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[Intervention Review]

Non-surgical interventions for eosinophilic esophagitis

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ABSTRACT

Background

People with eosinophilic esophagitis (EE) have clinical symptoms of esophageal disease, an elevated intraepithelial eosinophil count (15 in one or more high power field at endoscopy), consistent endoscopic findings and failure to respond to gastric acid suppressants. The cause of EE is unknown, however dietary, environmental and immunological factors may contribute. Current medical therapies include steroids, dietary manipulation, mast cell inhibitors, leukotriene receptor antagonists and immune modulators; however there is no universal approach to treatment.

Objectives

To evaluate the benefits and harms of medical interventions for EE.

Search methods

We searched the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group trials register (*The Cochrane Library* Issue 1, 2009), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2009), MEDLINE (1966 to February 2009) and EMBASE (1980 to February 2009).

Selection criteria

Randomised controlled trials (RCTs) comparing a medical or dietary intervention for EE with a placebo or with another medical intervention.

Data collection and analysis

Two reviewers independently screened the titles of abstracts.

Main results

Three RCTs fulfilled inclusion criteria, two in children and one in adults. In one trial, topical fluticasone decreased vomiting more than placebo (67% versus (vs) 27%, $P < 0.05$) but did not improve dysphagia. Histological remission was reported in fluticasone group compared with placebo group (50% vs 9%, $P = 0.05$; RR 5.5, 95%CI 0.81 to 37.49). One recipient of fluticasone developed oral candidiasis. In trial comparing fluticasone with oral prednisone, symptom resolution and improvement of esophagitis were similar. Majority of participants were symptom free at four weeks with no difference between groups (RR 1.03, 95%CI 0.95 to 1.11). Symptom relapse usually occurred within six weeks of stopping therapy and 45% had symptom relapse at six month follow-up with no difference between groups. With prednisone, 40% suffered adverse effects and three withdrew early from treatment with severe adverse effects (hyperphagia, weight gain, cushingoid features). With fluticasone, 15% developed esophageal candidiasis and 45% had relapse in symptoms at week 24. Histological

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improvement occurred in majority at four weeks with no difference between groups. In the third trial comparing mepolizumab to placebo, there was no difference in symptom response with mepolizumab compared to placebo, but decrease in esophageal eosinophil count was greater with mepolizumab than placebo (67% vs 25%).

Authors' conclusions

As only three relevant RCTs were identified, we have limited capacity to compare the benefits and harms of medical interventions currently used for treating EE. Further RCTs on therapies for EE are required.

PLAIN LANGUAGE SUMMARY

Medical treatments for eosinophilic esophagitis (a chronic disease associated with increased numbers of eosinophils in the esophagus and symptoms of esophagitis)

Eosinophilic esophagitis (EE) is emerging globally as a significant cause of upper gastrointestinal disease in people with clinical symptoms of esophageal disease including a typical appearance of the esophagus and an increased number of eosinophil white blood cells when the esophagus is examined by an endoscope using high magnification.

The cause of EE is unknown, however dietary and/or environmental factors may be contributing factors. People with EE may have difficulty swallowing, vomiting, regurgitation, chest and/or abdominal pain and frequently fail to respond to treatment with antacids or anti-reflux surgery. Current therapies include steroids, therapies that target specific components of the immune system, such as mast cell inhibitors, leukotriene receptor antagonists, and immune modulators; dietary manipulation and esophageal dilatation, however there is no universal approach to treatment. Our systematic review of the literature identified only three randomised controlled trials evaluating the benefits and harms of medical treatments for EE, two in children and one in adults. One trial compared fluticasone, a steroid spray that is swallowed, with oral steroid (prednisone), one compared fluticasone (a steroid) with placebo and the third compared mepolizumab, a monoclonal antibody, with placebo. In children, fluticasone decreased vomiting more effectively than placebo but did not improve dysphagia. Histological remission was more marked in the fluticasone group compared with the placebo group. Esophageal candidiasis (thrush) was diagnosed in one participant on fluticasone. Another trial showed symptom improvement that was similar with fluticasone and with oral prednisolone. The majority of participants were symptom free at four weeks with no difference between the groups. Symptom relapse usually occurred within six weeks of stopping therapy and had occurred in 45% of all trial participants at six month follow-up with no difference between treatment groups in the rate or timing of relapse. There was improvement as assessed by examining the biopsies taken from the esophagus, in the majority of participants at four weeks, with no difference between the two groups. In the prednisone group, 40% had adverse effects and three withdrew early with severe adverse effects (hyperphagia, weight gain, and the 'moon-shaped' face often seen with steroid treatment (cushingoid features)). In the fluticasone group, 15% were diagnosed with esophageal candidiasis and 45% had a relapse of symptoms at week 24. In the third trial in adults, using monoclonal antibody, there was no difference in symptom response with mepolizumab compared to placebo, but the decrease in esophageal eosinophils was more marked with mepolizumab than placebo.

