-13, serum periostin (measured by ELISA)

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
26	Eluri 2017[70] Cohort Retrospective (n = 33/55 treated and with at least two subsequent endoscopies) Incl: ≥ 15eos/hpf	Budesonide (90% of patients) 0.5-1.0mg 2x/d or fluticasone (10% of patients) or 0.44-0.88mg 2x/d for 8 weeks Median FU time: 11.7 months	Eos Remission defined as <15 eos/hpf	Median: 47	FU1: Median 0 FU2: 63 in 20 patients who lost response, 1 eos in patients with ongoing response	WE, R, E, F, S crêpe-paper (A/P)	Dysphagia, impaction, heartburn, and abdominal pain (A/P) No score used PRO: no	NA
27	Vermeulen[71]a 2017 Cohort Retrospective (n = 71) Incl: ≥15 eos/hpf	Topical corticosteroids not specified Median FU time: 56 months (range: 3-252)	Eos Remission not defined	NR	NR	E, F, R, S, narrowing, crêpe-paper	Dysphagia, food impaction, chest pain, heartburn, regurgitation, dyspeptic symptoms No score used PRO: no	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
28	Reed 2017[72] Cohort Prospective (n = 51) Incl: ≥ 15eos/hpf	Budesonide 1mg 2x/d or fluticasone 0.88mg 2x/d for 8 weeks Exact FU time	Eos Remission defined as <15eos/hpf	Median: 93	Median: 2	WE, R, E, F, S, crêpe-paper (A/P)	Dysphagia severity in the past 30 days (A/P) 10-cm VAS (anchored at 0 with 'no trouble swallowing' and at 10 with 'unable to even swallow saliva'), 10-point Likert scale (anchored at 0 with 'not at all severe' and at 10 with 'very severe'), and MDQ 30days[39] VAS: BL: 3.6 and EOT: 1.4 ($p<0.001$) Likert scale: BL: 6 and EOT: 2 ($p<0.001$) MDQ: BL: 20 and EOT: 10 ($p<0.001$) (medians) PRO: yes	NA
29	Greuter 2017[73] Cohort Retrospective (n = 351) Incl: ≥ 15eos/hpf	Budesonide of fluticasone 1mg 2x/d (induction for 2-4 weeks), followed by 0.25mg 2x/d (maintenance) Median FU time: 6 years	Eos, Remission defined as <5eos/hpf, severity of lamina propria fibrosis	94.6	33 (9.4%) achieved deep remission.	EREFS	Bolus impaction (A/P) PRO: no	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
30	Kia 2018[74] Cohort Retrospective (n = 40) Incl: ≥15 eos/hpf	Fluticasone median dose 0.5 mg 2x/d FU time: min. of 4 weeks, no further specified	Eos Remission defined as <15 eos/hpf	56.7	13.3	EREFS (Edema 0-1, rings 0-3, exudates 0-2, furrows 0-2, for a total score of 8) Strictures were given a numerical score by estimating the luminal diameter using the diameter of the endoscope as a reference. BL: 3.9 and EOT: 3.2	Presence, frequency and duration of dysphagia and heartburn, chest pain EoEQ: EoE Questionnaire where five questions were asked, with each answer scored using a number ranging from 0 to 10 depending on the number of answer choices. Responses from each question were then added with a maximum possible score of 24 EoEQ: BL: 7.3 and EOT: 5.6 PRO: yes	NA
31	Greuter 2018[75] Cohort Retrospective (n = 229) Incl: ≥ 15eos/hpf	Budesonide or fluticasone 1mg 2x/d (induction for 2-4 weeks), followed by 0.25mg 2x/d (maintenance) Median FU time: 5 years	Eos Remission defined as <15 eos/hpf	Median: 25	Median: 5	EREFS Endoscopic remission defined as absence of endoscopic inflammation (WE, F, E), mild rings may be present	Proportion of patients reaching clinical remission, defined as absence of any EoE-attributed symptoms (dysphagia, retrosternal pain, heartburn) 10-point Likert scale of symptom severity PRO: no	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
32	Reed 2018a[76] Cohort Retrospective (n =48) Incl: ≥ 15eos/hpf	Budesonide 2.4mg 1x/d for 8-12 weeks, then reduction of dosage according to discretion of provider. Mean final compounded budesonide dosage of 2.2mg/d. Mean FU time: 17 months	Eos Remission defined as <15eos/hpf	Median: 58	Median: 15	WE,R,E,F,S	Dysphagia, heartburn, chest pain, vomiting, global improvement (A/P) No score used PRO: no	NA
33	Reed 2018b[24] Cohort Prospective (n = 62) Incl: ≥ 15eos/hpf	Budesonide 2.14 mg or Fluticasone 1.79mg for 8 weeks Exact FU time	Eos	123.7	34.6	WE, E, R, F, S, crêpe paper, narrowing (A/P, scored 0 to 5)	Dysphagia severity in the past 30 days by VAS (A/P). 10-cm VAS (anchored at 0 with 'no trouble swallowing' and at 10 with 'unable to even swallow saliva')[72] VAS: BL: 3.4 and EOT: 1.7 PRO: yes	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
34	Eluri 2019[77][a] Cohort Prospective (n = 83 of which 80 had concomitant PPI treatment) Incl: ≥15 eos/hpf	Budesonide mean dose of 2.107 mg 1x/d or fluticasone mean dose of 1.707 mg 1x/d for 8 weeks FU time: 8 weeks of more	Eos, BZH, degranulation, LP fibrosis, microabscesses, spongiosis	128.1	35.1	EREFS	Dyspepsia, heartburn SODA[78,79](severity of dyspepsia assessment): measures pain intensity, nonpain symptoms, and satisfaction with dyspepsia-related health. Scores range from 11 to 105, with higher scores indicating more severe symptoms. QoL: GERD-HRQL[80,81] (gastroesophageal reflux disease health-related quality of life). The heartburn-specific items were scored from 0 to 30, with '0' indicating no heartburn symptoms and '30' indicating the worst heartburn symptoms. Cases with histologic remission: GERD-HRQL: BL: 4.3 and EOT: 2.6 SODA: BL: 39.9 and EOT: 35.5 Cases without histologic remission: GERD-HRQL: BL: 5.2 and EOT: 3.1 SODA: BL: 41.7 and EOT: 45.1 PRO: yes	NA

