

# Recognition, assessment and management of eosinophilic oesophagitis

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Received 26 March 2013

Accepted 4 June 2013

Published Online First

28 June 2013

## ABSTRACT

Eosinophilic oesophagitis (EO) is a chronic immune/antigen-mediated oesophageal disease, with the immune reaction most likely directed to foods but on occasion also to aeroallergens. Clinically, it is characterised by symptoms of oesophageal dysfunction in subjects who typically have other indicators of an atopic tendency. Older children (and adults) frequently present with dysphagia and can have strictures (which may require dilatation). The diagnosis is dependent on an eosinophil-predominant oesophageal inflammation, with 15 or more eosinophils per high-powered field, now generally accepted as a necessary cut-off level of infiltration, which together with other clinical data (eg, oesophageal pH/impedance studies) can help discriminate EO from other potential causes of symptoms such as gastro-oesophageal reflux disease. Recommended therapies, which may need to be long term, are dietary antigen exclusion (with elemental feeds or an exclusion diet) and/or topical corticosteroids.

## INTRODUCTION

Eosinophilic oesophagitis (EO) is a chronic immune-mediated inflammatory disease of the oesophagus characterised by eosinophilic infiltration and gastrointestinal (GI) symptoms suggesting oesophageal dysfunction. The most likely cause is an immune reaction to food or inhaled antigens, with management directed to allergen avoidance and/or topical corticosteroids. Clinically and histologically, there are several similarities with gastro-oesophageal reflux disease (GORD). Recently developed and refined diagnostic criteria have significantly helped clarify case definition, which is dependent on the degree and localisation of the eosinophilic infiltration in cases where GORD (reflux oesophagitis) has been excluded.

## EPIDEMIOLOGY/PATHOGENIC BACKGROUND

Eosinophils have been shown to play a key role in the pathogenesis of EO providing the histological signature of the condition. Eotaxin-3 (an eosinophil chemoattractant) and interleukin-13 (a T-helper 2 cytokine) play a major role in pathogenesis, with mast cell infiltration and activation contributing to the inflammatory process. The inflammatory process is, however, not limited to the epithelium with transforming growth factor- $\beta$  contributing to the development of fibrosis.<sup>1</sup>

In recent years, there have been increasing reports of cases of EO worldwide. In North America (Ohio), from 2000 to 2003, a paediatric incidence of around 1 per 10 000 new cases per year and a prevalence at four per 10 000 has been reported, and in Western Australia and Southern Denmark,

figures for incidence of 0.89 per 10 000 and 0.16 per 10 000 have been published.<sup>2–4</sup> Studies consistently show a male predominance (70%–75% of cases). An association of EO with urban areas has also been suggested.<sup>5</sup> Such an observation if further confirmed offers an interesting parallel with other atopic disease such as asthma.

The question remains as to whether this relatively newly described condition is truly becoming more common, or whether the current reported cases represent changes in case definition/better case ascertainment. Large retrospective reviews of oesophageal biopsy specimens (1982–1999) have suggested that many historic cases can be redefined as EO, and that much of the apparent emergence of EO over recent decades can be explained by better disease recognition, and probably also greater availability of upper GI endoscopy with more frequent mucosal biopsy.<sup>6</sup> Others have, however, suggested that the recent increase in incidence is a true change.<sup>3</sup>

## CLINICAL FEATURES

The classical patient with EO is male (male to female ratio of 3:1), atopic and presents with upper GI symptoms in childhood or the third or fourth decade of adult life. The nature of the upper intestinal symptoms varies according to the age of presentation. Typically, in infants and toddlers, the main symptoms are feeding difficulties, vomiting, regurgitation and feed refusal, which can result in poor weight gain. Later in childhood, and also in adulthood, patients typically present with symptoms of retrosternal pain, upper abdominal pain, dysphagia and food impaction (table 1). In a minority of cases, where the allergy reaction appears to be directed to aeroallergens, symptoms may vary through the year reflecting the seasonality of the allergen.

