# Eosinophilic oesophagitis – A guide for primary care

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### *Background*

Eosinophilic oesophagitis (EoE) is an increasingly recognised inflammatory disorder of the oesophagus. The incidence of this chronic, food-triggered disease is rising in Australia and diagnosis should be considered in patients who complain of dysphagia.

### *Objective*

This article provides an overview of the pathogenesis, evaluation and management of EoE. It is intended as a useful tool for general practitioners (GPs) in the primary care setting and to raise awareness of EoE.

### *Discussion*

EoE is an increasingly prevalent allergic disorder of the oesophagus. It is characterised clinically by symptoms of oesophageal dysfunction and microscopically by eosinophilic inflammation of the oesophagus. Treatment involves avoiding trigger foods and corticosteroid therapy, which may be necessary intermittently or long term, given the relapsing nature of the condition. EoE can significantly impair quality of life and GPs are key to recognising the disease and directing patients' long-term care.


Eosinophilic oesophagitis (EoE) is a chronic inflammatory disorder of the oesophagus that leads to oesophageal dysfunction and symptoms including dysphagia and heartburn. The first cases of oesophageal eosinophilia were described as early as the 1960s and 1970s. However, EoE was formally recognised in a 1993 case series describing patients with oesophageal eosinophilia that lacked evidence of acid reflux.[1–3] In the past, most cases of EoE were labelled as gastro-oesophageal reflux disease (GORD). However, this diagnosis came to be questioned, given that patients' oesophageal pH studies were normal and symptoms were non-responsive to acid suppression.[4]

## Aetiopathogenesis

The current understanding of EoE pathogenesis is limited. It is a chronic disease that involves an interrelationship between genetic and environmental factors. Alteration in the host's immune response manifests as an allergic oesophageal reaction to food-based proteins consumed in the diet. Antigens from various foods (eg milk, wheat, soy, eggs and seafood) have been implicated.

Chronic inflammation and eosinophilic infiltration of the oesophagus leads to deposition of subepithelial fibrous tissue.[5] Oesophageal remodelling and dysfunction follow with time. At end-stage, the disease may progress to a strictured lumen, which causes dysphagia and produces food bolus obstruction.[6]

EoE is a distinct clinical and pathological entity that is not analogous to GORD. It is different from GORD as it is not associated with acid reflux.

## Epidemiology

The prevalence of EoE in Australia is estimated to be 1 in 100 adults and 1 in 10,000 children.[7] Its prevalence appears to be rising, and studies have shown that detection is growing at rates not accounted for by improved awareness alone.[8] The hygiene hypothesis has been suggested as a cause.[5,9]

Most patients will have a history of other atopic conditions (eg asthma, allergic rhinitis or atopic dermatitis). EoE is more common in males, and usually presents in those aged 40 years and younger.[6] Family history is evident in only 7% of cases.[5]

## Clinical features

The clinical features of EoE differ depending on the patient's age. Children are likely to present with difficulty feeding, failure to thrive or vomiting. Adolescents and adults generally complain of difficulty swallowing or food impaction.[4,10] Other symptoms may include heartburn, dyspepsia and chest pain. Many patients come to attention after undergoing acid-suppression for presumed GORD, which results in minimal improvement in their symptoms.

The natural history of EoE is largely unknown. Case-control series suggest that most untreated patients develop symptoms eventually, that their symptoms rarely self-resolve and, in most instances, worsen over time.[11–17] EoE is accompanied by a diffuse loss of oesophageal compliance. In critical disease, patients present with food bolus impaction as a result of a narrow-calibre oesophagus and dysmotility.[12] Patients with advanced forms of the disease are at risk of spontaneous oesophageal perforation (Boerhaave's syndrome) and perforation during endoscopy, both of which have been reported in Australia.[18,19]

Chronic EoE is not known to induce intestinal metaplasia, or evolve into Barrett's oesophagus, and does not predispose to oesophageal adenocarcinoma.[6]

## Investigations and diagnosis

The diagnosis of EoE should be based on symptoms, endoscopic appearance and histological findings. The most widely accepted diagnostic criteria were released by the American College of Gastroenterology (ACG) in 2013 (*Box 1*).