BACKGROUND

Description of the condition

Eosinophilic esophagitis (EE) is an inflammatory disorder of the esophagus causing upper gastrointestinal symptoms and characterised by increased esophageal infiltration with intraepithelial eosinophils (IEE). It was originally described during the 1970s in adults with symptoms of esophagitis, who often had allergies, and who had high esophageal eosinophil counts. The American Gastroenterology Association (AGA) guidelines' diagnostic criteria for EE are clinical symptoms of esophageal disease, a histological abnormality of 15 or more IEE per High Power Field (hpf) on endoscopy, the exclusion of gastroesophageal reflux disease (GERD) and consistent endoscopic findings (Furuta 2007). However, the criteria for the diagnosis of EE are not well defined (Bohm 2008). EE affects men more than women, the mean age of onset being nine (one to 21) years in children and 38 (14 to 89) years in adults (Furuta 2007). In young children, symptoms may be associated with food intolerance, however dysphagia and food impaction occur more often in adults (Faubion 1998; Liacouras 1998; Orenstein 2000; Croese 2003). In EE, the mucosa may look normal macroscopically, however thickening, ringing, furrowing and erosion have been reported (Hassall 1996; Khan 2003; Orenstein 2000).

People with EE often have a family history of allergic disease including asthma, eczema, allergic rhinitis and food allergy and may have abnormal skin prick tests (Spergel 2002; Faubion 1998; Liacouras 1998). Intolerance to ingested food or inhaled allergens has been suggested as a contributor to esophageal damage by eosinophils. Experiments in mice suggest that EE may be associated with inhaled allergens, rather than with oral allergens (Mishra 2001). In EE, mast cell numbers are increased, correlating with eosinophil numbers, and there is some cellular evidence that the inflammation in EE is similar to that occurring in other allergic diseases (Stone 2008). Up to 75% of patients with EE may be atopic and many have measurable food allergen-specific IgE (Stone 2008). EE may respond clinically and histologically to a restricted diet, however the EE often recurs on the return to a normal diet (Stone 2008). The Guidelines of the AGA (Furuta 2007) highlight our lack of understanding of the pathophysiology of EE and the way in which eosinophils contribute to tissue damage.

Description of the intervention

Any non-surgical treatment for EE including metered dose steroids (e.g. fluticasone), oral steroids (e.g. prednisone), mast cell inhibitors (e.g. sodium cromoglycate), immune modulators (e.g. mepolizuma), leukotriene receptor antagonists (e.g. montelukast) or dietary intervention (e.g. elemental or exclusion diets).

Why it is important to do this review

There is no universally accepted treatment of EE. Corticosteroids (Faubion 1998; Liacouras 1998; Teitelbaum 2002), hypoallergenic diets (Kelly 1995; Markowitz 2003), sodium cromoglycate (Perez-Millan 1997), and montelukast (Attwood 2003) have all been used to treat EE. The purpose of this review is to search for high-level evidence in the form of randomised controlled trials evaluating non-surgical interventions for EE.

OBJECTIVES

To evaluate the benefits and harms of medical interventions for people with EE.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing a medical intervention (e.g. metered dose steroid, oral steroids, sodium cromoglycate, leukotriene receptor antagonists) or dietary intervention (e.g. elemental milk formulae, exclusion diets) with placebo, or comparing one of the above interventions with another.

Types of participants

People of any age with a diagnosis of EE based on an increased number of eosinophils (15/hpf) on esophageal biopsy and with esophagitis that is unresponsive to acid suppression (with H2 antagonists or proton pump inhibitors).

Types of interventions

- Steroids (oral or swallowed metered dose (topical) steroids) (Faubion 1998; Liacouras 1998).
- Hypoallergenic diets (elemental milk formulae, exclusion diets) (Kelly 1995; Markowitz 2003).
- Mast cell inhibitors (sodium cromoglycate) (Perez-Millan 1997).
- Leukotriene receptor antagonists (e.g. montelukast) (Attwood 2003).
- Immune modulators such as anti IL-5 (mepolizumab) and anti-IgE.

Types of outcome measures

Primary outcomes

- Improvement in symptoms (e.g. dysphagia, pain, vomiting).
- Decrease in the number of IEE to <15 per high power field on endoscopy.
- Harms: Side effects of oral and swallowed metered dose steroids, e.g. oral candidiasis, effects on longitudinal growth and other adverse effects. Side effects of dietary intervention e.g. nutritional deficits, non-compliance. Side effects of leukotriene receptor antagonists. Relapse of symptoms and/or histological abnormalities after discontinuation of therapy.

Secondary outcomes

- Improved quality of life assessed using a validated questionnaire.
- Improvement in macroscopic appearance of the esophagus on endoscopy.

Search methods for identification of studies

Electronic searches

We conducted searches to identify all published and unpublished randomised controlled trials (RCTs). The search strategy included studies in all languages. We searched the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group trials register (The Cochrane Library Issue 1, 2009), the Cochrane Central Register of

Controlled Trials (The Cochrane Library Issue 1, 2009), MEDLINE (1966 to February 2009) and EMBASE (1980 to February 2009). The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE, Sensitivity maximising version, Ovid format (Higgins 2008), was combined with the search terms in Appendix 1 to identify RCTs in MEDLINE. The MEDLINE search strategy was adapted for use in the other databases searched.