Since EO is a relatively recently characterised condition, its long-term natural history has not been fully described. Spergel has reported the outcome of a large cohort of cases over a 14-year period, with resolution over time occurring in only a small minority. Older cases tend to have more oesophageal strictures implying progression to fibrosis.<sup>7</sup>

Many of the clinical features of EO are similar to GORD (table 2), but lack of response to proton pump inhibitor (PPI) therapy and/or lack of evidence of reflux with oesophageal pH and/or impedance monitoring support a diagnosis of EO (discussed below under 'treatment'). Being a histologically defined entity, upper GI endoscopy with mucosal biopsy is required to establish the diagnosis.

**To cite:** Fell JME. *Arch Dis Child* 2013;**98**:702–706.

**Table 1** Symptoms suggestive of eosinophilic oesophagitis at different ages

| Infant/toddler                                       | Older child/adult                                    |
|------------------------------------------------------|------------------------------------------------------|
| Feed aversion                                        | Dysphagia                                            |
| Regurgitation/vomiting                               | Epigastric pain                                      |
| Fail to thrive                                       | Retrosternal pain                                    |
| GORD-type symptoms not responding to medical therapy | GORD-type symptoms not responding to medical therapy |
|                                                      | Food impaction                                       |
|                                                      | Oesophageal stricture                                |

GORD, gastro-oesophageal reflux disease.

## DIAGNOSIS AND INVESTIGATION

### Endoscopy

Endoscopy with mucosal biopsy is necessary to establish a diagnosis of EO. Certain macroscopic appearances have been described in EO, such as oedema, longitudinal furrowing, transient and fixed oesophageal rings, which are sometimes described as trachealisation, diffuse oesophageal narrowing and whitish exudates (figure 1). The mucosa may be prone to laceration and bleeding, a tendency that can cause significant complications when a stricture is dilated. Normal appearances are, however, not infrequent even in cases where subsequent biopsy demonstrates significant eosinophilia.<sup>8</sup> It is currently recommended that 2–4 mucosal biopsy specimens should be obtained from the proximal and distal oesophagus to maximise the diagnostic yield,<sup>9</sup> and to help distinguish from distal reflux oesophagitis inflammation. Multiple biopsies from each site reflect the patchy nature of the infiltrate in some cases. The exact number of biopsies is not as yet completely mandated, but one systematic study showed that three biopsies from different sites were required to achieve a diagnosis of EO in 97% of cases.<sup>10</sup> There is also a role for repeat endoscopy and biopsy to confirm the diagnosis in cases where there is diagnostic doubt following the initial endoscopy, for example, in patients who have not been treated with

**Table 2** Discriminators and similarities between eosinophilic oesophagitis and reflux oesophagitis

| EO                                                   | GORD                                                             |
|------------------------------------------------------|------------------------------------------------------------------|
| Clinical                                             |                                                                  |
| Vomit/epigastric pain                                | Vomit/epigastric pain                                            |
| Food impaction in older children/adults              | Food impaction rare                                              |
| Male to female ratio of 3 : 1                        | Male to female ratio of 1 : 1                                    |
| Usually associated with atopy and food sensitisation | May be associated with atopy and food sensitisation              |
| Oesophageal impedance/pH study                       |                                                                  |
| Normal (or mild GOR)                                 | Identifies GOR                                                   |
| Endoscopy                                            |                                                                  |
| Oesophagitis/furrowing/trachealisation/white papules | Oesophagitis (distal)                                            |
| Histopathology                                       |                                                                  |
| Proximal and distal inflammation                     | Distal inflammation                                              |
| Epithelial hyperplasia                               | Some epithelial hyperplasia                                      |
| 15 or more eosinophils per high-powered field        | Typically scanty eosinophils (occasionally more in atopic cases) |

EO, eosinophilic oesophagitis; GOR, gastro-oesophageal reflux; GORD, gastro-oesophageal reflux disease.