#	Study authors, study type, number of patients, inclusion criterion	Treatment, time to outcome assessment, and follow-up time	Histologic outcomes	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality of life outcomes	Biomarkers/ Immunological dissection
35	Greuter 2020[82] Cohort Retrospective (n = 82) Incl: >15 eos/hpf	Budesonide (n = 22) or fluticasone (n = 60) <2.5mg/day Mean FU time: 2.2 years	Eos Remission defined as: <15 eos/hpf; Deep remission defined as: 0–1 eos/hpf; Relapse defined as: ≥15 eos/hpf	0	47.5	EREFS BL: 1 EOT: 3	Bolus impaction (A/P) Physician's global assessment (scoring NR) PRO: no	NA

Abbreviations: A/P, absence/presence; BL, baseline; BZH, basal zone hyperplasia; E, edema; EA, eosinophilic microabscesses; EE, erosive esophagitis; EORTC-QLQOES18, Treatment of Cancer Quality of Life Questionnaire-Oesophageal Module 18; Eos, eosinophils; EOT, end of treatment; EP, epithelium; F, furrows; FU, follow-up; hpf, high power field; LP, lamina propria; MDQ, Mayo Dysphagia Questionnaire; NA, not assessed; NR, not reported; NS, not significant; PRO, patient-reported outcome; R, rings; S, strictures; SDI, Straumann Dysphagia Index; VAS, visual analogue scale; WE, white exudates.

[a] Majority of patients utilized STC. As such, the study was categorized as that related to use of STC to prevent double extraction, even though some patients might have been treated with other therapies.

345 **Table 3.** Histologic, endoscopic, symptom-based, and quality of life outcomes as well as biomarkers used in adult EoE patients undergoing treatment
346 with dietary therapy.
347

#	Study authors, study type, number of patients, inclusion criteria	Type of diet (number of foods eliminated, empiric vs. targeted), and time to outcome assessment	Histologic endpoints	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality-of-life outcomes	Biomarkers/Immunological dissection
1	Hsu Blatman 2011[83] Case-control Prospective (n = 21) Step-down Incl: >15 eos/hpf	Empiric 8 foods 6 weeks (without re-introduction)	Eos Remission defined as <15 eos/hpf (and resolution of reported symptoms)	NR	NR	NR	NR	Mast cell–associated gene expression in esophageal biopsies: the b chain of the high-affinity IgE receptor, the histamine-synthesizing enzyme histidine decarboxylase, and 2 mast cell–specific proteases: tryptase a/b1 and carboxypeptidase

#	Study authors, study type, number of patients, inclusion criteria	Type of diet (number of foods eliminated, empiric vs. targeted), and time to outcome assessment	Histologic endpoints	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality-of-life outcomes	Biomarkers/Immunological dissection
2	Gonsalves 2012[84] Cohort Prospective (n=50) Incl: ≥ 15 eos/hpf	Empiric 6 foods 6 weeks (without re-introduction) Step-down	Eos, ki-67 Remission defined as complete ≤ 5 eos/hpf; near complete ≤ 10 eos/hpf; partial - > 50% reduction in peak eosinophil count	34 in proximal 48 in distal esophagus	8 in proximal 13 in distal esophagus	NR	Frequency, intensity and duration of dysphagia episodes, lifestyle modifications related to dysphagia evaluated using non-validated instrument; range 2- 18, higher scores reflect greater dysphagia intensity[85] Score: BL: median 12 and EOT: median 3.5 QoL: The Short Form-36[51] PRO: yes	NA
3	Lucendo 2013[86] Cohort Prospective (n = 67) Incl: ≥ 15 eos/hpf	Empiric 6 foods 6 weeks Step-down	Eos Remission defined as complete: peak count 0-5 eos/hpf, partial: 6-14 eos/hpf, failure: ≥ 15 eos/hpf	Responders: 47.9 Non-responders: 52.5	Responders: 3.5 Non-responders: 64.4	NR	Frequency and severity of the dysphagia, heartburn and regurgitation as assessed by instrument for achalasia by Zaninotto et al.[87] Score in responders: BL approx. 7.5 and EOT approx. 0 (estimated from a graph) PRO: no	NA

#	Study authors, study type, number of patients, inclusion criteria	Type of diet (number of foods eliminated, empiric vs. targeted), and time to outcome assessment	Histologic endpoints	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality-of-life outcomes	Biomarkers/Immunological dissection
4	Rodríguez-Sánchez 2013[88] Case series Prospective (n = 30) Incl: ≥ 15 eos/hpf	Empiric (6 foods) and targeted 6 weeks Step-down	Eos	39.6	1.9	WE, R, E, F, S (A/P)	Severity of dysphagia, chest pain when swallowing, globus sensation, regurgitation, heartburn, epigastric pain, impaction Visual Analogue Scale (ELSA-VAS EoE index, severity of each symptom scored 0 – 10 for a total score ranging from 0 to 70) Score: BL 28.10 and EOT: NR PRO: yes	total serum IgE, serum eosinophil cationic protein, peripheral blood eosinophilia
5	Peterson 2013[89] Cohort Prospective (n = 18) Incl: ≥ 15 eos/hpf	Elemental 4 weeks (or 2 weeks if response was complete)	Eos, mast cells, BZH Complete remission defined as ≤5 eos/hpf, nearly complete as 6-10 eos/hpf, partial as ≥ 10eos/hpf but final eos < half pretreatment eos count)	54	10	WE, R, F, S (A/P)	Dysphagia frequency and severity, food avoidance, heartburn, and acid regurgitation evaluated using Mayo Dysphagia Questionnaire (MDQ) 30-day version[43] Score NR PRO: yes	NA

#	Study authors, study type, number of patients, inclusion criteria	Type of diet (number of foods eliminated, empiric vs. targeted), and time to outcome assessment	Histologic endpoints	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality-of-life outcomes	Biomarkers/Immunological dissection
6	Molina-Infante 2014[90] Cohort Prospective (n = 52) Incl: >15 eos/hpf	Empiric 4 foods 6 weeks Step-down	Eos, distribution, degranulation, EA Remission defined as < 15 eos/hpf in both proximal and distal esophagus	56.6 in proximal and 55.1 in distal esophagus	23.7 in proximal and 24.0 in distal esophagus	WE,R,E,F,S, crêpe-paper, narrowing, felinization, (A/P)	Frequency, intensity and duration of dysphagia episodes, lifestyle modifications related to dysphagia evaluated using non-validated instrument; range 2- 18, higher scores reflect greater dysphagia intensity[86] Remission defined as a decrease of more than 50% of baseline score after therapy Food impaction, heartburn (A/P) BL: 9.12 and EOT: 4.3 PRO: yes	NA
7	Wolf 2014[91] Cohort Retrospective (n = 31) Incl: ≥ 15 eos/hpf	Empiric 6 foods or targeted 6 weeks Step-down	Eos Remission defined as complete < 15 eos/hpf and ≥ 50% reduction in peak eosinophil count	77	39	Endoscopic improvement (no signs specified)	Subjective symptom improvement (A/P) No score used PRO: no	NA