Searching other resources

We handsearched reference lists from trials identified by electronic searching to identify further relevant trials. Other sources that were searched included reference lists of textbooks, reviews (Cochrane Database of Systematic Reviews and others), previous trials, and conference proceedings.

Data collection and analysis

Other methods to be used in updates of this review, should a meta-analysis be possible, can be found in Appendix 2.

Selection of studies

Two reviewers (DT, EE) screened the titles of abstracts resulting from the literature searches. Study eligibility for inclusion in the review was assessed against defined criteria.

Adverse outcomes

We recorded adverse events and described the information qualitatively.

Assessment of risk of bias in included studies

We assessed risk of bias in the included studies according to defined criteria:

- Generation of the random sequence: adequate (computer generated random numbers, table of random numbers or similar) or inadequate (other methods or not described)
- Allocation concealment: adequate (central independent unit, sealed envelopes, or similar) or inadequate (not described or open table of random numbers or similar)
- Blinding: adequate (identical placebo tablets or similar) or inadequate (not performed e.g. tablets versus injections or similar). Blinding of participants, study investigators and assessors was recorded.
- Follow-up: adequate (number and reasons for drop-outs and withdrawals described) or inadequate (number or reasons for drop-outs or withdrawals not described).
- Incomplete outcome data: we assessed whether outcome data were reported in full, and whether data on attrition and exclusions were reported: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias).
- Selective reporting: we assessed whether study report was free of selective outcome reporting: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias).
- Other bias: we assessed whether the study was apparently free from any other problems that could put it at a high risk of bias.

RESULTS

Description of studies

Results of the search

The search of the literature yielded 283 records, from which full papers for 18 abstracts were extracted. From these we identified three RCTs relevant to the subject of the review (Konikoff 2006; Schaefer 2008; Straumann 2008). In the previous version of this review we identified two relevant trials, which have now been published. One, a conference abstract identified previously as Gupta 2003, has now been published as Schaefer 2008. The second trial that was in progress at the Cincinnati Children's Hospital Medical Center is now published as Konikoff 2006. No trials were identified that evaluated mast cell stabilizers or dietary interventions.

Included studies

Details of the characteristics of the included studies are given in the 'Characteristics of included studies' table.

Design

The included studies were all RCTs.

Sample sizes

Thirty-six children were included in Konikoff 2006 and 80 children in Schaefer 2008. Straumann 2008 was a pilot study with 11 adult participants.

Setting

Konikoff 2006 was hospital based, with children being recruited from Cincinnati Children's Hospital Medical Center and Children's Hospital, San Diego, USA. Schaefer 2008 was conducted in the outpatient clinic population of the James Whitcomb Riley Hospital for Children, Indianapolis, Indiana, USA. Straumann 2008 was a clinical trial published as conference proceedings, the setting of the study was not reported.

Participants

Two RCTs were conducted in children and evaluated the role of steroids (Konikoff 2006; Schaefer 2008), however they reported different criteria for the diagnosis of EE, for the inclusion of participants in the trial and for determining the histological response.

Konikoff 2006 included participants in the age range three to 16 years, and in Schaefer 2008, the participants were aged one to 16 years. In the third study, the participants were adults (Straumann 2008).

In the studies with child participants, all the included children had a diagnosis of EE confirmed endoscopically. In Konikoff 2006 endoscopic diagnosis included the presence of >24 eosinophils per hpf in one or more esophageal biopsies and epithelial hyperplasia; failure to respond to prior acid suppression therapy (proton pump inhibitor, PPI) was not necessary for the diagnosis of EE. In Schaefer 2008 the children were diagnosed with EE (≥ 15 eosinophils per hpf) and had a negative pH probe study. 58% of the participants in this study (Schaefer 2008) were positive for food allergies at entry to the trial and were asked to eliminate the relevant food.

Exclusion criteria in [Konikoff 2006](#) were: food allergy by skin prick testing and response to an exclusion diet; if the participants had recently been prescribed steroids; or if they were pregnant. [Schaefer 2008](#) excluded participants from this study if they had any other gastrointestinal condition, e.g. *Helicobacter pylori* infection, chronic inflammatory bowel disease, or if they were on current corticosteroid treatment.

In the third study, published as an abstract in conference proceedings, [Straumann 2008](#) included adult participants with EE (N=11).

Interventions

Two RCTs were conducted in children and evaluated the role of steroids. One study compared fluticasone propionate with placebo; fluticasone (400µg twice daily for 23 months) was administered by a metered-dose inhaler but swallowed. Normal diet and PPI (if taken) were continued in both groups ([Konikoff 2006](#)). In the second study ([Schaefer 2008](#)), participants were randomised to four weeks treatment with either oral prednisone (1mg/kg/dose twice daily (each dose maximum of 30mg) and then weaned off the treatment over the next eight weeks, or topical (swallowed) fluticasone given by via metered dose inhaler (110µg per puff (age one to 10 years) and 22µg per puff (≥11 years of age) for three months.

Neither study evaluated long term maintenance therapy. In the third study, published as an abstract in conference proceedings, mepolizumab was compared with placebo ([Straumann 2008](#)). Mepolizumab, a humanized monoclonal antibody to interleukin-5 (IL-5), was given at a dose of 750mg at zero and seven days by intravenous infusions and, if the histological response was incomplete, two doses of 1500mg were given at four-weekly intervals up to a maximum of four doses.