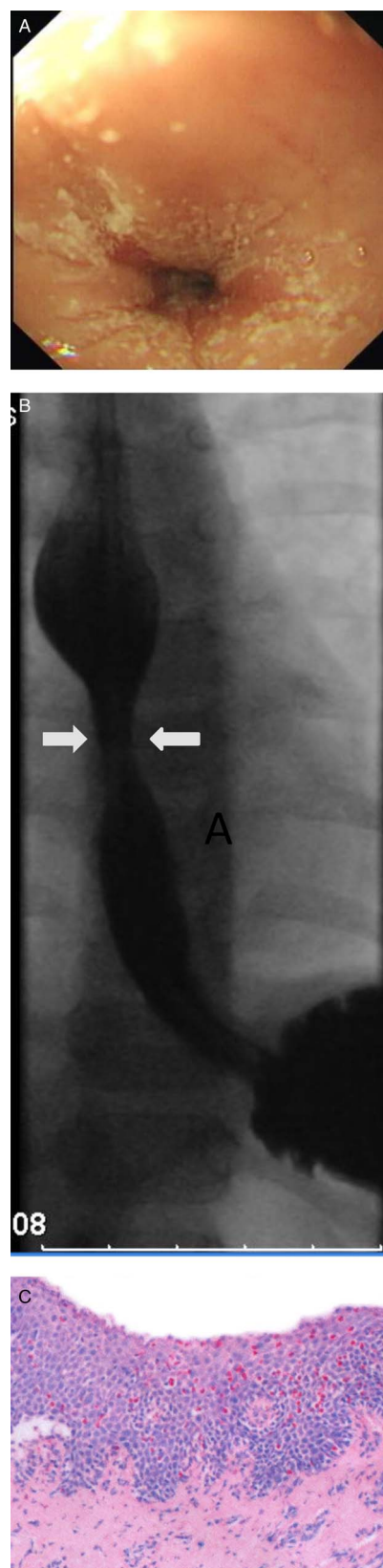


**Figure 1** An example of some of the typical features of eosinophilic oesophagitis. (A) Endoscopic view of the mid-oesophagus showing pinpoint white exudate proximal to a structure. (B) Mid-oesophageal stricture identified at barium swallow. (C) Typical histopathological features of eosinophilic oesophagitis; basal zone hyperplasia with elongation of papillae and infiltration of the epithelium by numerous eosinophils.

## Review

PPIs, and also as a means of assessing and confirming the response to therapy.

Apart from oesophageal pH/impedance monitoring that will help to distinguish EO from GORD, other assessments of the oesophagus may also be undertaken, particularly in cases presenting with dysphagia. Upper GI contrast radiological study may identify, for example, a stricture (figure 1) although such findings are not always confirmed at endoscopy, suggesting transient contraction. Disordered motility can be confirmed by manometry studies, with a variety of abnormalities reported in EO. Endoscopic ultrasound has also been used to assess the deeper oesophageal structures. A study of 11 children reported significant thickening of the oesophageal wall, with not only the mucosa affected but also the submucosa and muscularis propria.<sup>11</sup>

### Histology

In a healthy oesophagus, eosinophils are not present in the oesophageal mucosa. An oesophageal eosinophilic infiltrate can occur in association with more generalised GI or eosinophilic disorder (eg, inflammatory bowel disease or hypereosinophilic syndrome), or be localised to the oesophagus (eg, GORD or EO) (table 3). The biopsy findings thus need to be interpreted in relation to the biopsy site (proximal/distal oesophagus) and in the clinical (symptom/atopic) context. Furthermore, the recent description of cases with an eosinophilic infiltrate that respond to PPI therapy (but do not have GORD) has raised the prospect of a related clinical entity of 'PPI-responsive oesophageal eosinophilia' (discussed below under the heading, 'treatment').<sup>12</sup>

With these diagnostic caveats, oesophageal eosinophilic infiltration is one of the characteristics of EO. An arbitrary cut-off of 15 or more eosinophils in at least one high-powered field is now generally accepted as necessary to aid this diagnosis in all but exceptional circumstances<sup>9 13</sup> (figure 1). Further features also reported include eosinophilic microabscesses and eosinophil degranulation in the presence of eosinophils in superficial epithelial layers. Basal zone hyperplasia and papillary lengthening are also well described together with deeper lamina propria fibrosis. Other inflammatory cells have also been identified in the epithelium, notably mast cells, as well as lymphocytes and polymorphonuclear leucocytes.