#	Study authors, study type, number of patients, inclusion criteria	Type of diet (number of foods eliminated, empiric vs. targeted), and time to outcome assessment	Histologic endpoints	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality-of-life outcomes	Biomarkers/Immunological dissection
8	Rodríguez-Sánchez 2014[92] Case series Prospective (n = 43) Incl: ≥ 15 eos/hpf	Empiric (six foods) and targeted 6 weeks Step down and then up	Eos Remission defined as complete <5 eos/hpf, partial 5-14 eos/hpf, and failure ≥ 15 eos/hpf	Targeted: 48.6 in proximal and 53.1 in distal esophagus 6-food: 34.3 proximal and 33.9 distal	Targeted: 1.21 in proximal and 2.8 in distal esophagus 6-food: 1 proximal and 2.3 distal	WE, R, E, F, S (A/P)	Severity of dysphagia, chest pain, globus sensation, regurgitation, heartburn, epigastric pain, impaction Visual Analogue Scale (ELSA-VAS EoE index, severity of each symptom scored 0 – 10 for a total score ranging from 0 to 70) Targeted: BL: 27.1 and EOT: 5.31 6-food: BL: 23.6 and EOT: 3.7 PRO: yes	NA

9	Arias 2015[93] Case-control Prospective (n = 10) Incl: ≥ 15 eos/hpf	Empiric 6 groups of foods 6 weeks Step-down	Eos, mast cells	56.8	3	NA	Frequency and severity of the dysphagia, heartburn and regurgitation as assessed by instrument for achalasia by Zaninotto et al.[88] Score in responders: BL approx. 6 and EOT approx. 0 (estimated from a graph) PRO: no	Esophageal biopsies: Gene expression by PCR of chemoattractants for eosinophils (CC chemokine ligands [CCL]11, CCL24, and CCL26), mast cells (stem cell factor), and their receptors (CC chemokine receptor [CCR]3 and stem cell factor receptor). Gene (PCR) and protein (immunofluorescence) expression of specific MC proteases (Carboxypeptidase A3, chimase, and tryptase β-2)
10	Van Rhijn 2015[94] Cohort Prospective (n = 15) Incl: ≥ 15 eos/hpf	Targeted Number of foods NR 6 weeks	Eos, EA, mast cells, BZH (absent/mild/moderate/severe), spongiosis (absent/mild/moderate/severe),	Median 50	Median 70	EREFS	Dysphagia assessed by non-specified score BL: 9.5 and EOT: 7 QoL: The Short Form-36[51] PRO: yes	Blood: eos, serum: total IgE

#	Study authors, study type, number of patients, inclusion criteria	Type of diet (number of foods eliminated, empiric vs. targeted), and time to outcome assessment	Histologic endpoints	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality-of-life outcomes	Biomarkers/Immunological dissection
			Remission: ≤10 eos/hpf					
11	Philpott 2016[95] Cohort Prospective (n = 56/82 treated) Incl: ≥ 15 eos/hpf	Empiric (6 foods) 3 – 9 months Step-down	Eos Remission: <15 eos/hpf	NR	NR	NR	NR	NA
12	Reed 2017[96] Cohort Retrospective (n = 52) Incl: ≥ 15 eos/hpf	Empiric 6-food, targeted, combination of empiric 6-food and targeted Median: 24.9 months Step-down	Eos Remission: <15 eos/hpf	60.3	44.8	EREFS BL: 4.1 and EOT: 2.7 (range 0-9)	Dysphagia, heartburn, chest pain, abdominal pain, patient-reported subjective improvement (A/P) No score used PRO: no	NA

#	Study authors, study type, number of patients, inclusion criteria	Type of diet (number of foods eliminated, empiric vs. targeted), and time to outcome assessment	Histologic endpoints	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality-of-life outcomes	Biomarkers/Immunological dissection
13	Warners 2017a[97] Cohort Prospective (n = 17) Incl: ≥ 15 eos/hpf	Elemental 4 weeks	Eos, mast cells, EA, spongiosis, BZH Remission defined as complete if ≤15 eos/hpf, partial if ≥ 15 eos/hpf but with a decrease of more than 50% of pre-diet peak eos count	40	9	EREFS including crêpe paper BL: 7 and EOT: 3	5-point Likert scale (0 represents no symptoms in the past week and 5 represents daily symptoms) for frequency of dysphagia, and 5-point Likert scale (the where 0 represents no complains and 5 represents severe complains) for severity of dysphagia. Total score ranged from 0 to 10. Analogous to SDI. BL: 6 and EOT: 0 Reflux disease questionnaire[64] QoL: The Short Form-36[51] PRO: yes	Blood: eos, serum: total IgE Esophageal biopsy gene expression (PCR) of interleukin-5 (IL-5), IL-13, CCL26, periostin, and thymic stromal lymphopoietin

#	Study authors, study type, number of patients, inclusion criteria	Type of diet (number of foods eliminated, empiric vs. targeted), and time to outcome assessment	Histologic endpoints	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality-of-life outcomes	Biomarkers/Immunological dissection
14	Eckmann 2017[98] Open-label Prospective (n = 8) Incl: ≥15 eos/hpf	Combination of empiric (6-foods or more) and targeted 7 or more foods 6 weeks Step-down	Eos Remission defined as <15 eos/hpf	Average 87 (range: 55-120)	Average: 4.2 (range 0-15)	EREFS BL: average 4.3 (range: 3-5) EOT: NR	Dysphagia frequency and severity, food avoidance, heartburn, and acid regurgitation evaluated using Mayo Dysphagia Questionnaire (MDQ) 30-day version[43] Clinical response was assessed using the MDQ-30. Partial response was defined as continued symptoms, but with a frequency < once per week. Symptom remission was defined as an answer of “no” to the question of “Have you had trouble swallowing unrelated to a sore throat or cold over the last 2 weeks?” QoL: NR PRO: yes	NR
15	Letner 2017[99] Cohort Retrospective (n = 39) Incl: >15 eos/hpf	Empiric 7 or more foods Number of weeks not specified	Eos	Median: mid: 27 distal: 32.5	NR	EREFS	NR	Serum IgE, blood eosinophil count