Outcomes

[Konikoff 2006](#) assessed histological remission (≤1 eosinophil per hpf) and recorded adverse effects. [Schaefer 2008](#) reported the following outcomes; histological improvement and resolution of presenting symptoms between weeks zero and four of treatment. Therapeutic response was assessed using a histological grading score incorporating both the esophageal eosinophil count and basal cell zone thickness symptom remission; adverse drug effects; and symptom relapse. [Straumann 2008](#) assessed participants "clinically, endoscopically, histologically and via biomarkers of inflammation".

Excluded studies

Please see [Characteristics of excluded studies](#).

Risk of bias in included studies

For details see 'Risk of bias' tables in the section [Characteristics of included studies](#). The following gives a brief overview.

Allocation

Randomisation was computer generated in [Konikoff 2006](#), and the authors reported allocation concealment, but provided no further details. Participants were randomised using random number assignment in [Schaefer 2008](#). While the authors reported allocation concealment, the method was not reported. [Straumann 2008](#) was published in abstract form, The authors did not report

whether there was adequate sequence generation or allocation concealment ([Straumann 2008](#)).

Blinding

[Konikoff 2006](#) blinded participants, clinicians, histologists to the allocation. There was no blinding reported in the [Schaefer 2008](#) study, and [Straumann 2008](#) was reported as double-blind but with no further details provided.

Incomplete outcome data

In the comparison of fluticasone propionate versus placebo, one participant was excluded from the fluticasone group after randomisation as the inclusion criteria for eosinophilic esophagitis were not met. Four patients withdrew from the placebo group: three for increased symptoms and one for noncompliance. These five patients were excluded from the analysis, because they did not have follow-up esophageal biopsy specimens on which to base their response to treatment ([Konikoff 2006](#)).

Dropouts were accounted for and only complete data from participants was included in the analysis of oral prednisone versus fluticasone propionate. The authors stated that a patient exited the study if any of the following occurred: clinical resolution was not achieved with the allocated therapy; no histologic improvement was found; relapse of symptoms was noted at follow-up evaluation; and/or if the subject was noncompliant with the medication or tests ([Schaefer 2008](#)).

No dropouts were reported in the study of mepolizumab versus placebo and it was unclear as to whether there was any incomplete outcome data ([Straumann 2008](#)).

Selective reporting

Two of the included studies were free of selective outcome reporting ([Konikoff 2006](#); [Schaefer 2008](#)). In [Straumann 2008](#), the methods state that participants were assessed clinically, endoscopically, histologically and via biomarkers of inflammation, however only results for esophageal eosinophil count and swallowing difficulties are reported. It is also unclear what the biomarkers of inflammation were or how they were measured.

Other potential sources of bias

We looked at statistical power of the included studies as a additional potential source of bias. Both [Konikoff 2006](#) and [Schaefer 2008](#) had adequate sample power.

There was only a small number of participants in [Straumann 2008](#), five in the treatment group and six in the placebo group. Sample power was not reported but was likely to have been low. Clinical improvements were reported for a subset of participants, two in the treatment group and one in the placebo group but, with such a small number, bias may be present in the results.

Effects of interventions

Fluticasone versus placebo

Primary outcomes

Improvement in symptoms

In the one RCT that compared fluticasone propionate to placebo ([Konikoff 2006](#)), vomiting decreased more in the fluticasone group

than in the placebo group (67% vs 27%, $P<0.05$; RR 2.38, 95%CI 0.86 to 6.59; [Analysis 1.1](#)), but there was no improvement in dysphagia. The response to fluticasone was greater in young children who were non-allergic (using skin-prick testing). Some participants did not respond to fluticasone.

Decrease in the number of eosinophils to <15 per high power field

Fluticasone propionate decreased esophageal eosinophil levels more than placebo (65.9 ± 25.3 vs 1.4 ± 1.1 eosinophils/hpf in the proximal esophagus, $P<0.05$; and 84.6 ± 19.7 vs 19.6 ± 12.9 eosinophils/hpf in the distal esophagus, $P<0.05$). The response was better in non-allergic children. The study reported more marked histological remission in the fluticasone group compared to the placebo group (50% vs 9%, $P<0.05$). There is no significant difference in relative risk between groups (RR 5.50; 95% CI 0.81 to 37.49; [Analysis 1.2](#)). In the fluticasone group, the quantity of CD-8⁺ T lymphocytes and mast cells in both the proximal and distal esophagus decreased more than in the placebo group ($P<0.05$).

Harms

One participant in the fluticasone group was diagnosed with esophageal candidiasis.

Secondary outcomes

Improved quality of life assessed using a validated questionnaire

This outcome was not reported in any of the included studies.

Improvement in macroscopic appearance of the esophagus on endoscopy

There was less distal esophageal furrowing observed in participants receiving fluticasone compared with placebo (50% vs 91%, $P<0.05$; RR 0.55, 95%CI 0.34 to 0.89; [Analysis 1.3](#)). There was greater reduction in epithelial hyperplasia in the proximal ($P<0.05$) and distal esophagus ($P<0.05$) with fluticasone compared to placebo.