### Allergy testing

As well as a personal and family history of allergic disease, specific testing for sensitisation to food and/or aeroallergens can help establish an EO diagnosis. These include skin prick tests (SPTs) or specific IgE radioallergosorbent test (RAST), which not only aid diagnosis but can also to a degree direct dietary

therapy (see below). Peripheral blood eosinophil counts and total IgE levels are also often elevated.<sup>14</sup>

## TREATMENT

### Elimination diets

The success of elimination diets in the management of EO not only offers an effective therapy for the condition but also provides strong evidence for dietary sensitisation as the cause of oesophageal inflammation in many cases. The choice of diet, its initiation, monitoring and maintenance, often long-term, represents a significant challenge for the physician, the dietician, child/patient and family. Although various strategies have been proposed, they essentially fall into three broad approaches: feeding exclusively on an amino acid formula diet, the elimination of specific foods as guided by allergy testing or an empirical exclusion diet that excludes common potential food triggers.

#### Hypoallergenic, amino acid-based formula diet

Using an amino acid-based formula as the sole source of nutrition was first described in 1995.<sup>15</sup> In a small series of 10 affected children, the authors reported clinical response and resolution in the eosinophilic infiltration. Although the efficacy of this therapeutic approach has been confirmed,<sup>16</sup> its use in clinical practice has been limited by the acceptability of the stringent diet, which often requires tube feeding (nasogastric or gastrostomy). This has resulted in its use tending to be restricted to younger children with multiple food allergies. With relatively rapid histological remission reported (4–5 weeks), the children can then progress to systematic food reintroduction.

#### Specific food elimination (allergy test guided exclusion)

The exclusion of specific foods that have been identified by allergy testing to be potential triggers for oesophageal inflammation is an attractive alternative to an amino acid formula diet. Unfortunately, SPTs and RASTs have a poor predictive value for identifying those foods that induce inflammation. Spergel has, however, reported a high clinical and histological response rate (77% of 112 patients) after 6 weeks of an exclusion diet guided by the results of combined SPTs and atopy patch tests (APT).<sup>17</sup> In general, however, APTs are not widely used in clinical practice, which limits the practical application of this approach.

#### Elimination of likely food triggers

An alternative approach is to eliminate foods that have been commonly implicated in EO, namely, cow's milk, egg, wheat, soya, peanut and fish/shellfish (six food exclusion). Using this diet, Kagalwalla *et al*<sup>18</sup> reported clinical and histological remission in 74% of 35 children at 6 weeks.

If dietary manipulation (4–6 weeks amino acid formula and 8–12 weeks elimination diet) is successful in achieving a remission, then foods can be reintroduced. This process not only makes the prescribed elimination more tolerable, but can also further identify causative foods.<sup>19</sup> The clinical responses can be further validated by repeat mucosal biopsy, which also applies to most of the therapies described here.

## PHARMACOLOGICAL THERAPY

Not all cases of EO are suitable for dietary therapy. The child (or adult patient) may not be prepared to accept the dietary restrictions or may fail to respond to this approach. Furthermore, a subgroup of EO cases appears not to be sensitised to foods but to aeroallergens. These cases often tend to have a seasonal variability to their symptoms and will require

**Table 3** Causes of oesophageal eosinophilia

| Localised oesophageal disease           | Part of a generalised gastrointestinal or systemic disease |
|-----------------------------------------|------------------------------------------------------------|
| Eosinophilic oesophagitis               | Eosinophilic gastroenteritis                               |
| PPI responsive oesophageal eosinophilia | Crohn's disease                                            |
| Gastro-oesophageal reflux disease       | Hypereosinophilic syndrome                                 |
| Infection (Candida, Herpes)             | Connective tissue disease                                  |
|                                         | Drug hypersensitivity                                      |

PPI, proton pump inhibitor.

medicines to alleviate symptoms. The mainstay of drug therapy is the topical administration of corticosteroids, although PPIs have a general role to play, and so in practice, combinations of drugs and diets are often employed.

### Proton pump inhibitor therapy

In some cases, patients with oesophageal eosinophilia respond to PPIs. The term 'PPI responsive oesophageal eosinophilia' has been devised to account for these cases.<sup>12</sup> The clinical response to PPIs may also point to a diagnosis of GORD, which can be further confirmed by oesophageal pH monitoring/impedance study, although the histological distribution of the infiltrate is characteristically of distal location. These alternative diagnoses have led to the recommendation of a trial period of PPI treatment (2 months at 1 mg/kg twice daily)<sup>9</sup> prior to other EO therapies and the inclusion of prior PPI therapy in the diagnostic criteria for EO.