The initial diagnostic test for patients suspected with EoE should be an upper gastrointestinal (GI) endoscopy with biopsies. Diagnosis requires persistent oesophageal eosinophilia following a course of proton pump inhibitor (PPI) treatment. PPI treatment for a period of 8 weeks (as per ACG guidelines) preceding the diagnosis of EoE is important to distinguish between true EoE and GORD.[20] Many patients undergo immediate upper GI endoscopy prior to commencement of a PPI trial because dysphagia is an alarm symptom for cancer. Repeat endoscopy following completion of PPI treatment could determine the persistence of eosinophilia.

Histological diagnostic criteria require a minimum of 15 eosinophils per high power field (hpf) on microscopy.[6,20] Most gastroenterologists prefer to take biopsies from multiple sites in the proximal and distal oesophagus because the distribution of EoE can be patchy.[20] There is a range of conditions that may cause eosinophilic inflammation (*Box 2*), and it is important to consider and exclude these if appropriate.

A number of endoscopic features can be identified in EoE. Endoscopic abnormalities are visible in 90% of cases (*Box 3*; *Figure 1*).[5]

Radiological investigations are generally unhelpful in EoE, although they can offer additional information when searching for alternative diagnoses. For example, barium swallow may occasionally detect stricture length or highlight segmental indentations from severe trachealisation.

**Box 1. Diagnostic criteria of eosinophilic oesophagitis[20]**

Includes all of the following:

- symptoms related to oesophageal dysfunction
- ≥15 eosinophils/hpf on oesophageal biopsy
- persistence of eosinophilia after a proton pump inhibitor trial
- secondary causes of oesophageal eosinophilia excluded.

**Box 2. Causes of oesophageal eosinophilia[9,20]**

- Eosinophilic oesophagitis
- Gastro-oesophageal reflux disease
- Proton pump inhibitor-responsive oesophageal eosinophilia
- Achalasia
- Crohn's disease
- Parasitic infection
- Drug hypersensitivity
- Connective tissue disease (eg scleroderma, dermatomyositis)
- Coeliac disease
- Hypereosinophilic syndrome

**Box 3. Endoscopic features of eosinophilic oesophagitis[5]**

- Longitudinal furrows
- Trachealisation
- White exudate
- Wall friability
- Narrowing
- Loss of vascular pattern

### Differentiating EoE from GORD

Many patients with EoE are misdiagnosed with GORD. Differentiating EoE from GORD is important and usually straightforward (*Table 1*). Both conditions can present with dysphagia, but heartburn and regurgitation tend to be the most prominent presenting symptoms in GORD. This is particularly true in adults. Oesophageal pH and impedance studies will identify GORD, but these measurements are seldom undertaken in clinical practice. The characteristic endoscopic findings of EoE are lacking in patients with GORD. Both conditions can feature eosinophilia on biopsy, but levels are typically higher in EoE.

Consideration must also be allowed for 'PPI-responsive oesophageal eosinophilia'. This is a recently devised term that describes patients with oesophageal eosinophilia in whom PPI therapy is effective despite having no evidence of acid reflux.[21] PPI-responsive EoE remains a poorly understood entity. Some suggest that PPIs have a direct anti-inflammatory effect, which causes eosinophil regression, whereas others regard these cases as a subtype of GORD where improvement is due to the anti-secretory effect of PPIs.[21] The practical relevance of this condition is yet to be determined.

## Management

Treatment of EoE consists of dietary, pharmacological and endoscopic interventions. There are no Australian clinical guidelines for the management of EoE. In many cases, treatment decisions are empirical and the use of pharmacological therapies are off-label.

### Dietary modification

Dietary modification is an effective first-line treatment for EoE in children and adults. There are three dietary methods that have gained widespread acceptance.

### Targeted elimination diet

This approach involves removal from the diet of foods identified on allergy testing or patient history. Allergy testing typically involves skin prick or patch tests of a wide variety of foods.[22] Although this approach is often preferred by patients, the success rate is <50%.[23]

### Six food elimination diet

This involves avoidance of the six food types that are most commonly associated with allergy. Milk and wheat are the most frequently implicated foods.[1,22] Other foods include eggs, soy, nuts and seafood. A comprehensive meta-analysis of dietary interventions showed this method achieved histological remission in approximately 72% of patients.[23] The six food elimination diet is probably the preferred dietary therapy, given its relatively high success rate and acceptability by patients.[23]

### The elemental diet

This regimen substitutes all food intake with a liquid formula composed of amino acids, carbohydrates, fats and minerals. The success rate of elemental diets is in the order of 90% but, in practice, they are rarely tolerated by patients.[23] Barriers include high cost, unpleasant taste and the need to forgo all food, with the social limitations that entails.

## Pharmacological treatment

Medical management is necessary in patients who do not respond to dietary measures alone. Topical glucocorticoids, namely fluticasone and budesonide, are currently regarded as the initial therapy of choice. Although there are no direct comparative data available, both agents are regarded as efficacious.[5]

These agents are administered by having the patient swallow glucocorticoid solutions, which would normally be inhaled, thereby coating the oesophagus. This is an off-label use of these preparations in Australia. Fluticasone is delivered via a metered dose inhaler (MDI) without a spacer. The drug should be sprayed into the mouth and the patient should be instructed to swallow the contents with 5 mls of water instead of inhaling it. Budesonide is available as a liquid suspension, usually for nebulisation, but for EoE this viscous slurry should be delivered by swallowing. Patients should not eat or drink for 30 minutes following administration, to allow sufficient bind time in the oesophagus.

Studies have consistently shown that both topical agents provide resolution of symptoms and eosinophilic inflammation in the majority of patients.[24–26]

Optimal dosing is yet to be established and there are no current Australian guidelines. However, recent recommendations have been issued by the ACG. The ACG suggests that patients placed on a budesonide suspension should be prescribed 1 mg daily if younger than 10 years of age, or 2 mg daily for older children or adults.[27] With regard to fluticasone, dosages recommended by the ACG are unavailable in Australia.

For example, the ACG recommends that children aged 1–4 years should be started on a 44 µg inhaler, with two sprays twice daily.[27] The lowest dose option available in Australia is a 50 µg inhaler, so it is reasonable in the Australian setting to prescribe 50 µg with two sprays twice daily. Patients aged 5–10 years should take a 100 µg inhaler, two sprays twice daily, whereas older children and adults can be prescribed a 250 µg inhaler, two sprays twice daily. Adults may be titrated to a maximum of 1750 µg per day if necessary.[27,28] These doses as outlined are available in Australia and deviate only marginally from ACG recommendations.[27,29]

Most patients are treated with an 8-week course of topical steroids and re-assessed. The vast majority will be symptom-free following this treatment.[30,31] Patients who remain symptomatic require a repeat of the 8-week prescription. Studies have shown that topical glucocorticoid therapy usually

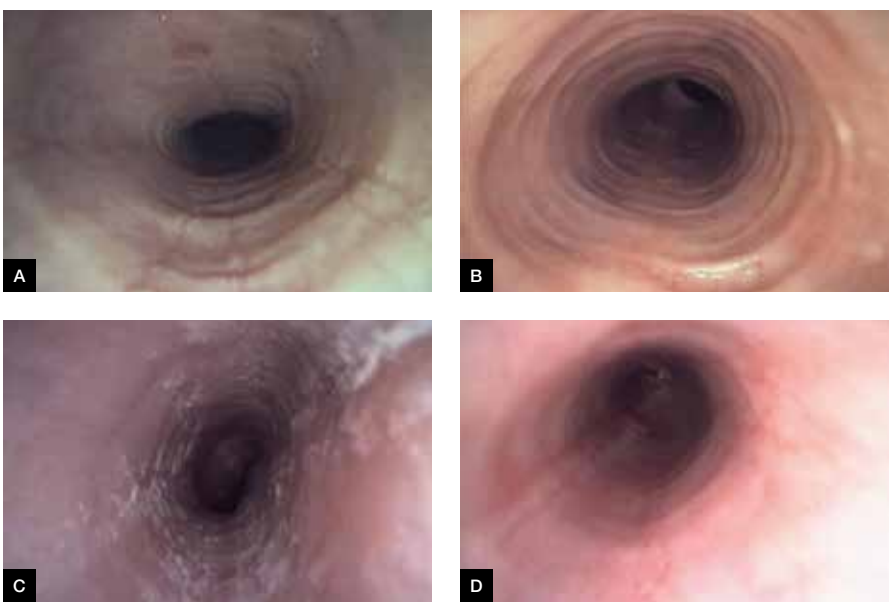


**Figure 1**. Major endoscopic features of eosinophilic oesophagitis[5]

*(A) Longitudinal furrows; (B) Concentric rings of the oesophageal wall, properly termed trachealisation given the resemblance to the trachea; (C) White exudates; (D) Loss of vascular markings implying oedema of the oesophageal mucosa.*

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induces symptomatic remission for approximately 4–6 months, but almost never more than 12 months, after which a second course of steroids is generally necessary.[30–32] These data apply to patients not commenced on dietary modification, which should provide a longer period of remission if implemented in addition.[32]

Consensus on an appropriate maintenance regimen for EoE has not been reached. The disease almost always recurs in patients who discontinue treatment and it is generally agreed that ongoing therapy, whether dietary or pharmacological, is necessary.[6] The strategy accepted by most gastroenterologists is to aim for a nutritional regimen that keeps the patient asymptomatic, and to supplement this with topical glucocorticoids only on an as-needed basis.[32,33]

The correlation between symptoms and the histological severity of EoE is weak, so periodic surveillance endoscopic examination is probably warranted.[9] An upper GI endoscopy every three years seems reasonablr for asymptomatic patients or those who require short courses of topical steroids to ensure adequate disease control on histology.[6] Therapy can be adjusted accordingly if biopsies reveal ongoing subclinical disease. Endoscopy should be repeated early in patients whose symptoms change or worsen.[6]

Maintenance therapy with topical agents is generally well tolerated. However, candidal oesophagitis is reported in 15–20% of patients and may be an explanation if symptoms worsen.[30,34]

Expert consensus recommends systemic steroid treatment for patients with debilitating disease or disease unremittent to topical steroids. Several trials have shown the rapid efficacy of oral corticosteroids for EoE but not confirmed if they are superior to topical agents.[27,30,35]

## Endoscopic treatment

Oesophageal dilation is very effective in widening the oesophageal diameter and providing rapid relief of dysphagia.[27] It is usually reserved for patients who have failed more conservative measures, or whose oesophageal stenosis is critical.[34] This process is onerous for the patient as it involves a series of endoscopic treatments over several weeks.

The results are unlikely to be permanent as endoscopic dilation has no therapeutic effect on the underlying inflammation. Trial data suggest that patients treated with dilation alone (without dietary modification or pharmacotherapy) can expect to remain asymptomatic for approximately 2 years before symptoms return.[36,37]

The risks include a small but significant chance of laceration, bleeding and perforation during the procedure.[36–39] Approximately 2% of patients are also hospitalised with severe post-procedural chest pain, which exposes them to potentially unnecessary work-up or treatment for what is usually a self-resolving discomfort.[40]

## Other considerations

Avoiding allergens can often reverse the disease process of EoE. Successful implementation of a suitable dietary plan can be made easier with assistance from a dietitian. Resources for patients can be found in *Box 4*.

There is a role for acid suppression in patients with EoE, but it is not a curative measure. The already inflamed oesophagus in EoE is predisposed to injury and hypersensitive to physiologic levels of acid exposure.[41] PPI therapy can aid healing and improve symptoms, but it fails to induce total histological remission.[5] A suitable PPI regimen for adults with EoE is omeprazole 20 mg taken once-daily before meal.[25,41] Children can be prescribed esomeprazole at a daily dose of 0.4–0.8 mg/kg.[42]

## Summary

EoE is a chronic, relapsing, food-triggered inflammatory disorder with increasing prevalence in Australia. The recognition of EoE as a distinct entity is a major advance for patients presenting with dysphagia and food bolus obstruction.

**Table 1. Discriminators of eosinophilic oesophagitis and reflux oesophagitis[10]**

| Eosinophilic oesophagitis | Gastro-oesophageal reflux disease |
|---|---|
| **Clinical** | |
| • Food impaction in older children and adults<br>• Male to female ratio = 3:1<br>• Usually atopic comorbidities | • Food impaction rare<br>• Male to female ratio = 1:1<br>• Occasionally atopic comorbidities |
| **Oesophageal impedance and pH studies** | |
| • Normal | • Evidence of acid reflux |
| **Endoscopy** | |
| • Classic features (*Box 3*) | • Distal oesophagitis |
| **Histopathology** | |
| • Proximal and distal inflammation<br>• Epithelial hyperplasia<br>• ≥15 eosinophils/hpf | • Scanty eosinophils (sometimes widespread) |

**Box 4. Patient resources for allergy and dietary advice**

- Australasian Society of Clinical Immunology and Allergy: www.allergy.org.au
- Allergy and Anaphylaxis Australia: www.allergyfacts.org.au/
- Food Allergy Week: www.foodallergyaware.com.au
- Dietitians Association of Australia: www.daa.asn.au

EoE requires long-term multimodal care. The general practitioner will often be required to coordinate a management plan with specialists and allied health practitioners. Structured evaluation and regular reassessment in primary care are fundamental for the successful management of EoE.


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