Oral prednisone versus topical fluticasone

Primary outcomes

Improvement in symptoms

In the RCT that compared prednisone with fluticasone ([Schaefer 2008](#)), the majority of participants were symptom free at four weeks with no difference between the groups (RR 1.03, 95%CI 0.95 to 1.11; [Analysis 2.1](#)).

Symptom relapse usually occurred within six weeks of stopping therapy and had occurred in 45% of all trial participants at six month follow-up with no difference between treatment groups in the rate or timing of relapse.

Decrease in the number of eosinophils to <15 per high power field

There was histological improvement in the majority of participants at four weeks with no difference between the two groups RR 1.06, 95%CI 0.96 to 1.16; [Analysis 2.2](#).

Harms

In the prednisone group, 40% had adverse effects and three children withdrew from the study less than four weeks after commencing therapy with severe adverse effects (hyperphagia, weight gain, cushingoid features).

In the fluticasone group, 15% were diagnosed with esophageal candidiasis and at week 24, 45% had a relapse in symptoms.

Secondary outcomes

Improved quality of life assessed using a validated questionnaire

This outcome was not reported any of the included studies.

Improvement in macroscopic appearance of the esophagus on endoscopy

This outcome was not reported any of the included studies.

Mepolizumab versus placebo

Primary outcomes

Improvement in symptoms

In the one RCT (a pilot study) that compared compared mepolizumab with placebo ([Straumann 2008](#)), there was no difference in symptom response. However, there was symptomatic improvement in a small subgroup of participants in the mepolizumab group ($N=2$), while one participant improved in the placebo group.

Decrease in the number of eosinophils to <15 per high power field

There was a greater reduction in esophageal eosinophils in the treatment compared with the placebo group (67% vs 25%).

Harms

No clinically relevant events occurred.

Secondary outcomes

Improved quality of life assessed using a validated questionnaire

This outcome was not reported.

Improvement in macroscopic appearance of the esophagus on endoscopy

This outcome was not reported.

DISCUSSION

Summary of main results

A systematic search of the literature for RCTs evaluating treatments for EE identified three relevant RCTs. Two studies evaluated steroid therapy: one comparing swallowed fluticasone with placebo in children ([Konikoff 2006](#)); and one comparing oral prednisone with topical (swallowed metered dose) fluticasone in children ([Schaefer 2008](#)). One study compared mepolizumab to placebo ([Straumann 2008](#)) in adults.

In the trial comparing fluticasone and placebo, the histological response was significantly higher in the treatment group (50% versus 9%, $P<0.047$). Nevertheless, only half the children responded to fluticasone ([Konikoff 2006](#)). The response was better in non-allergic children (skin prick negative). Fluticasone decreased esophageal eosinophil levels more than the placebo in the proximal esophagus: (65.9 ± 25.3 vs 1.4 ± 1.1 eosinophils/hpf; $P<0.05$), and in the distal esophagus (84.6 ± 19.7 vs 19.6 ± 12.9 eosinophils/hpf; $P<0.05$). Fluticasone decreased vomiting more than the placebo (67% versus 27%), but did not decrease dysphagia, which is a more frequent symptom in adults.

In the trial comparing oral prednisone with topical (swallowed metered dose) fluticasone in children, the majority of the participants were symptom free at four weeks with no difference between the two groups. Symptom relapse usually occurred within six weeks of stopping therapy and had occurred in 45% of all trial participants at six month follow-up with no difference between treatment groups in the rate or timing of relapse. In the prednisone group, 40% had adverse effects and three children withdrew from the study before four weeks with severe adverse effects (hyperphagia, weight gain, cushingoid features). In the fluticasone group, 15% were diagnosed with esophageal candidiasis and at week 24, 45% had a relapse in symptoms (Schaefer 2008). In one small trial, there was greater reduction in esophageal eosinophils with mepolizumab compared to placebo (67% vs 25%) but there was no difference in symptom response (Straumann 2008).

Overall completeness and applicability of evidence

Steroids are often used to treat EE and several uncontrolled studies (Furuta 2007; Bohm 2008) indicate that they may improve histological abnormalities and clinical symptoms. Case series have reported treatment with metered dose steroids (Faubion 1998), oral corticosteroids (Liacouras 1998). The more recent use of topical steroids (fluticasone propionate or beclomethasone), administered

by a metered-dose inhaler and swallowed, has been reported in uncontrolled studies with differing effectiveness for the initial treatment for EE and few adverse effects (Furuta 2007; Bohm 2008). There is little evidence on the long-term use of topical or oral steroids, and some studies indicate that discontinuation of steroids often results in relapse. The only two RCTs evaluating steroids are both in children, one of which compared fluticasone with placebo (Konikoff 2006) and one which compared oral prednisone with swallowed fluticasone (Schaefer 2008). The presentation of EE differs considerably in children and adults and thus these results may not be applicable to adults. In the third RCT included in this review, mepolizumab was compared with placebo in adults (Straumann 2008).