Although the mechanism by which PPIs influence oesophageal eosinophilia is not clear, regression of the eosinophilic infiltrate has been reported in a significant number of cases with typical EO phenotype following PPI treatment.<sup>20–21</sup> PPIs may also be useful as 'co-therapy' in EO by alleviating symptoms of secondary GOR.<sup>9</sup>

### Corticosteroids

Topical corticosteroids have been shown to be effective in inducing clinical and histological response (and remission) in children and adults with EO. Thus far, two preparations have been assessed, namely, fluticasone and budesonide. Fluticasone can be administered by metered-dose inhaler. Since the aim is topical application, the doses are deliberately swallowed, with the recommendation not to eat or drink for 30 min thereafter. Alternatively, oral viscous budesonide, typically the type of preparation used for a nebuliser, can be used.<sup>9</sup> The nebuliser budesonide suspension can then be mixed with sucralose (a food additive) to aid administration.

The efficacy of these approaches has now been confirmed by randomised controlled trials. For example, Dohil *et al*<sup>22</sup> reported the effects of treating 24 children with EO with either oral viscous budesonide or placebo (divided dose of 1–2 mg/day depending on the size) for 3 months (together with lansoprazole in all cases). Symptoms improved in 87% of oral viscous budesonide treated cases compared with no improvement in the placebo group. This was associated with a similarly significant difference in response to mucosal eosinophil counts.

The inflammatory process in EO is not confined to the epidermal layer and indeed some cases may present with severe dysphagia making topical therapy difficult. In such cases, conventional oral corticosteroids may have a role, with trial data demonstrating efficacy.<sup>23</sup> The side effects of oral therapy, however, limit its use to short courses in severely affected cases.

Topical therapy has relatively few side effects although fungal infection (candida) is a recognised potential complication. Unfortunately, at the end of a treatment course, relapse is common, leading on to longer term therapy. Low-dose topical corticosteroids are an option in this scenario and have been evaluated with some success, both clinical and histological, when used as maintenance for 1 year.<sup>24</sup> If this strategy is adopted for children, then careful monitoring for evidence of adverse effects, for example, on growth, will be essential.

### Other medical therapy

Other medical therapies such as cromolyn sodium and leukotriene receptor antagonists have not been shown to be effective

in treating EO. The same applies in the case of the small number of patients treated with azathioprine, 6-mercaptopurine, anti-tumour necrosis factor and anti-IgE monoclonal therapy. Anti-interleukin-5 therapy has also been evaluated, but results have been disappointing. Although the treatment resulted in a reduction in the mucosal eosinophil infiltrate, this was not associated with clinical symptom resolution.<sup>25</sup>

### Oesophageal dilation

Oesophageal strictures, which are a recognised complication of EO, can be effectively managed with oesophageal dilation. There have been concerns as to the risk of complications such as oesophageal perforation and haemorrhage. Large case series, mainly in adult practice, have now been reported with a relatively reassuring outcome. For example, Schoepfer *et al*<sup>26</sup> described the outcome of 207 patients, concluding that the risk of complications was not excessive, although postprocedure pain was common. The underlying inflammatory process is not improved following dilation, and so concomitant medical therapy is still recommended.<sup>9</sup>

### CONCLUSION

There is still significant scope for improving the diagnostic methods and treatment options for EO. Diagnosis currently depends on endoscopy and biopsy, which may need to be repeated to monitor the therapeutic response. Furthermore, even with endoscopy discrimination from GORD is not always straightforward, particularly, since PPI therapy can significantly influence the histological findings. There is thus a need for non-invasive tests for diagnosis and disease monitoring. A recent study, which measured eosinophil-derived proteins in luminal secretions to distinguish between EO and GORD, is a promising step in this direction.<sup>27</sup> Treatment options are also unfortunately limited. If an exclusion diet is not successful, or causative foods cannot be identified, then long-term elemental feeding or corticosteroid therapy may become necessary. The development of effective alternative therapy is thus a priority, particularly since progression to fibrosis/stricture formation is not an uncommon outcome.

**Competing interests** None.

**Provenance and peer review** Commissioned; internally peer reviewed.

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*Arch Dis Child* 2013 98: 702-706 originally published online June 28, 2013

doi: 10.1136/archdischild-2012-302838

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