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CLINICAL/NARRATIVE REVIEW

# Topical Steroid Therapy for the Treatment of Eosinophilic Esophagitis (EoE): A Systematic Review and Meta-Analysis

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**OBJECTIVES: Current guidelines recommend topical steroids as first-line treatment for patients with eosinophilic esophagitis (EoE). However, the evidence for this approach has been inconsistent in earlier reports. This meta-analysis aimed to clarify the efficacy of topical steroid treatment in active EoE using updated evidence.**

**METHODS: CENTRAL, MEDLINE and EMBASE databases were searched for randomized controlled trials (RCTs) published up to May 2014 that compared topical steroids with control treatments for active EoE. Study bias was assessed using the Cochrane Collaboration Tool, and outcomes were pooled using random effects models. The primary outcome was the mean change in eosinophil counts. Secondary outcomes were symptom responses and adverse events.**

**RESULTS: In total, seven RCTs (226 patients) were included. Topical steroids were associated with a significant reduction in esophageal mucosal eosinophil counts compared with control therapy although substantial heterogeneity between studies was observed (weighted mean difference (WMD) −27.2, 95% confidence interval (CI) −45.3 to −9.1, $I^2 = 56.2\%$). Subgroup analysis indicated the reduction in eosinophil counts was only present in studies where a proton pump inhibitor (PPI) trial was used to exclude other diagnoses (WMD −46.3, 95% CI −61.3 to −31.4, $I^2 = 0.0\%$). Subdivision of studies on the use of a PPI trial also accounted for the majority of heterogeneity among RCTs. No clear trends in symptom resolution were observed. Eleven out of 127 patients who received topical steroids developed asymptomatic esophageal candidiasis.**

**CONCLUSIONS: These data provide updated high-quality evidence that support current guidelines for first-line EoE treatment with topical steroids after an initial PPI trial to exclude non-EoE pathologies (PROSPERO ID: CRD42014008828).**

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## INTRODUCTION

Eosinophilic esophagitis (EoE) is characterized clinically by eosinophil-driven inflammation and esophageal dysfunction.[1–4] Although the etiology of EoE is not fully understood, it is considered to be an immune-mediated condition with strong links to atopy.[5,6] EoE carries a significant burden of disease, as it requires intensive monitoring and treatment to prevent and manage complications, such as dysphagia, food impaction, stricture formation, and nutritional deficiencies.[2,7–9] Despite being initially considered a rare condition, current evidence suggests a prevalence of ~57 per 100,000 persons with an annual health-care burden of up to $1.4 billion in the United States.[10]

EoE represents a major clinical challenge due to the lack of specific clinical signs. Esophageal mucosal eosinophilia is characteristic of EoE, but is also frequently observed in gastro-esophageal reflux disease (GERD) and proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE).[2] In addition, there are a number of less common conditions, such as eosinophilic gastritis and hypereosinophilic syndrome, which can present with esophageal eosinophilia that also require exclusion. Current American College of Gastroenterology (ACG) Consensus Guidelines recommend an 8-week trial with proton pump inhibitors (PPI) to exclude PPI-responsive GERD and PPI-REE and allow for formal diagnosis of EoE,[2] followed by topical steroids as first-line treatment.[2]

However, these current recommendations are based on limited evidence and inconsistent results, as most clinical trials assessing topical steroid treatment in EoE have been performed on a small number of patients using relatively diverse methodologies.[2,11–18] Although the EoE literature has been extensively reviewed,[3,18,19] a robust quantitative synthesis of the data has not been performed to date. Meta-analysis aims to summarize available data and provide conclusions that are stronger than the evidence from individual trials. Therefore, we aimed to provide an updated systematic review

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and meta-analysis to assess the evidence base for the use of topical steroids and PPI in the current management guidelines for EoE. We focused solely on high-quality evidence in the literature (i.e., randomized controlled trials (RCTs)).

## METHODS

**Registration.** This meta-analysis was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/). PROSPERO ID: CRD42014008828.

**Inclusion and exclusion criteria.** The eligibility criteria for the study were defined a priori and included RCTs that compared topical steroid therapy with control therapies as induction treatment for active EoE in both adult and pediatric populations. Studies with any of the following characteristics were excluded: non-RCTs, RCTs comparing topical steroid therapy with oral steroid therapy, or RCTs not assessing the treatment of active EoE (Figure 1).