Quality of the evidence

All three included studies were RCTs (two placebo-controlled trials and one comparing two current therapies; Konikoff 2006; Schaefer 2008; Straumann 2008) and provide Grade A evidence. The quality of each study was assessed and the results were summarised. All three studies had some methodological limitations such as small sample size, inconclusive results, or potential confounding from simultaneous use of co-therapy. Further details are provided in the "Risk of bias" tables in the section [Characteristics of included studies](#) (Figure 1).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Konikoff 2006	+	+	+	+	+	?
Schaefer 2008	+	+	-	+	+	?
Straumann 2008	?	?	+	?	-	?

Agreements and disagreements with other studies or reviews

A range of pharmacological therapies has been used to treat EE, including oral and inhaled (swallowed) corticosteroids, sodium chromoglycate, proton pump inhibitors, montelukast (a leukotriene inhibitor), and mepolizumab (an IL-5 monoclonal antibody). Dietary interventions include restricted or elemental diets but none has been tested in a RCT. No trials evaluating dietary interventions, including exclusion and hypoallergenic diets (Kelly 1995; Markowitz 2003), have been evaluated by RCT.

Currently, there are insufficient RCTs to form a strong evidence base for practice. Two of the RCTs were conducted in children and evaluated the role of steroids (Konikoff 2006; Schaefer 2008), but used different criteria for the diagnosis of EE, for inclusion of trial participants and for determining histological response and neither evaluated long term maintenance therapy. There is only one small RCT (N=11) evaluating a novel therapy in adults with EE (Straumann 2008).

AUTHORS' CONCLUSIONS

Implications for practice

At present a wide variety of interventions are used to treat EE, but few are based on high quality evidence. The AGA guidelines on management of EE in children and adults identify our lack of understanding of the pathophysiology of EE and the lack of universally accepted criteria for the diagnosis and treatment of EE (Furuta 2007). Yet the frequency of EE is increasing and it is recognised as a chronic disease. A recent retrospective review of 89 children with EE supports the observation that EE is both chronic and relapsing: 79% of the 66% who initially responded to treatment had relapsed within the eight year follow-up period (Assa'ad 2007).

We identified only three RCTs evaluating medical treatments for EE and all had methodological limitations. The trial of fluticasone versus placebo (Konikoff 2006) supports the use of fluticasone for EE in children but highlights the high proportion of potential non-responders. The lack of improvement in dysphagia in this study may reflect the small sample size and the fact that this symptom is more common in adults, but raises the possibility that the results may not easily extrapolate to adults.

The trial comparing oral and metered dose steroids (Schaefer 2008) shows that both are effective as treatment for EE. A possible confounder is the fact that 58% of participants who tested positive for food allergies prior to commencing the study were asked to eliminate the relevant food during the trial. Although the

proportion receiving a special diet was similar in each group, it is possible that benefits of the diet resulted in an overestimation of the beneficial effect of both medications. In view of the similar effectiveness of the two steroid preparations and the potential adverse effects of oral steroids documented in this RCT, inhaled (swallowed) steroids should be used in preference to oral steroids as initial treatment for uncomplicated EE.

Although the trial comparing mepolizumab with placebo (Straumann 2008), which was a pilot study, indicated that treatment with mepolizumab resulted in an improved histological response, there was symptomatic improvement only in a small subgroup of two participants, with the symptoms of one participant improving in the placebo group.

Implications for research

More highly powered RCTs are required to evaluate the efficacy, in the short, medium and long term, of the range of non-surgical therapies currently used for EE, including pharmacological and non-pharmacological (dietary) interventions. Although this review identified three RCTs evaluating treatments for EE, these studies had methodological limitations, including small sample size. Furthermore, they used varying diagnostic and inclusion criteria for participants and different outcome measures. Universal diagnostic criteria for EE should be adopted and important relevant outcome measures standardised, so that the results of future RCTs on EE can be compared. Due to the high relapse rate of EE after stopping treatment, the long term use of treatments requires evaluation for efficacy and adverse effects. Because of the varying clinical characteristics of EE and the apparent variability of disease in young children, older children, and adults, participants in future trials should be well-described and analysis performed according to age.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Konikoff 2006

Methods	RCT
Participants	<p>Included: 36 children (age range 3 to 18 years) with EE (≥ 24 eosinophils per 400 X hpf in at least one biopsy from either the distal or proximal esophagus; and the presence of epithelial hyperplasia). Prior acid suppression therapy was not necessary for the diagnosis of EE.</p> <p>Excluded: Participants identified with a food allergy on skin prick testing and who responded to an exclusion diet; previous poor tolerance to Fluticasone Propionate; steroid use within the last 3 months; pregnant.</p>
Interventions	<p>Intervention: Fluticasone propionate (400μg twice daily for 3 months) via metered dose inhaler and swallowed</p> <p>(N=20).</p> <p>Comparison: Placebo (twice daily for 3 months) via metered dose inhaler (N=11).</p> <p>Normal diet and PPI (if taken) were continued in both groups.</p>
Outcomes	<p>Histological remission (≤ 1 eosinophil per hpf).</p> <p>Adverse effects.</p>
Notes	<p>hpf = high power field.</p> <p>PPI = proton pump inhibitor.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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Konikoff 2006 (Continued)