#	Study authors, study type, number of patients, inclusion criteria	Type of diet (number of foods eliminated, empiric vs. targeted), and time to outcome assessment	Histologic endpoints	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality-of-life outcomes	Biomarkers/Immunological dissection
16	Warners 2017b[100] Cohort Prospective (n = 17) Incl: ≥ 15 eos/hpf	Elemental 4 weeks	Eos, spongiosis, BZH	Median peak: 43	Median peak: 9	WE, R, E, F, S, crêpe-paper (A/P)	NR	Esophageal biopsy gene expression (PCR) of zonula occludens 1, desmoglein-1, claudin-1, filaggrin. In vitro analysis of mucosal integrity (Ussing chambers): transepithelial resistance, electrical tissue impedance spectroscopy, fluorescein and rhodamine flux Lactulose mannitol test

#	Study authors, study type, number of patients, inclusion criteria	Type of diet (number of foods eliminated, empiric vs. targeted), and time to outcome assessment	Histologic endpoints	BL mean peak eos/hpf	EOT mean peak eos/hpf	Endoscopic outcomes	Symptom-based and quality-of-life outcomes	Biomarkers/Immunological dissection
17	Philpott 2018[101] Cohort Retrospective (n = 7) Incl:>15 eos/hpf	Empiric 3-6 foods 13-28 weeks Step-down	Eos Remission defined as <15 eos/hpf	38.5	5.2	EREFS	Dysphagia, odynophagia, and food bolus impaction events graded as absent, mild, moderate or severe by treating physician, subjective symptom improvement (A/P) No score used PRO: no	NA

Abbreviations: A/P, absence/presence; BL, baseline; BZH, basal zone hyperplasia; E, edema; EA, eosinophilic microabscesses; EE, erosive esophagitis; EORTC-QLQOES18, Treatment of Cancer Quality of Life Questionnaire-Oesophageal Module 18; Eos, eosinophils; EOT, end of treatment; EP, epithelium; F, furrows; FU, follow-up; hpf, high power field; LP, lamina propria; MDQ, Mayo Dysphagia Questionnaire; NA, not assessed; NR, not reported; NS, not significant; PRO, patient-reported outcome; R, rings; S, strictures; SDI, Straumann Dysphagia Index; VAS, visual analogue scale; WE, white exudates.

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355 **Table 4.** Histologic, endoscopic and symptom-based endpoints for EoE patients that underwent dilation.
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#	Study authors, study type, number of patients, inclusion criteria	Number of dilations per patient (X), type of dilator and increase in esophageal diameter/dilation (mm), median time of FU	Esophageal eosinophilia (mean peak eos/hpf)	Endoscopic outcomes at BL Indication for dilation	Mean diameter in mm before dilation	Mean diameter in mm after dilation(s)	Complications reported	Symptom-based outcomes	Co-treatment
1	Croese 2003[102] Cohort Retrospective (n = 17/31) Incl: ≥ 30eos/hpf	Mean 3.4X Savary FU time: NR	BL: 101	R, F, S, EE, (A/P) Indication for dilation: bolus impaction (requiring endoscopic removal/previous, recent protracted obstruction)	NR	NR	Chest pain, mucosal tear	Dysphagia, chest pain, heartburn (A/P) Self-reported improvement by patients in 16/17 patients undergoing dilation Score NR PRO: no	NR
2	Kaplan 2003[103] Case series Retrospective (n = 8) Incl: >25 eos/hpf	1X Unknown dilation method FU time: 2 -- 10 years	NR	R, stiff, ulcer, rent Indication for dilation: NR	NR	NR	Mucosal tear, perforation, chest pain	Dysphagia, chest pain, nausea, vomiting, weight loss, diarrhea No score used PRO: no	PPI (n = 2) Prednisone (n = 3)

#	Study authors, study type, number of patients, inclusion criteria	Number of dilations per patient (X), type of dilator and increase in esophageal diameter/dilation (mm), median time of FU	Esophageal eosinophilia (mean peak eos/hpf)	Endoscopic outcomes at BL Indication for dilation	Mean diameter in mm before dilation	Mean diameter in mm after dilation(s)	Complications reported	Symptom-based outcomes	Co-treatment
3	Cohen 2007[104] Case series Retrospective (n = 8/36 dilated) Incl: ≥ 15eos/hpf	NR Savary, through the scope balloon (TTB) FU time: not applicable	NR	WE, R, F, S (A/P) Indication for dilation: stricture(s)	NR	NR	Mucosal tear, perforation (3 with pneumediastinum, 1 with Boerhaav)	NR	NR
4	Pasha 2007[105][a] Case series Retrospective (n = 18/42 dilated) Incl: >20 eos/hpf	2X (range 1-5) Maloney, balloon and bougie FU time: specified	Eos, BZH, microabscesses, fibrosis	F, R, S, narrowing Indication for dilation: NR	NR	15 - 20	Mucosal tear, perforation	Dysphagia, food impaction, regurgitation No score used PRO: no	NR

#	Study authors, study type, number of patients, inclusion criteria	Number of dilations per patient (X), type of dilator and increase in esophageal diameter/dilation (mm), median time of FU	Esophageal eosinophilia (mean peak eos/hpf)	Endoscopic outcomes at BL Indication for dilation	Mean diameter in mm before dilation	Mean diameter in mm after dilation(s)	Complications reported	Symptom-based outcomes	Co-treatment
5	Bohm 2010[106] Case series Prospective (n=9/16 dilated, 8/16 included in FU) Incl: ≥ 15eos/hpf	1X Savary, Maloney FU time: 22 months	BL: 120 in proximal and 165 in distal esophagus FU: 120 in proximal and 165 in distal esophagus	WE, R, F (A/P) Indication for dilation: severity of dysphagia and narrowing/stricture(s)	NR	17	Chest pain	Frequency of dysphagia assessed using non-validated scale, where 0=none, 1=monthly, 2=several times/month, 3=several times/week, 4=daily, and 5=every meal. BL: 2.1 and EOF: 0.3 PRO: yes Food impaction (A/P)	PPI (n=9) Fluticasone (n=1) Diet (n=1)
6	Schoepfer 2010[107] Cohort Retrospective (n = 207) Incl: ≥ 15eos/hpf	Swiss cohort: Mean 2.4X US cohort: Mean 2.1X Savary, TTB FU time: Swiss cohort: 18 months; US cohort: 21 months	Swiss cohort BL: 121 EOT: 104	S: grade 1 = low-grade stricture, diameter 11–13 mm, passage of the standard endoscope with elevated pressure; grade 2 = intermediate-grade stricture, diameter between 7 and 10 mm, passage of 6 mm endoscope possible, but impossible with a	Swiss Cohort: 11 mm US cohort: 10 mm	Swiss Cohort: 16 mm US cohort: 17 mm	Chest pain	Dysphagia was evaluated using dysphagia score by Vakil et al[108] (0 = able to eat a normal diet, 1 = dysphagia with some solid foods but able to eat other solid foods, 2 = able to eat semisolids only, unable to eat solids; 3=able to swallow liquids only, 4 = complete inability to eat)	Topical corticosteroids, dietary therapy in US cohort only

#	Study authors, study type, number of patients, inclusion criteria	Number of dilations per patient (X), type of dilator and increase in esophageal diameter/dilation (mm), median time of FU	Esophageal eosinophilia (mean peak eos/hpf)	Endoscopic outcomes at BL Indication for dilation	Mean diameter in mm before dilation	Mean diameter in mm after dilation(s)	Complications reported	Symptom-based outcomes	Co-treatment
				standard gastroscope; grade 3 = high-grade stricture, passage of a 6 mm endoscope not possible Focal strictures (length ≤1cm) were differentiated from extensive strictures (length >1 cm) Indication for dilation: NR				In Swiss cohort BL: 1.7 and EOF: 0.9 In US cohort BL: 1.9 and EOF: 1 PRO: no Subjective improvement in dysphagia (no dysphagia, slight dysphagia, considerable dysphagia, no improvement) and duration PRO: yes	
7	Jung 2011[[109]] Case series Retrospective (n = 161) Incl: ≥ 15eos/hpf	Mean 1.8X Savary, TTB FU time: NR	40	WE, R, S, crêpe-paper, narrow caliber esophagus, Schatzki ring (A/P) Indication for dilation: dysphagia, food impaction, refractory to medical treatment, iron deficiency anemia	11.4	NA	Chest pain, deep mucosal tear, hemorrhage, perforation	NR	NR

#	Study authors, study type, number of patients, inclusion criteria	Number of dilations per patient (X), type of dilator and increase in esophageal diameter/dilation (mm), median time of FU	Esophageal eosinophilia (mean peak eos/hpf)	Endoscopic outcomes at BL Indication for dilation	Mean diameter in mm before dilation	Mean diameter in mm after dilation(s)	Complications reported	Symptom-based outcomes	Co-treatment
8	Madanick 2011[110] Case series Retrospective (n = 13) Incl: ≥ 15eos/hpf	1X TTB FU time: 5.2 months	NA	WE, R, F, S, narrowing (A/P) Indication for dilation: stricture(s)	NR	NR (+1.4 mm compared to the initial diameter)	Mucosal tear	Subjective symptom improvement PRO: no	PPI (n=6) Budesonide (n=2) Fluticasone (n=4) Montelukast (n=1) Diet (n=1)
9	Ally 2013[111] Case series Retrospective (n = 54/196 dilated, in total 66 dilations) Incl: ≥ 15eos/hpf	1 – 4X Savary, Maloney, TTB FU time: NR	NA	WE, R, F, S, EE, Schatzki rings (A/P) Indication for dilation: persisting symptoms despite medical therapy	NR	≥ 15	Chest pain, mucosal tear	NR	PPI and/or tropical fluticasone
10	Lipka 2014[112] Cohort Retrospective (n = 13) Incl: >15eos/hpf	Mean 12.1X Savary, Maloney, TTB FU time: 13.6 years	NR	WE, R, F, S, narrowing, Barrett's esophagus (A/P) Hiatal hernia Indication for dilation: recurrence symptoms	10.9	16-17	Chest pain, hospitalization, deep mucosal tear	Dysphagia, food impaction, (A/P) Subjective improvement in dysphagia PRO: no	PPI and/or H2 receptor antagonist

#	Study authors, study type, number of patients, inclusion criteria	Number of dilations per patient (X), type of dilator and increase in esophageal diameter/dilation (mm), median time of FU	Esophageal eosinophilia (mean peak eos/hpf)	Endoscopic outcomes at BL Indication for dilation	Mean diameter in mm before dilation	Mean diameter in mm after dilation(s)	Complications reported	Symptom-based outcomes	Co-treatment
11	Ukleja 2014[113] Case series Retrospective (n = 22/61) Incl: ≥ 15eos/hpf	Mean 1.3X Savary, TTB FU time: 5 years	53	WE, R, E, F, S, EE, Schatzki rings, narrowing (A/P) Indication for dilation: NR	NR	18.4	Chest pain, small and deep mucosal tear	Dysphagia, food impaction No score used PRO: no	Topical fluticasone, ciclesonide, budesonide

#	Study authors, study type, number of patients, inclusion criteria	Number of dilations per patient (X), type of dilator and increase in esophageal diameter/dilation (mm), median time of FU	Esophageal eosinophilia (mean peak eos/hpf)	Endoscopic outcomes at BL Indication for dilation	Mean diameter in mm before dilation	Mean diameter in mm after dilation(s)	Complications reported	Symptom-based outcomes	Co-treatment
12	Kavitt 2016[114] Randomized single-blind trial Prospective (n = 17) Incl: ≥15 eos/hpf	1X Maloney FU time: 2 months	Median 30 eos/hpf in proximal and 30 eos/hpf in distal esophagus at BL Remission not defined	Rings (0–3), exudates (0–2), furrows (0–2), edema (0–2), stricture (A/P) and F (A/P), narrow calibre (A/P), crêpe paper(A/P) Indication for dilation: NR Score at BL: 7.5 for proximal and 7.5 for distal esophagus	NR	NR	Chest pain	Dysphagia scores were classified on a 0–9 ordinal scale, with frequency of dysphagia assessed on a scale of 0–5 (0=never, 1=less than 1day/week, 2=1day/week, 3 = 2–3 days/week, 4 = 4–6 days/week, 5 = every day) and severity of dysphagia assessed on a scale of 0–4 (0 = able to eat normal diet/no dysphagia, 1 = able to swallow some solid foods, 2 = able to swallow only semi-solid foods, 3 = able to swallow liquids only, 4 = unable to swallow anything/total dysphagia). BL: 6.0 and EOT: 1.6 PRO: yes	Fluticasone 0.44 mg 2x/d and dexlansoprazole 60 mg 1x/d post-endoscopy for 60 days

#	Study authors, study type, number of patients, inclusion criteria	Number of dilations per patient (X), type of dilator and increase in esophageal diameter/dilation (mm), median time of FU	Esophageal eosinophilia (mean peak eos/hpf)	Endoscopic outcomes at BL Indication for dilation	Mean diameter in mm before dilation	Mean diameter in mm after dilation(s)	Complications reported	Symptom-based outcomes	Co-treatment
13	Runge 2016[115] Cohort Retrospective (n = 164) Incl: ≥ 15eos/hpf	Mean 3X Savary, TTB FU time: 15 months	82	WE, R, E, F, S, EE, narrowing, crêpe-paper (A/P) Indication for dilation: dysphagia, food impaction narrowing/ring(s)	12.5	15.2	Chest pain, emergency room visit, hospitalization (aspiration pneumonia)	Symptom improvement based on patient global report (A/P) No score used PRO: no	Topical corticosteroids, dietary elimination therapy, PPI
14	Runge 2017[116] Cohort Retrospective (n = 55) Incl: ≥ 15eos/hpf	Mean 3X Savary, TTB FU time: 15 months	BL: 83 EOT with steroids: 35	WE, R, E, F, S, narrowing, crêpe-paper (A/P) Indication for dilation: dysphagia, in presence of narrowing/strict, ring(s)	11.2	16.2	NR	NR	Topical budesonide, fluticasone

#	Study authors, study type, number of patients, inclusion criteria	Number of dilations per patient (X), type of dilator and increase in esophageal diameter/dilation (mm), median time of FU	Esophageal eosinophilia (mean peak eos/hpf)	Endoscopic outcomes at BL Indication for dilation	Mean diameter in mm before dilation	Mean diameter in mm after dilation(s)	Complications reported	Symptom-based outcomes	Co-treatment
15	Lipka 2018 [117] Cohort Retrospective (n=30, 8/30 with prior complications, 22/30 without) Incl: ≥ 15eos/hpf	8/30: 4X 22/30: 2.32X Maloney, TTS, Savory FU time: 8/30: mean 7.63 months 22/30: mean 4.59 months	NR	S (A/P)	n=8/30: 9.1 22/30: 11.73	n=8/30: 15.8 22/30: 16.1	Chest pain	Symptoms of esophageal dysfunction (not specified) No score used PRO: no	High dose bid PPI
16	Schupack 2020[118] Cohort Retrospective (n = 77) Incl: ≥15 eos/hpf	1 - 2X Savary, TTB Median FU time: 150 weeks	BL: 50.2 EOT with drug-based therapies: 51 patients (<15 eos/hpf) Remission: <15 eos/hp	Indication for dilation: symptomatic dysphagia with clear structural abnormality (stricture, Schatzki's ring, diffuse narrowing), dysphagia alone, and structural abnormality without current reported dysphagia	NR	18.5	NR	Dysphagia, heartburn, regurgitation, food impaction No score used PRO: no	Topical budesonide, fluticasone, PPI, diet

#	Study authors, study type, number of patients, inclusion criteria	Number of dilations per patient (X), type of dilator and increase in esophageal diameter/dilation (mm), median time of FU	Esophageal eosinophilia (mean peak eos/hpf)	Endoscopic outcomes at BL Indication for dilation	Mean diameter in mm before dilation	Mean diameter in mm after dilation(s)	Complications reported	Symptom-based outcomes	Co-treatment
17	Kim 2020[119] Cohort Retrospective (n=66) Incl: ≥15 eos/hpf	Mean 4.33 Savary, TTB	BL: 54.1 EOT with drug-based therapies: 47 patients (<15 eos/hpf), 43 patients (<5 eos/hpf) Remission: <15 eos/hpf	Rings (0–3), exudates (0–2), furrows (0–2), edema (0–2), stricture (A/P) and F (A/P), narrow calibre (A/P)	7.95	15.05	Chest pain, hospitalization	NR	Topical corticosteroids, fluticasone, PPI, diet, montelukast, prednisone, ranitidine, famotidine, azathioprine, and others

Abbreviations: NR, not reported; NA, not assessed; FU, follow-up; hpf, high power field; Eos, eosinophilia; F, furrows; WE, white exudates; E, edema; R, rings; S, strictures; EE, erosive esophagitis; BL, baseline; EOT, end of treatment; A/P, absence/presence; PPI, proton-pump inhibitors; PRO, patient-reported outcome; TTB, through-the-scope balloon.

[a] Majority of patients were managed with dilation. As such, the study was categorized as that describing dilation to prevent double extraction, even though some patients might have been treated with other therapies.

362 **Table 5.** Summary of EoE-related outcomes used in observational studies of swallowed topical corticosteroids and diet therapy.

		Histology		Endoscopy	Symptoms		Biomarkers/ Immunological Dissection
	Eos	**Remission**	**Other features**	**Features (A/P)/ EREFS**	**Concepts described**	**PRO (Y/N)**	
STC studies							
Arora 2003	•		BZH		Dysphagia (language not specified) frequency, FCD, impactions		
Lucendo 2005	•		BZH, papillary elongation	R,S	Subjective symptom improvement		•
Kumar 2005	•			F, R	Dysphagia (language not specified) and impaction		•
Remedios 2006	•			WE,R,F,S, narrowing	Dysphagia (food sticking, SDI (liquid to clear), need to consult physician, or undergo dilation, or impaction requiring hospital admission) based on deMeester symptom score, chest pain, impaction *(scored)		
Lucendo 2007	•		BZH, papillary elongation, spongiosis	WE,R,E,F,S, narrowing	Dysphagia (choking, number of episodes), impactions, FCD, SAI/SDI (times required to eat a meal and volume of liquid), chest pain *(scored)	•	
Helou 2008					Dysphagia (trouble swallowing) frequency, FCD, impactions, based on MDQ *(scored)	•	
Enns 2010	•				Subjective improvement		
Peterson 2010	•	complete ≤5 eos/hpf, partial ≤15 eos/hpf		WE,R,F	Dysphagia (solid food dysphagia) frequency based on dysphagia frequency scale *(scored)	•	
Bergquist 2011	•				Dysphagia (swallowing problem) frequency, FCD based on Watson Dysphagia Score Dysphagia (trouble eating, chocking when swallowing) severity, severity of pain when eating, severity of chest pain, based on EORTC QLQ-OES18 *(scored)	•	
Lucendo 2011	•		LPF	WE,R,F,S, crêpe-paper	Subjective symptom improvement, impactions		•

Francis 2012	●	<5 eos/hpf		R,F	Dysphagia (trouble swallowing) severity based on MDQ *(scored)	●	
Lee 2012					Dysphagia (frequency and severity of trouble swallowing), SAI (food avoidance), FCD, impaction (food sticking), based on MDQ *(scored)	●	
Leung 2012	●	≤7 eos/hpf			Dysphagia (food sticking), SDI (liquid to clear), need to consult physician, or undergo dilation, or impaction requiring hospital admission) based on deMeester symptom score, chest pain, impaction *(scored)	●	●
Moawad 2013	●	<7 eos/hpf		WE,R,F,S, crêpe-paper	Dysphagia (frequency and severity of trouble swallowing), SAI (food avoidance), FCD, impaction (food sticking), based on MDQ *(scored)	●	
Tomomatsu 2013	●		EA	WE,R,E,F,S, crêpe-paper	Subjective symptom improvement		
Katzka 2014	●		spongiosis				●
Schlag 2014	●		mast cells	WE,R,F,S	Severity of dysphagia (language not specified), retrosternal pain, and globus sensation assessed using 0-10 VAS	●	●
Kuchen 2014	●		BZH, papillary elongation	EREFS (scoring not specified)	Impaction requiring endoscopic removal		
Iwakura 2015	●		basophils	WE,R,F,S	Subjective improvement of dysphagia (language not specified), impaction		
Dellon 2015	●			WE,R,E,F,S, crêpe-paper, narrowing			●
Van Rhijn 2015	●	<15 eos/hpf	EA, BZH, spongiosis, mast cells	EREFS (scoring 0 to 8)	Frequency and severity of dysphagia (language not specified) assessed using 6-point Likert scale, where 0 represents “no dysphagia” and 5 “daily/severe” dysphagia in analogy to reflux disease questionnaire *(scored)	●	●
Larsson 2015					Dysphagia (swallowing problem) frequency, FCD based on Watson Dysphagia Score Dysphagia (trouble eating, chocking when swallowing) severity, severity of pain when eating, severity of chest pain, based on EORTC QLQ-OES18 *(scored)	●	
Nennstiel 2016	●			WE,R,E,F,S, crêpe-paper, narrowing (each	Frequency of dysphagia (trouble swallowing) and severity of dysphagia (delayed food passage, food sticking,		

				scored 0 to 3 for total of 21)	impaction requiring endoscopic removal) based on Straumann Dysphagia Index *(scored)		
Albert 2016	•	<15 eos/hpf		WE,R,E,F,S	Subjective improvement		
Dellon 2016	•			WE,R,E,F,S, crêpe-paper, narrowing			•
Eluri 2017	•	<15 eos/hpf		WE,R,E,F,S, crêpe-paper	Dysphagia (language not specified), impaction		
Vermeulen 2017	•			E, F, R, S, narrowing, crêpe-paper	Dysphagia (difficulty of swallowing solid or liquid foods passing the oesophagus into the stomach), impaction (sensation of food bolus obstruction in the oesophagus), chest pain (pain located central or retrosternal on the chest following on consuming food), regurgitation (reflux of swallowed foods in the oropharyngeal cavity), heartburn (retrosternal or epigastric burning sensation in the chest or upper abdomen)		
Reed 2017	•	<15 eos/hpf		WE,R,E,F,S, crêpe-paper	Dysphagia (difficulty swallowing) severity based on 10-cm VAS (0 with 'no trouble swallowing', 10 with 'unable to even swallow saliva'), 10-point Likert scale (0 with 'not at all severe', 10 with 'very severe'), and MDQ (frequency and severity of trouble swallowing, SAI (food avoidance), FCD, impactions (food sticking))	•	
Greuter 2017	•	<5 eos/hpf	LPF	EREFS (scoring 0 to 9)	Impaction		
Kia 2018	•	< 15 eos/hpf		EREFS (exudates 0-2, rings 0-3, edema 0-1, furrows 0-2, for a total score of 8)	Dysphagia (frequency and severity of trouble swallowing), SAI (food avoidance and modification), FCD, heartburn, chest pain	•	
Greuter 2018	•	<15 eos/hpf		EREFS (scoring 0 to 8) *remission as absence of WE,F,E (mild R allowed)	10-poing VAS of symptom severity (language not specified)		

Reed 2018a	•	<15 eos/hpf		WE,R,E,F,S	Dysphagia (language not specified), chest pain		
Reed 2018b	•			WE,R,E,F,S, crêpe-paper, narrowing	Dysphagia (difficulty swallowing) severity based on 10-cm VAS (anchored at 0 with 'no trouble swallowing' and at 10 with 'unable to even swallow saliva')	•	
Eluri 2019	•	< 15 eos/hpf	BZH, LPF degranulation, microabscesses	EREFS (scoring not specified)			
Greuter 2020	•	Remission defined as: <15 eos/hpf; Deep remission defined as: 0–1 eos/hpf; Relapse defined as: ≥15 eos/hpf		EREFS (scoring 0 to 8)	Physician global assessment		

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		Histology		Endoscopy	Symptoms		Biomarkers/ Immunological Dissection
	Eos	**Remission/Response**	**Other features**	**Features (A/P)/ EREFS**	**Concepts described**	**PRO (Y/N)**	
Diet studies							
Hsu Blatman 2011	•	<15 eos/hpf					•
Gonsalves 2012	•	complete ≤5 eos/hpf, near complete ≤10 eos/hpf, partial > 50% reduction in eos/hpf			Frequency, intensity and duration of dysphagia (attacks, retching, obstruction) episodes, lifestyle modifications related to dysphagia evaluated using Straumann instrument *(scored)	•	
Lucendo 2013	•	complete ≤5 eos/hpf, partial 6-14 eos/hpf, failure ≥ 15 eos/hpf			Frequency and severity of the dysphagia (language not specified) based on Zaninotto achalasia instrument *(scored)		
Rodriguez-Sanchez 2013	•			WE,R,E,F,S	Severity of dysphagia (difficulty swallowing), chest pain when swallowing, impaction based on VAS (0-10, ELSA-VAS EoE index) *(scored)	•	•
Peterson 2013	•	complete ≤5 eos/hpf, near complete 6-10 eos/hpf, partial ≥ 10 eos/hpf AND final eos < 50% of pre-diet eos/hpf	BZH, mast cells	WE,R,F,S	Dysphagia (difficulty swallowing) frequency and severity, FCD, SAI (food avoidance), impactions (food sticking) based on MDQ *(scored)	•	

Molina-Infante 2014	●	<15 eos/hpf in both proximal and distal esophagus	EA, distribution degranulation	WE,R,E,F,S, crêpe-paper, narrowing	Frequency, intensity and duration of dysphagia (attacks, retching, obstruction) episodes, lifestyle modifications related to dysphagia evaluated using Straumann instrument *(scored)	●	
Wolf 2014	●	<15 eos/hpf ≥ 50% reduction in eos/hpf from baseline		Improvement (signs not specified)	Subjective symptom improvement		
Rodriguez-Sanchez 2014	●	complete <5 eos/hpf, partial 5-14 eos/hpf, failure ≥15 eos/hpf		WE,R,E,F,S	Severity of dysphagia (difficulty swallowing), chest pain when swallowing, impaction based on VAS (0-10, ELSA-VAS EoE index) *(scored)	●	
Arias 2015	●		Mast cells		Frequency and severity of the dysphagia (language not specified) based on Zaninotto achalasia instrument *(scored)		●
Van Rhijn 2015	●	≤10 eos/hpf	EA, BZH, mast cells, spongiosis	EREFS (scoring to 8)	Dysphagia (language not specified)	●	●
Philpott 2016	●	<15 eos/hpf					
Reed 2017	●	<15 eos/hpf		EREFS (scoring 0 to 9)	Dysphagia (language not specified), chest pain		
Warners 2017a	●	complete ≤15 eos/hpf, partial ≥15 eos/hpf AND >50% reduction in pre-diet peak eos count	EA, BZH, mast cells, spongiosis	EREFS (scoring not specified)	Frequency and severity of dysphagia (trouble swallowing, both on 5-point Likert scale) analogous to SDI	●	●
Eckmann 2017	●	< 15 eos/hpf		EREFS (scoring 0 to 9)	Dysphagia (frequency and severity of trouble swallowing), SAI (food avoidance), FCD, impaction (food sticking), based on MDQ *(scored)	●	
Letner 2017	●			EREFS (scoring not specified)			●
Warners 2017b	●		BZH, spongiosis mast cells	WE,R,E,F,S, crêpe-paper			●
Philpott 2018	●	<15 eos/hpf		EREFS (exudates 0-2, rings 0-3, edema 0-1, furrows 0-2, for a total score of 8)	Dysphagia (language not specified), odynophagia, and food bolus impaction events graded as absent, mild, moderate or severe by treating physician Subjective symptom improvement		

365 **Table 6.** Summary of EoE-related outcomes used in observational studies of dilation.

Dilation studies	Histology	Endoscopy	Symptoms	Complications
Croese 2003	•	R, F, S, EE	Dysphagia (language not specified), chest pain	•
Kaplan 2003		R, stiff, ulcer, rent	Dysphagia (language not specified), chest pain, nausea, vomiting, weight loss, diarrhea	•
Cohen 2007		WE, R, F, S		•
Pasha 2007	•	F, R, S, narrowing	Dysphagia (language not specified), impaction, regurgitation	•
Bohm 2010	•	WE, R, F	PRO: Dysphagia frequency (language not specified) assessed using non-validated scale (from 0=none, 1=monthly, 2=several times/month, 3=several times/week, 4=daily, and 5=every meal), food impaction	•
Schoepfer 2010	•	S: 1 = low-grade stricture; 2 = intermediate-grade stricture; 3 = high-grade stricture Focal strictures ≤1 cm and >1 cm	PRO: Dysphagia severity(language not specified) based on food consistencies (0 = able to eat a normal diet, 1 = dysphagia with some solid foods but able to eat other solid foods, 2 = able to eat semisolids only, unable to eat solids; 3=able to swallow liquids only, 4 = complete inability to eat) based on Vakil score Subjective dysphagia improvement and duration	•
Jung 2011	•	WE, R, S, crêpe-paper, Schatzki rings, narrowing		•
Madanick 2011		WE, R, F, S, narrowing	Subjective symptom improvement (language not specified)	•
Ally 2013		WE, R, F, S, EE, Schatzki rings		•

Lipka 2014		WE, R, F, S, narrowing, hiatal hernia, Barrett's esophagus	Subjective dysphagia improvement (language not specified), dysphagia, food impaction	•
Ukleja 2014	•	WE, R, E, F, S, EE, narrowing, Schatzki rings	Dysphagia (language not specified), food impaction	•
Kavitt 2016	•	EREFS (scoring 0 to 9), crêpe-paper, narrowing	PRO: Dysphagia (trouble swallowing) frequency and severity Dysphagia scores were classified on a 0–9 ordinal scale, with frequency of dysphagia assessed on a scale of 0–5 (0=never, 1=less than 1day/week, 2=1day/week, 3 = 2–3 days/week, 4 = 4–6 days/week, 5 = every day) and severity of dysphagia assessed on a scale of 0–4 (0 = able to eat normal diet/no dysphagia, 1 = able to swallow some solid foods, 2 = able to swallow only semi-solid foods, 3 = able to swallow liquids only, 4 = unable to swallow anything/total dysphagia).	•
Runge 2016	•	WE, R, E, F, S, crêpe-paper, EE, narrowing	Subjective symptom improvement	•
Runge 2017	•	WE, R, E, F, S, crêpe-paper, narrowing		•
Lipka 2018		S	Not specified	•
Schupack 2020	•	S, narrowing, Schatzki rings	Dysphagia (language not specified), heartburn, regurgitation, food impaction	
Kim 2020	•	EREFS (scoring 0 to 9), narrowing		•

366 **Abbreviations**: F, furrows; WE, white exudates; E, edema; R, rings; S, strictures; EE, erosive esophagitis; A/P, absence/presence; PRO, patient-
367 reported outcome.

Supplementary File 1. Search strategy

MEDLINE (OVID)

1 exp Esophagitis/
2 esophag*.tw.
3 oesophag*.tw.
4 1 or 2 or 3
5 exp Eosinophils/
6 exp Eosinophilia/
7 eosinophil*.tw.
8 5 or 6 or 7
9 4 and 8
10 Epidemiologic Studies/
11 exp Case-Control Studies/
12 exp Cohort Studies/
13 Cross-Sectional Studies/
14 (epidemiologic adj (study or studies)).tw.
15 case control.tw.
16 (cohort adj (study or studies)).tw.
17 cross sectional.tw.
18 cohort analy*.tw.
19 (follow up adj (study or studies)).tw.
20 longitudinal.tw.
21 retrospective*.tw.
22 prospective*.tw.
23 (observ$ adj3 (study or studies)).tw.
24 adverse effect?.tw.
25 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
26 ((identify$ or develop$ or design$ or test$ or assess$ or evaluat$ or robust$ or optim$ or effic$ or effect$ or sensitiv$ or simpl$ or specific$ or precis$) adj3 (search strat$ or search filter?)).tw.
27 25 and 26
28 exp animals/ not humans/
29 25 not 28

30	9 and 29
31	swallowed.tw.
32	exp Administration, Topical/
33	exp Steroids/
34	fluticasone.tw.
35	mometasone.tw.
36	exp Budesonide/
37	corticosteroid*.tw.
38	exp Glucocorticoids/
39	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40	30 and 39
41	exp Diet/
42	diet.tw.
43	dieta*.tw.
44	diete*.tw.
45	41 or 42 or 43 or 44
46	30 and 45
47	dilation*.tw.
48	dilatation*.tw.
49	47 or 48
50	30 and 49
51	40 or 46 or 50
52	exp "review"/
53	51 not 52

Supplementary Figure 1. The flow diagram.

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