**Search strategy for identification of studies.** A comprehensive literature search with no language restrictions was conducted to identify all published and unpublished RCTs. The electronic reference databases searched included MEDLINE (January 1966 to May 2014), Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE (1980 to May 2014). The Cochrane Highly Sensitive Search Strategy for identifying randomized trials on MEDLINE was used.[20] Sensitivity Maximizing Version, Ovid format, was combined with relevant MeSH terms and other search terms to identify RCTs on MEDLINE. The MeSH terms used in the search were "esophagitis", "eosinophils", and "eosinophilia", as well as all lower branches under these MeSH terms. The full search strategy is displayed in Appendix 1. This MEDLINE search strategy was adapted to the other databases searched. Search terms included "eosinophilic esophagitis", "swallowed", "randomized", "steroids", "fluticasone", "mometasone", and "budesonide". In addition, reference lists from the identified publications were analyzed to identify further relevant trials. A manual search of textbooks, reviews, and conference proceedings (abstracts presented at Digestive Disease Week and European Gastroenterology Week from 2013 to 2014) was also performed.

**Study selection and data abstraction.** Two reviewers (MC, MC) screened abstracts from the literature searches. Each study's eligibility for the meta-analysis and systematic review was assessed on the bais of defined inclusion and exclusion criteria, and any uncertainty was resolved through discussion. Selected full-text articles were further reviewed by the same two reviewers. There were no discrepancies between reviewers following full-text review. For each study, data on the methodology, inclusion and exclusion criteria, diagnostic criteria, interventions, outcomes, and risk of bias were collected. Authors were contacted for any missing data.

**Assessment of the risk of bias.** The same two reviewers (MC, MC) also independently critically appraised the methodology of each included study using the Cochrane

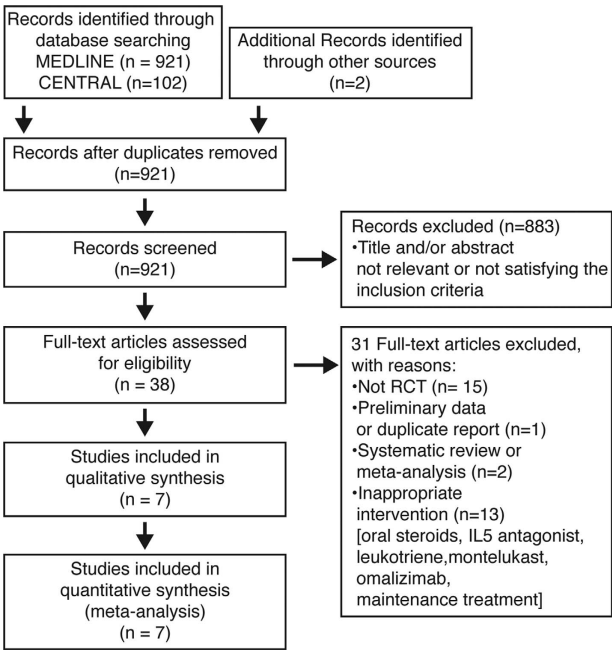


**Figure 1** Study selection process.

Collaboration tool for determining the risk of bias[20] assessing random sequence generation, allocation concealment, blinding, completeness of data, and selective reporting. Each item was assessed as having a low, high, or unclear risk of bias.

**Outcome and data analysis.** The primary outcome was the mean change in eosinophil count on biopsies following topical steroid vs control treatments. Our secondary outcomes were symptom resolution and adverse events from treatment. Results were reported as weighted mean differences (WMD), which compares the mean change in eosinophil counts following topical steroid treatment vs the mean change in eosinophil counts following control treatments ($\text{WMD} = (\text{post-treatment} - \text{pretreatment eosinophil counts})_{\text{topical steroid group}} - (\text{post-treatment} - \text{pretreatment eosinophil counts})_{\text{control group}}$). The pooled WMDs are "weighted" using the s.d. in the changes in eosinophil counts in the topical steroid and control groups using the DerSimonian and Laird method. A negative WMD indicates a greater reduction in eosinophil counts following topical steroid compared with control treatment, whereas a positive WMD indicates a greater reduction following control treatment. The s.d. of the mean difference was estimated from the pre- and post-treatment s.d. using the method outlined in the Cochrane Handbook.[20] For each meta-analysis, a random effects model was specified using the DerSimonian and Laird method with the estimate of heterogeneity being taken from the Mantel–Haenszel model. Heterogeneity of net change estimates was assessed using Cochrane's Q and the $I^2$ statistics where $I^2 = 100\% \times (Q - df)/Q$. Following the Cochrane Handbook, $I^2$ values were interpreted as showing moderate (30–60%), substantial (50–90%), and considerable (75–100%) heterogeneity.[20] Results of each meta-analysis were displayed graphically using Forest plots. The potential for "small study effects", including publication bias, was

examined by visual inspection of funnel plots, in which the s.e. was plotted against the net change for each study. All analyses were performed in Stata (version 12.1, StataCorp, TX, USA) using the metan, metabias, and metafunnel commands. A priori subgroup analyses were also conducted according to the exclusion of PPI responders, the type of control, and the type of topical steroid used.

## RESULTS

**Study selection.** The initial literature search yielded 921 articles (Figure 1). Studies were excluded for being meta-analyses or systematic reviews, for having a non-randomized design, for assessing other intervention strategies, and for reporting preliminary or duplicate data. In total, seven RCTs were included.[11–17]

**Study characteristics.** The key characteristics of the included RCTs are shown in Table 1. Two studies recruited pediatric patients (<18 years old),[13,14] three studies recruited adult patients (>18 years old),[11,15,16] and two recruited a mixed population.[12,17] The criteria used to define EoE among the included studies were highly variable with a range of eosinophil counts from 15 to 24 eosinophils per high-powered field, as well as different requirements for epithelial hyperplasia or clinical symptoms (Supplementary Table 2). Treatment regimes, including the type of topical steroid, dosage and length of treatment, also varied greatly between studies. All seven included studies had a low risk of selection bias (Supplementary Table 1). Two studies had a high risk of attrition bias.[11,13]

The seven trials contained a total of 260 patients. Eosinophil count data was available for 226 patients, 127 in the topical steroid treatment group and 99 in the control group. The number of participants in each study ranged between 30 and 42. All studies included predominantly male participants, with a male:female ratio of ~5:1.

### Primary outcome

*Reduction in esophageal eosinophil counts.* Eosinophil counts pre- and post-topical steroid and control treatments were obtained for all studies as a quantitative measure of eosinophil-driven esophageal inflammation.[11–17] The results from each study were pooled using the WMD. The WMD is calculated as the change in eosinophil counts following steroid treatment minus the change in eosinophil counts following control treatment. Compared with control treatment, topical steroid treatment was associated with a significantly greater reduction in eosinophil counts in the esophageal mucosa (WMD −27.2, 95% CI −45.3 to −9.1; Figure 2). "Moderate" to "substantial" heterogeneity was observed when pooling all studies ($I^2$ = 56.2%, Q = 13.69, *P*-heterogeneity = 0.03).

This result was robust when the meta-analysis was repeated by pooling post-treatment eosinophil counts from topical steroid vs control treatments using a standardized mean difference method. Although the trend was maintained, this result was no longer significant when the two studies with a high risk of attrition bias[11,13] were excluded (WMD −19.48, 95% CI −41.95 to 2.99).

**Table 1** Randomized controlled trial characteristics

| Study | EoE definition | Treatment strategy | Control | PPI trial | Length | Cohort size | Mean age (range) | Males (%) |
|---|---|---|---|---|---|---|---|---|
| Konikoff *et al.*[14] | >24 eos/hpf and epithelial hyperplasia | Swallowed aerosolized fluticasone (440 µg twice daily) | Placebo | No | 12 weeks | 36 | 9.6 (3–18) | 72 |
| Straumann *et al.*[17] | >20 eos/hpf and dysphagia | Swallowed nebulized budesonide (2 mg daily) | Placebo | Full | 15 days | 36 | 36 (16–79) | 86 |
| Dohil *et al.*[13] | >20 eos/hpf | Oral viscous budesonide daily (1 or 2 mg daily per weight) | Placebo | Partial | 12 weeks | 32 | 7.8 (3–17) | 83 |
| Peterson *et al.*[16] | >15 eos/hpf and dysphagia/food impaction/ chest pain | Swallowed aerosolized fluticasone (440 µg twice daily) | PPI[a] | No | 8 weeks | 30 | 37 (18–79) | 77 |
| Alexander *et al.*[11] | >20 eos/hpf and dysphagia | Swallowed aerosolized fluticasone (880 µg twice daily) | Placebo | Partial | 6 weeks | 42 | 37.5 (19–57) | 81 |
| Moawad *et al.*[15] | >15 eos/hpf and dysphagia/food impaction/ heartburn | Swallowed aerosolized fluticasone (440 µg twice daily) | PPI[a] | No | 8 weeks | 42 | 37.5 (2–17) | 90 |
| Butz *et al.*[12] | >24 eos/hpf | Swallowed aerosolized fluticasone (880 µg twice daily) | Placebo | Full | 12 weeks | 42 | 12.6 (3–30) | 83 |

EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; PPI, proton pump inhibitor.
[a]40 mg esomeprazole daily.

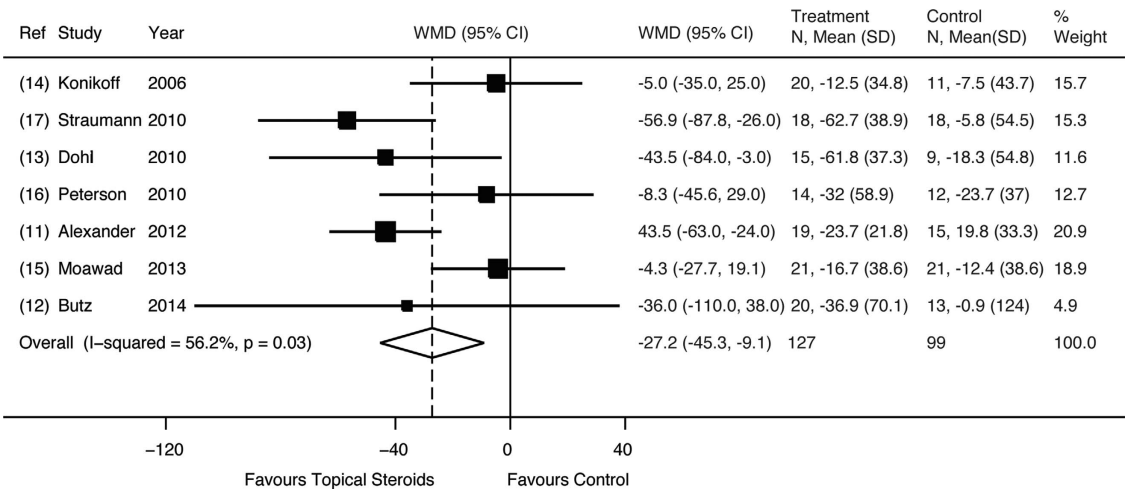


**Figure 2** Forest plot of all randomized controlled trials comparing the effect of topical steroid therapy on the reduction in eosinophil counts. A significantly negative WMD indicates a significant reduction in eosinophil counts following topical steroid vs control treatment. WMD, weighted mean difference.

### Subgroup analyses

*Exclusion of PPI responders before study.* An a priori subgroup analysis was performed on the exclusion of PPI responders before enrollment into the trial. Two studies fully excluded PPI responders,[12,17] two studies partially excluded PPI responders,[11,13] and three studies did not exclude PPI responders[14–16] (Table 1).

Among studies that partially or fully excluded PPI responders, a significantly greater reduction in eosinophil counts was observed with topical steroid treatment compared to control treatment (WMD −46.3, 95% CI −61.3 to −31.4; Figure 3). The magnitude of effect was slightly greater among studies that fully excluded PPI responders[18,21] (WMD −53.8, 95% CI −83.3 to −25.3) relative to studies that partially excluded PPI responders[17,19] (WMD −43.5, 95% CI −61.1 to −25.9). Among studies that did not exclude PPI responders,[20,22,23] no significant difference in eosinophil counts was observed between topical steroid and control treatments (WMD −5.3, 95% CI −21.8 to 11.2; Figure 3).

These results were robust when the meta-analysis was repeated by pooling post-treatment eosinophil counts using a standardized mean difference method and when excluding the two studies with a high risk of attrition bias.[11,13]

A major reduction in heterogeneity was observed following subdivision on the exclusion of PPI responders, with minimal heterogeneity in both subgroups ($I^2 = 0.0\%$ and 0.0%; Figure 3).

*Type of control used (placebo vs PPI).* An a priori subgroup analysis was performed on the type of control used in each study. Five studies used placebo treatment in the control group[11–14,17] and two studies used PPI treatment in the control group[15,16] (Table 1).

Among studies that used placebo treatment in the control group, a significantly greater reduction in eosinophil counts was observed with topical steroid treatment compared with control treatment (WMD −37.2, 95% CI −56.0 to −18.5; Figure 4). Among studies that used PPI treatment in the control group, no significant difference in eosinophil counts was observed between topical steroid and PPI treatment (WMD −5.4, 95% CI −25.2 to 14.4; Figure 4).

This result was robust in a *post-hoc* analysis, which excluded the study that placed all patients in both topical steroid- and placebo-treatment groups on PPI therapy.[13] This result was also robust when the meta-analysis was repeated by pooling post-treatment eosinophil counts using a standardized mean difference method, but not when excluding the two studies with a high risk of attrition bias.[11,13]

An overall reduction in heterogeneity was observed following subdivision on control type, although the "topical steroids vs placebo" subgroup still retained "moderate" heterogeneity ($I^2 = 38.3\%$, $Q = 6.48$, $P$-heterogeneity $= 0.17$).

*Type and dosage of topical steroid used (budesonide vs fluticasone).* An a priori subgroup analysis was performed on the type and dosage of topical steroid used. Five studies used swallowed aerosolized fluticasone,[11,12,14–16] one study used swallowed nebulized budesonide,[17] and one study used oral viscous budesonide[13] (Table 1).

Compared with placebo treatment, topical steroid treatment was associated with a significant reduction in esophageal eosinophil counts among studies that used budesonide (WMD −52.0, 95% CI −76.5 to −27.4), but not among studies that used fluticasone (WMD −18.6, 95% CI −38.9 to 1.7; Supplementary Figure 1 online). However, when this analysis was restricted to studies that partially or fully excluded PPI responders,[11–13,17] a significant reduction in eosinophil counts was observed in both studies that used budesonide (WMD −51.97, 95% CI −76.54 to −27.39) and studies that used fluticasone (WMD −43.01, 95% CI −61.87 to −24.15; Figure 5).

These results were robust when the meta-analysis was repeated by pooling post-treatment eosinophil counts using a standardized mean difference method. Repeating this meta-analysis following exclusion of the studies with a high risk of attrition bias was not possible due to insufficient study numbers.[11,13]

Of the studies using swallowed aerosolized fluticasone, two studies used a high dose (880 μg twice daily)[11,12] and three

studies used a low dose (440 μg twice daily).[14–16] Among studies that used the high dose, a significantly greater reduction in eosinophil counts was observed with topical steroid treatment compared with control treatment (WMD −43.0, 95% CI −61.9 to −24.2; Supplementary Figure 2). Among studies that used the low dose, no difference in eosinophil counts was observed between topical steroid and control treatments (WMD −5.3, 95% CI −21.8 to 11.2; Supplementary Figure 2). However, this analysis was complicated by other study design characteristics as the three studies in the low-dose group also failed to exclude PPI responders before the trial[14–16] (Figure 3).

### Secondary outcomes

*Symptom response.* Although all of the studies provided some measure of a "symptom response" when symptoms before and after treatment were compared, the symptom response scoring tools varied so widely between studies that a meaningful meta-analysis was not possible (Supplementary Table 2). For instance, one study used a combined score from multiple symptoms,[13] two studies reported binary changes in multiple symptoms,[12,14] and four studies presented a study-specific dysphagia score.[11,15–17]

Two studies reported a statistically significant improvement in dysphagia,[13,17] whereas the other five studies showed no improvement.[11,12,14–16] Interestingly, the two studies that showed the significant symptom improvement were the only two studies where budesonide was used as the topical steroid (Table 1).

*Adverse events.* Topical steroid therapy was associated with an increased risk of esophageal candidiasis compared with non-steroid therapies. A total of 11 cases of esophageal candidiasis were observed in 127 patients treated with topical

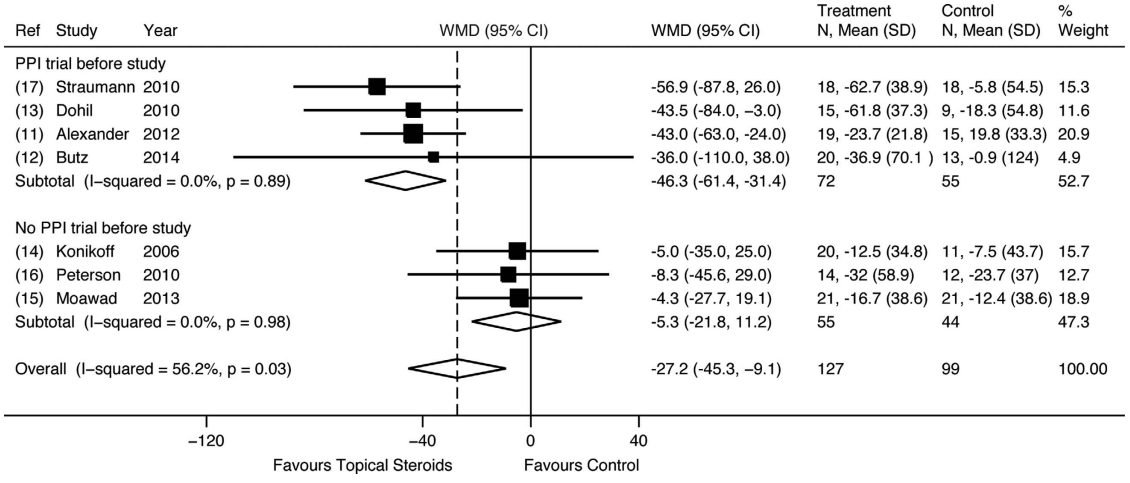


**Figure 3** Forest plot of all randomized controlled trials comparing the effect of topical steroid therapy on the reduction in eosinophil counts, subdivided on the exclusion of PPI responders. A significantly negative WMD indicates a significant reduction in eosinophil counts following topical steroid vs control treatment. WMD, weighted mean difference.

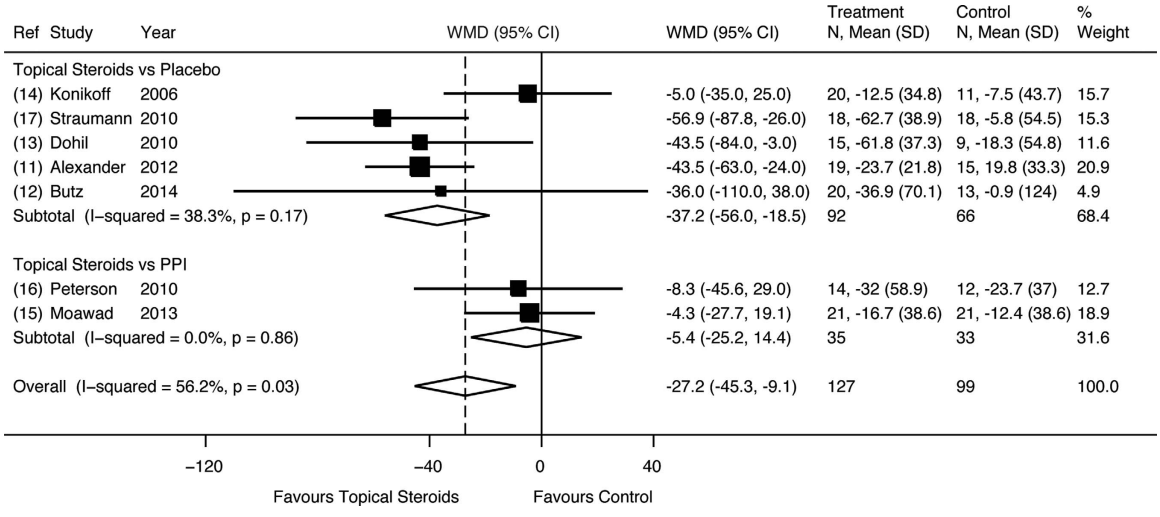


**Figure 4** Forest plot of all randomized controlled trials comparing the effect of topical steroid therapy on the reduction in eosinophil counts, subdivided on the type of control. A significantly negative WMD indicates a significant reduction in eosinophil counts following topical steroid vs control treatment. WMD, weighted mean difference.

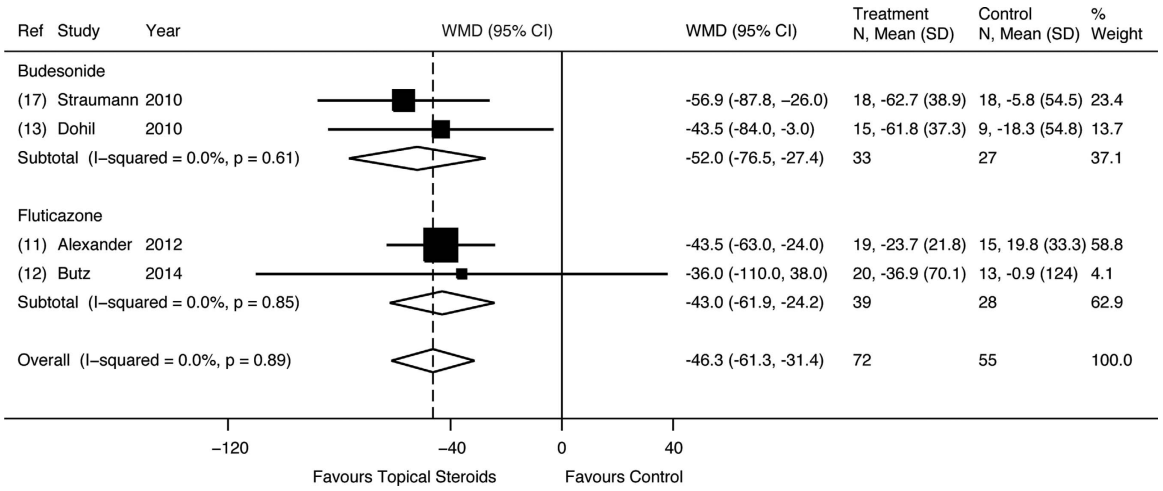


**Figure 5** Forest plot of randomized controlled trials that excluded PPI responders comparing the effect of topical steroid therapy on the reduction in eosinophil counts, subdivided on the type of steroid. A significantly negative WMD indicates a significant reduction in eosinophil counts following topical steroid vs control treatment. WMD, weighted mean difference.

steroids compared with none in the control groups (placebo and PPI). The number needed to harm was nine. All cases were asymptomatic findings that responded to antifungal treatment. No other consistent side effects were observed.

**Publication bias.** Publication bias was explored using a funnel plot (Supplementary Figure 3). The funnel plot appeared symmetrical suggesting a lack of publication bias, although the relatively low number of studies and the heterogeneity in study design limits interpretation of this analysis.

## DISCUSSION

EoE is an increasingly well-recognized cause of dysphagia with a major disease burden.[1–4,10,22] The condition is thought to be an eosinophil-driven, immune-mediated disease and thus current treatment approaches are aimed at limiting antigen exposure with dietary restriction and reducing inflammation with agents such as topical steroids, systemic steroids, or biologics.[2,3] In clinical studies, eosinophil counts in the esophageal mucosa are typically used as a quantitative measure of esophageal inflammation and thus treatment outcome. Importantly, eosinophil counts correlate well with symptom responses (the end goal of treatment), but only when optimized symptom analysis tools are used.[21,23,24] This meta-analysis showed that topical steroid treatment significantly reduced eosinophil counts in the esophagus when compared with control treatments in patients with active EoE after a diagnostic trial of PPI (Figure 3).

In the meta-analysis, we also observed "moderate to significant" heterogeneity among RCTs (Figure 2), in agreement with the inconsistent results highlighted by earlier qualitative reviews of the EoE literature.[1–4,22] However, subgroup analysis identified the exclusion of PPI responders and the choice of control treatment as key contributors to this heterogeneity (Figures 3 and 4). In an undifferentiated cohort of patients presenting with symptoms of esophageal dysfunction and esophageal eosinophilia, a mixture of patients with GERD, PPI-REE, and true EoE would be expected. Importantly, GERD and PPI-REE patients are PPI responsive and steroid resistant, whereas EoE patients are PPI resistant and steroid sensitive. Indeed, current ACG guidelines recommend a failed PPI trial to diagnose true EoE and exclude the more common PPI-sensitive diagnoses of GERD/PPI-REE. We decided to retain studies that did not exclude PPI responders in our meta-analysis, despite them not meeting the current recommended guidelines for EoE, as the evidence for a PPI trial still remains of low quality.[2]

In support of the importance of a PPI trial, we observed a significant reduction in eosinophil counts following topical steroid treatment only in studies that excluded PPI responders (Figure 3). The heterogeneous patient mix in studies not excluding PPI responders (GERD, PPI-REE, and EoE) would be expected to bias the effect measures towards the null, explaining the nonsignificant result in this subgroup.[14–16] This situation is further complicated in the two studies[15,16] that compared topical steroid with PPI therapy (Figure 4). In addition to the inclusion of patients with other steroid-resistant diagnoses, the topical steroid and PPI therapies were effectively treating different subsets of patients (EoE vs GERD/PPI-REE, respectively), thus confounding the comparison (Figure 4). Importantly, both studies included a subgroup analysis comparing the effectiveness of the two treatments in patients subdivided on a diagnosis of GERD[15] or an abnormal pH status.[16] As might be expected, topical steroid therapy was most effective in patients without a diagnosis of GERD and in patients with a normal pH status, further supporting the importance of excluding PPI responders before treating EoE with topical steroids. Taken together, this meta-analysis provides strong evidence for the diagnostic use of a PPI trial in EoE, as well as strong evidence for the use of topical steroids in the treatment of true EoE.

We also observed weak evidence for a difference in efficacy of budesonide relative to fluticasone treatment (Figure 5). A number of factors may have potentially influenced this result, including true differences in steroid effectiveness,[25–27] confounding differences in study design (Table 1), or differences in

the route of administration.[28] In the trials included in this meta-analysis, fluticasone was administered as a swallowed aerosolized dose through an inhaler,[11,12,14–16] whereas budesonide was administered as an oral viscous solution[13] or as a swallowed nebulized mixture,[17] which may suggest an effect related to the route of administration. This observation is also consistent with a recently published RCT that showed different efficacies for budesonide administered via different routes.[28]

Although a robust association was observed between topical steroid treatment and a reduction in eosinophil counts in the esophagus, the data on symptom resolution was less clear.[29–31] Only two studies showed an improvement in dysphagia or combined symptom score following treatment.[13,17] Interestingly, both studies used budesonide, providing further evidence for an increased effectiveness of budesonide relative to fluticasone (as discussed above). However, the use of different symptom measures in the studies cannot be excluded as a factor influencing this observation. Furthermore, symptom responses are easily confounded by concurrent dietary/lifestyle factors, person-to-person variation, and the relative reversibility/irreversibility of the underlying dysfunction making interpretation of symptoms scores extremely difficult. Indeed, the difficulty in assessing symptom resolution is a major factor in the choice of the objective reduction in eosinophil counts as the primary outcome in this meta-analysis (and the majority of RCTs). The absence of a widely accepted validated, objective symptom-scoring system for EoE continues to hinder assessment of the true effects of topical steroid treatment on symptom resolution. However, a new symptom-based activity index specific to EoE has been recently developed, which showed good correlation with symptom responses and eosinophil counts in the EoE patients.[21] New RCTs utilizing this or similarly validated symptom tools may enhance our understanding of the relationship between eosinophilic inflammation and symptom resolution following topical steroid treatment.

Consistent with previous reports,[11–17] topical steroid treatment was associated with minimal side effects overall. The most common adverse events were asymptomatic candida infections that resolved with antifungal treatment. This result suggests that topical steroid treatment is not only effective but also safe.

We identified seven RCTs in our updated meta-analysis,[11–17] three of which had not been included in a previous systematic review.[11,12,15] We were able to provide strong, high-quality evidence for the first-line EoE treatment with topical steroids for a number of reasons. First, we restricted our analysis to RCTs, which provide the highest-level evidence available. Second, the majority of the included studies had a low risk of individual bias. Third, the strongest reduction in eosinophil counts was observed in the subgroup analysis pooling studies that excluded PPI responders, consistent with current guidelines. Furthermore, this result was robust when the two studies with a high risk of attrition bias were excluded from the meta-analysis.[11,13] Fourth, we were able to attribute the "moderate to significant" heterogeneity among studies to the exclusion of PPI responders, the type of control, and the type of steroid (Figures 3, 4, and 5), and thus the quality of the evidence was not limited by study heterogeneity. In addition, this reduction in heterogeneity following a priori-defined subgroup analyses strengthens the decision to pool the evidence from these RCTs into a single meta-analysis. Finally, the pooled results appeared to be precise with narrow CIs.

There are a number of limitations in this meta-analysis that need to be considered when interpreting these results. Although the results from this meta-analysis are highly consistent, the outcomes are still based on a relatively small number of RCTs with limited cohort sizes, and the results presented here need to be interpreted in this context. Large, multicenter RCTs that utilize the new symptom analysis tools are still required in order to further strengthen the evidence for topical steroid treatment in EoE. In addition, the studies included in this systematic review varied greatly in their definition of EoE (Table 1), which may influence the comparisons between studies. However, the observation of a robust positive effect despite these variable definitions could be interpreted as further support for the use of topical steroids in clinical practice, where EoE diagnosis will inherently vary until international consensus on EoE definitions are available. Finally, a meta-analysis on symptom response was not possible due to the variability in symptom score measures used in each study, limiting the analysis of this outcome.

## CONCLUSION

In conclusion, topical steroid therapy significantly reduced esophageal mucosal eosinophilia in EoE, but only in studies where PPI-responsive GERD and PPI-REE patients had been excluded. This meta-analysis provides the first high-level evidence for the diagnostic use of a PPI trial, as well as strong evidence for the use of topical steroids in the treatment of true EoE, consistent with the current ACG guidelines. Although topical steroid treatment was found to be safe and effective in reducing eosinophil counts, its effectiveness in symptom resolution was less clear. Further research is required to develop a validated symptom-scoring tool.

## CONFLICT OF INTEREST

**Guarantor of the article:** Robert Fraser, MBBS, FRACP, PhD.
**Specific author contributions:** Systematic review concept and design, analysis and interpretation of data, drafting of the manuscript, statistical analysis: Ming-yu (Anthony) Chuang; systematic review concept and design, analysis and interpretation of data, drafting of the manuscript: Mohamed A. Chinnaratha; analysis and interpretation of data, drafting of the manuscript, statistical analysis: David G. Hancock; statistical analysis: Richard Woodman; drafting of the manuscript: Geoffrey R. Wong; study supervision, drafting of manuscript, critical revision of the manuscript for important intellectual content: Charles Cock; study supervision, drafting of the manuscript, critical revision of the manuscript for important intellectual content: Robert Fraser. All authors approved the final manuscript.
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## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Eosinophilic esophagitis (EoE) is an increasingly well-recognized cause of dysphagia with a major disease burden.
- ✓ Current American College of Gastroenterology (ACG) Guidelines recommend an 8-week PPI trial, followed by topical steroids as first-line treatment for true EoE.
- ✓ However, evidence for these approaches has been inconsistent in earlier reports and robust meta-analysis has not been performed on the updated literature.

### WHAT IS NEW HERE

- ✓ Our meta-analysis identified seven randomized controlled trials (RCTs), including three RCTs that had not been previously included in a systematic review.
- ✓ Topical steroid therapy significantly reduced esophageal mucosal eosinophilia in EoE, but only in studies that used a PPI trial to exclude other diagnoses.
- ✓ Subdivision of RCTs on their use of a PPI trial also accounted for the majority of heterogeneity between trials.
- ✓ This meta-analysis provides high-level evidence for the use of diagnostic PPI trials and topical steroid treatment in the management of EoE, in agreement with the ACG guidelines.

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Supplementary Information accompanies this paper on the Clinical and Translational Gastroenterology website (http://www.nature.com/ctg)

## APPENDIX 1

### Medline (OVID) search strategy

1. Randomized controlled trial.pt. (366322)
2. Controlled clinical trial.pt. (87769)
3. randomized.ab. (265828)
4. placebo.ab. (143634)
5. drug therapy.fs. (1674284)
6. randomly.ab. (189286)
7. trial.ab. (274923)
8. groups.ab. (1219659)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (3136032)
10. exp animals/ not humans.sh. (3898895)
11. 9 not 10 (2667934)
12. oesophag$.tw. (26140)
13. Esophag$.tw. (94536)
14. gastro$.tw. (248340)
15. gastri$.tw. (188718)
16. exp esophagitis/ (9476) (MeSH Term [C06.405.117.620] and lower branches)
17. r 13 or 14 or 15 or 16 (480424)
18. exp eosinophils/ (19523) (MeSH Term [A11.118.637.415.345] and lower branches)
19. exp eosinophilia/ (19412) (MeSH Term [C15.378.553.231] and lower branches)
20. eosinophil$.tw. (53768)
21. 18 or 19 or 20 (61912)
22. 17 and 21 (3774)
23. 11 and 22 (921)

There were no language or publication restrictions.