Adequate sequence generation?	Low risk	Computer generated. Quote: "A clinical research coordinator dispensed metered-dose inhalers containing either active drug or placebo to each patient according to a computer-generated randomization list. No blocking or stratification schemes were used."
Allocation concealment?	Low risk	Quote: "A clinical research coordinator dispensed metered-dose inhalers containing either active drug or placebo to each patient according to a computer-generated randomization list." "All participants and study personnel (with the exception of the above clinical research co-ordinator) were blinded to treatment assignment for the duration of the study."
Blinding? All outcomes	Low risk	Participants, clinicians and histologists were all blinded. Quote: "All participants and study personnel (with the exception of the above clinical research co-ordinator) were blinded to treatment assignment for the duration of the study. Only the study statisticians had access to the unblinded data, but they did not have contact with study participants."
Incomplete outcome data addressed? All outcomes	Low risk	Quote: "One patient was excluded from the FP group after randomization, because this patient did not meet the inclusion criteria for the diagnosis of EE. Four patients withdrew from the placebo group: 3 for increased symptoms and one for noncompliance. These 5 patients were excluded from the analysis, because they did not have follow-up esophageal biopsy specimens on which to base their response to treatment."
Free of selective reporting?	Low risk	Quote: "The primary outcome measure, as specified before the study was initiated, was complete histologic response to treatment as defined by a peak eosinophil count of 1 eosinophil in all 400 HPFs in both the proximal and distal esophagus. Secondary outcome measures included presence of endoscopic furrowing, presence of epithelial hyperplasia, and presence of clinical symptoms." The outcomes were all reported.
Free of other bias?	Unclear risk	Small sample, adequate power. Follow-up at 3 months: 100%. Compliance monitored: yes.

Schaefer 2008

Methods	RCT
Participants	Included: 80 children (age range 1 to 16 years) with EE (≥ 15 eosinophils per hpf) and negative pH probe study. 58% of children tested positive for food allergies at entry and were asked to eliminate the relevant food. Excluded: other esophageal condition, <i>H. pylori</i> infection, chronic inflammatory bowel disease, current treatment with corticosteroids.
Interventions	1. Oral prednisone (1mg/kg/dose twice daily (each dose maximum of 30mg) for 4 weeks then weaned for 8 weeks n=32. 2. Topical (swallowed) fluticasone via metered dose inhaler (110 µg per puff (age 1 to 10 years) and 22 µg per puff (≥ 11 years of age) n=36.
Outcomes	Histological improvement (to <15 eosinophils per hpf) at 4 weeks;

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Schaefer 2008 (Continued)

Symptom remission;
Adverse drug effects;
Symptom relapse.

Notes
hpf = high power field.
PPI = proton pump inhibitor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Random number assignment. Quote: "Random number assignment was used to generate a concealed allocation schedule that was maintained by a research coordinator. No blocking or stratification schemes were used."
Allocation concealment?	Low risk	Quote: "concealed allocation schedule that was maintained by a research coordinator".
Blinding? All outcomes	High risk	Open label. Quote: "the allocated treatment was revealed to enrolled subjects after consent was obtained by the treating physician".
Incomplete outcome data addressed? All outcomes	Low risk	Quote: "The patient exited the study if any of the following occurred: 1. clinical resolution was not achieved with the allocated therapy, 2. no histologic improvement was found, 3. relapse of symptoms was noted at follow-up evaluation, and/or 4. if the subject was noncompliant with the medication or tests. Clinical response data were analyzed based on an intention-to-treat approach. In keeping with intention-to-treat analysis, complete data from all randomized patients were included, unavailable data were censored, and protocol deviations were reported."
Free of selective reporting?	Low risk	Quote "A daily symptom diary was maintained by the patient/guardian while on corticosteroid therapy. Clinical assessment was performed at weeks 4, 12, 18, and 24". "The primary end point was defined as a histologic response by an improvement in biopsy grade after 4 weeks of corticosteroid therapy. The secondary end point was defined as a clinical response to corticosteroids based on the presence or absence of the presenting symptom by patient/guardian report and by physician assessment at predetermined intervals." All prospectively stated outcomes were reported.
Free of other bias?	Unclear risk	Baseline characteristics: similar. ITT analysis: no. Adequate sample power. Follow-up: 6 months. Quote "We acknowledge the potential for allergy testing and food elimination to act as a confounder".

Straumann 2008

Methods
Pilot study (N=11) RCT.

Straumann 2008 (Continued)

Participants	Adults with EE.
Interventions	Up to four doses of mepolizumab compared to placebo group.
Outcomes	Quote: "assessed clinically, endoscopically, histologically and via biomarkers of inflammation".
Notes	Funded by GlaxoSmithKline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Reported as randomised with no further detail.
Allocation concealment?	Unclear risk	Not reported.
Blinding? All outcomes	Low risk	Reported as double-blind with no further detail.
Incomplete outcome data addressed? All outcomes	Unclear risk	The results for all participants, in the groups they were randomised to, are not fully reported in the results section of this report.
Free of selective reporting?	High risk	Methods report that participants were assessed clinically, endoscopically, histologically and via biomarkers of inflammation, however only results for esophageal eosinophil count and swallowing difficulties are reported. It is unclear what the biomarkers of inflammation were or how they were measured; this is not reported.
Free of other bias?	Unclear risk	This is conference abstract and insufficient information was reported to make a judgement.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Helou 2008	The study is not an RCT.
Kagalwalla 2006	The study is not an RCT.
Spergel 2002	The study is not an RCT.
Spergel 2005	The study is not an RCT.

DATA AND ANALYSES

Comparison 1. Fluticasone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vomiting	1	31	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [0.86, 6.59]
2 Histological remission	1	31	Risk Ratio (M-H, Fixed, 95% CI)	5.5 [0.81, 37.49]
3 Distal esophageal furrowing	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.34, 0.89]

Analysis 1.1. Comparison 1 Fluticasone versus placebo, Outcome 1 Vomiting.

Analysis 1.2. Comparison 1 Fluticasone versus placebo, Outcome 2 Histological remission.

Analysis 1.3. Comparison 1 Fluticasone versus placebo, Outcome 3 Distal esophageal furrowing.

Comparison 2. Prednisone versus fluticasone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Free of presenting symptoms at wk 4	1	68	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.11]
2 Histological improvement at wk 4	1	68	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.96, 1.16]

Analysis 2.1. Comparison 2 Prednisone versus fluticasone, Outcome 1 Free of presenting symptoms at wk 4.

Analysis 2.2. Comparison 2 Prednisone versus fluticasone, Outcome 2 Histological improvement at wk 4.

APPENDICES

Appendix 1. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. humans.sh.

11. 9 and 10
12. oesophag\$.tw.
13. esophag\$.tw.
14. gastro\$.tw.
15. gastri\$.tw.
16. exp esophagitis/
17. or/12-16
18. exp eosinophils/
19. exp eosinophilia/
20. eosinophil\$.tw.
21. or/18-20
22. 17 and 21
23. 11 and 22
24. limit 23 to yr="2006-2009"

Appendix 2. Methods to be used in updates of the review

Measures of treatment effect

For dichotomous outcomes, we plan to express results as relative risk with 95% confidence intervals and to pool the data using a random effects model. Where continuous scales of measurement were used to assess the effects of treatment, we plan to use the weighted mean difference between groups with 95% confidence intervals. The standardised mean difference (with 95% confidence intervals) will be used to compare different measurement scales.

Assessment of heterogeneity

We plan to assess statistical heterogeneity using the Cochran Q test on N-1 degrees of freedom, with an alpha of 0.1 used for statistical significance.

Data synthesis

Applicability of the results to individual patients will be expressed as relative risk reduction with therapy compared to the control.

Subgroup analysis

We plan to perform subgroup analyses where adequate information is given in reports of studies. The groups will be: age (18 years and under; over 18 years), allergy status (positive skin prick test; negative skin prick test), gender (male; female).

Investigation of heterogeneity

If substantial heterogeneity exists between studies for the primary outcome, we shall explore the reasons for heterogeneity; such as age, cancer stage, histological type and treatment type. If it is inappropriate to pool the data because of clinical or statistical heterogeneity a systematic review without meta-analysis will be reported.

Sensitivity analysis

We plan to conduct sensitivity analyses to examine the effects of excluding studies defined as those with a moderate or high risk of bias as described in the Cochrane Handbook of Systematic Reviews of Interventions ([Higgins 2008](#)).

WHAT'S NEW

Date	Event	Description
13 February 2012	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 3, 2004

Date	Event	Description
27 January 2010	New citation required but conclusions have not changed	Author line changed
27 January 2010	New search has been performed	New studies added, review updated
27 January 2010	New search has been performed	Updated.
30 October 2008	Amended	Converted to new review format.
8 May 2006	New search has been performed	Minor update.
2 February 2006	Amended	New studies sought but none found.
15 April 2004	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Diana Thomas and Elizabeth Elliott screened search results, retrieved papers, screened them against the inclusion criteria, appraised the quality of the papers and abstracted data. Diana Thomas and Elizabeth Elliott entered data into RevMan and analysed the data. Diana Thomas and Elizabeth Elliott provided methodological, policy and consumer perspectives. Diana Thomas and Elizabeth Elliott wrote the updated review, with clinical perspective provided by Elizabeth Elliot and Jonathan Markowitz.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Medical School (Paediatrics and Child Health), The University of Sydney, Australia.
- Department of Paediatrics, Royal Children's Hospital, University of Melbourne, Melbourne, Australia.
- The Centre for Evidence Based Paediatrics Gastroenterology and Nutrition, The Children's Hospital at Westmead, Australia.

External sources

- National Health and Medical Research Council, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There has been a minor adjustment in the importance attributed to some outcomes since the previous version, reflecting current knowledge on EE. The primary outcomes now include the decrease in the number of IEE, which was previously listed as a secondary outcome. Harms are also now included as a primary outcome, where previously they were included in the secondary outcomes. Other outcomes remain the same.

INDEX TERMS

Medical Subject Headings (MeSH)

Androstadienes [therapeutic use]; Anti-Inflammatory Agents [*therapeutic use]; Antibodies, Monoclonal [therapeutic use]; Antibodies, Monoclonal, Humanized; Eosinophilia [*drug therapy]; Esophagitis [*drug therapy]; Fluticasone; Prednisone [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans