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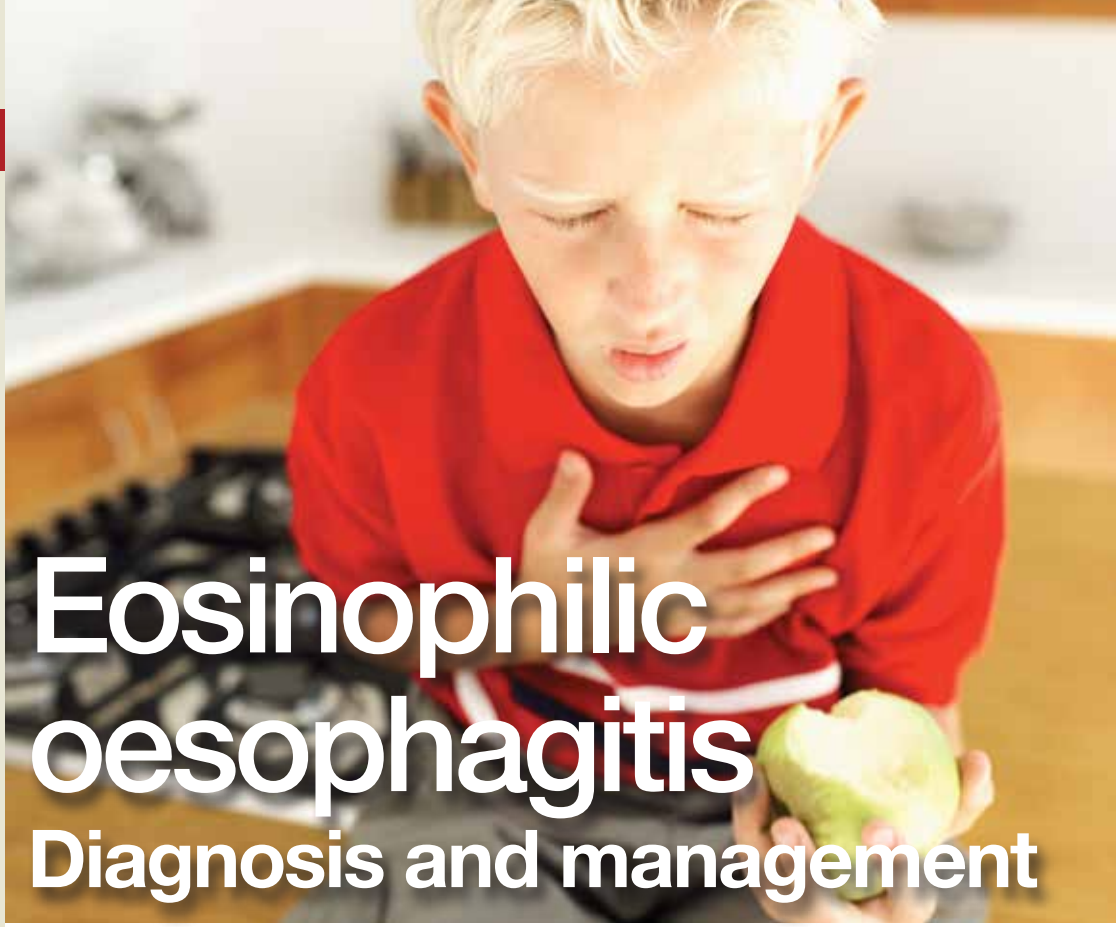

Eosinophilic oesophagitis
Diagnosis and management

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Eosinophilic oesophagitis is an immune-mediated disease that is increasingly being recognised and should be considered in any patient presenting with a swallowing difficulty. Diagnosis relies on endoscopy and histological examination of oesophageal biopsy specimens. Treatment options include medication, diet and oesophageal dilatation.

Key points

- Eosinophilic oesophagitis (EoE) is an increasingly recognised cause of dysphagia and food impaction; other presentations include chest pain and refractory heartburn.
- EoE is associated with atopic conditions such as asthma, allergic rhinitis and atopic dermatitis.
- As dysphagia is an alarm symptom, affected patients should be referred for investigation, particularly to exclude oesophageal malignancy.
- Diagnosis of EoE relies on clinical and pathological features.
- Typical features include oesophageal rings, linear furrows, white exudates and crepe-paper mucosa seen on endoscopy, and eosinophil-predominant inflammation on histological examination of biopsy specimens.
- Treatment options include diet, drugs and oesophageal dilatation; long-term strategies may be needed to prevent complications such as oesophageal stricture.

Eosinophilic oesophagitis (EoE) is an increasingly recognised cause of dysphagia in both children and adults and is typically associated with atopic conditions, including asthma. Its diagnosis is based on clinicopathological features and it should be considered in anyone presenting with a history of a swallowing difficulty.

EoE was first recognised as a distinct entity in 1993, although it was initially described in 1978.[1] Currently EoE is defined as a chronic, immune-mediated oesophageal disease characterised clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation. Uncertainty exists regarding the most accurate means of diagnosis, as well as the natural history and long-term management of this condition.

EPIDEMIOLOGY

Estimations of the prevalence of EoE range from 0.2 to 4 per 1000 among asymptomatic patients, but EoE is found in up to 15% of patients undergoing gastroscopy for dysphagia.[2] The incidence and prevalence of EoE are rising, with proposed explanations including expanding awareness of the condition, increasing numbers of endoscopies being undertaken as well as the hygiene hypothesis, in which limited exposure to microorganisms in childhood may result in hypersensitivity (as postulated for asthma and other allergic conditions).

Males are affected by EoE more commonly than females, with a reported sex ratio of 3:1. Although EoE affects all age groups, presentation is typically in childhood or during the third or fourth decades of life. Seasonal and

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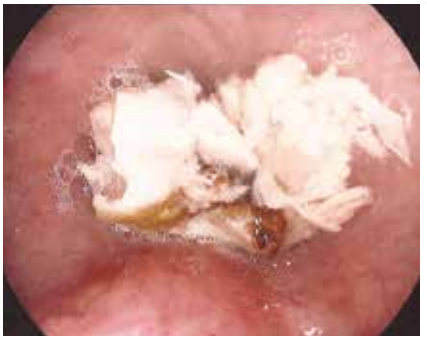
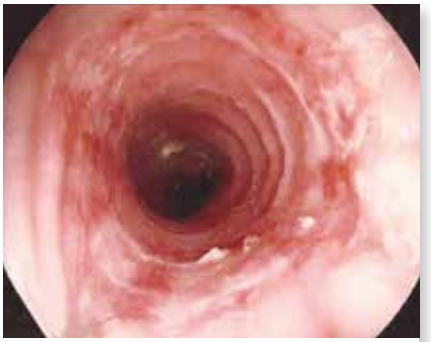




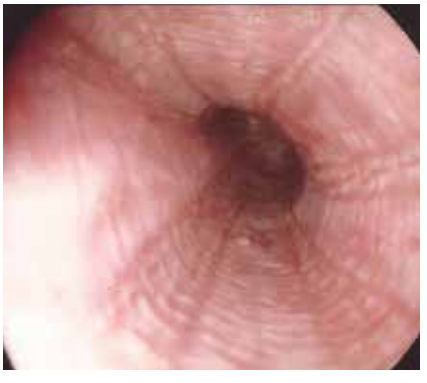
Figures 1a and b. Endoscopic appearance of the oesophagus in a patient with eosinophilic oesophagitis. a (left). Food bolus obstruction in the lower oesophagus. b (right). The oesophagus after removal of the food bolus showing rings and friable mucosa.

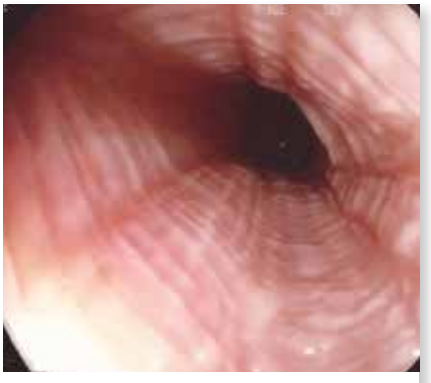
geographical variations have been observed, a likely reflection of the atopic aetiology of EoE. The disorder is associated with other atopic conditions, including asthma, allergic rhinitis and atopic dermatitis, as well as IgE-mediated food allergies. These conditions are thought to be 50% more common among people with EoE than in the general population.

PATHOGENESIS

EoE is classified as a T helper type 2 (Th2) mediated response to allergens, characterised by production of antigen-specific IgE in predisposed individuals. On re-exposure to the allergen, cross linking of IgE molecules bound to mast cells results in activation of these cells and release of mediators, including interleukin-5, which is an eosinophil activator. Activated eosinophils release preformed proinflammatory and profibrotic proteins and enzymes, with resultant tissue damage and oesophageal remodelling. For example, transforming growth factor beta (TGF-β1) produced by eosinophils is thought to play an important role in pathogenesis by initiating epithelial mesenchymal transformation and resultant fibrosis of the oesophagus.[3]

A genetic predisposition is likely to contribute to the development of EoE, with a number of variants in proinflammatory and epithelial cell genes being associated with EoE susceptibility.[4] These include variants in the gene encoding eosinophil chemoattractant eotaxin-3 (also known as CCL26).





Figures 2a and b. Oesophageal rings seen on endoscopy in patients with eosinophilic oesophagitis. a (left). Felinisation of the oesophagus, with transient stacked concentric rings and prominent linear furrows. b (right). Trachealisation of the oesophagus, with fixed rings creating a trachea-like appearance.

1. CHARACTERISTIC ENDOSCOPIC FEATURES OF EOSINOPHILIC OESOPHAGITIS

- Oesophageal rings
- Longitudinal linear furrows
- White exudates
- Friable oesophageal mucosa

CLINICAL FEATURES

Dysphagia and food impaction are the most common symptoms in EoE, and the condition is the underlying aetiology in up to half of the patients who present with a food bolus obstruction requiring endoscopic management (Figures 1a and b). Less common symptoms include chest pain, dyspepsia, upper abdominal pain and refractory heartburn. Clinicians should also be vigilant for compensatory behaviours, such as prolonged chewing, avoidance of particular foods such as meat and bread, and deliberate drinking of liquids after eating solid food.

SPECIALIST REFERRAL

Dysphagia is an alarm symptom, and any patient presenting with this or other alarm symptoms, such as haematemesis, weight loss or odynophagia, needs to be referred for investigation. A particular concern is to exclude an oesophageal malignancy.

DIAGNOSIS

Diagnosis relies on endoscopy of the oesophagus and histological examination of oesophageal biopsy specimens.

Endoscopic features

The characteristic endoscopic features of EoE are listed in Box 1. The hallmark endoscopic feature is the presence of oesophageal 'rings' (Figures 1b, 2a and 2b). Stacked transient concentric rings give an appearance similar to that of a cat's distal oesophagus, termed felinisation of the oesophagus. Fixed rings give a tracheal appearance, termed trachealisation. Other features of EoE include narrowing

of the oesophagus, longitudinal linear furrows and white exudates representing eosinophilic microabscesses. The oesophageal mucosa can be fragile, with reduced elasticity, termed crepe-paper mucosa (Figure 1b). This is associated with a risk of mucosal laceration and perforation on introduction of the endoscope.

However, in up to 10% of patients with EoE the oesophagus has a normal endoscopic appearance.[5] Hence biopsy is important when the diagnosis is being considered.

Additional indirect visualisation of the oesophagus, such as with a barium swallow, is unhelpful and is not recommended in the investigation of patients with suspected EoE. However, oesophageal pH monitoring can be a useful additional diagnostic test to evaluate for gastro-oesophageal reflux disease (GORD) in patients with oesophageal eosinophilia (see below).

Histological features

Classically, the detection of more than 15 eosinophils per high power field (HPF) on microscopic examination of oesophageal biopsy specimens has been considered necessary for the histological diagnosis of EoE. However, this definition is not always reliable as oesophageal eosinophilia may be patchy in EoE and patients with GORD alone may have 15 or more eosinophils per HPF. Additional histological features to assist with the diagnosis of EoE have been recognised, including eosinophil degranulation and eosinophilic microabscesses (Figure 3). If sufficient tissue is obtained, fibrosis of the lamina propria may also be evident. There does not appear to be a relationship between the severity of symptoms and histological findings.

Given the potential for patchy distribution of lesions in EoE, it is essential that multiple biopsies are taken from different sections of the oesophagus in all patients with unexplained dysphagia, even if endoscopic findings are normal. Two to four mucosal biopsies from the proximal and distal oesophagus are recommended.[6]

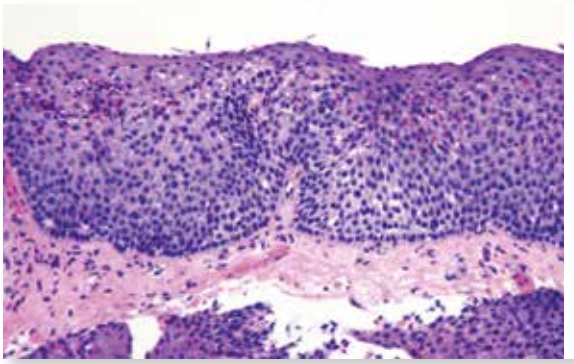


Figure 3. Oesophageal biopsy specimen showing florid eosinophilic oesophagitis, with a count of eosinophils (red-stained cells) of more than 50 cells per high power field and microabscesses.

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Antral and duodenal biopsies are also recommended, to exclude other causes of eosinophilic infiltration such as eosinophilic gastritis and enteritis.

In addition to histological findings of oesophageal eosinophilia, several studies have reported peripheral eosinophilia in adults and children with EoE, but the clinical utility of this finding remains questionable. Similarly, there are insufficient data to support measurement of serum IgE levels as a surrogate indicator of histological inflammation.[6]

Differential diagnosis

In recent years, the existence of eosinophilic infiltration responsive to proton pump inhibitor (PPI) therapy has been recognised but is yet to be completely defined. It is uncertain whether this represents a distinct entity, a variant of EoE, co-existing GORD and EoE, or merely GORD with eosinophils present secondary to associated oesophageal injury.[7] Features of EoE that may help differentiate it from GORD include younger patient age, symptoms of dysphagia, documented food allergies, endoscopic appearance, histological findings of a higher maximal eosinophil count and eosinophil degranulation, and persistence of oesophageal eosinophilia after a course of PPI therapy.[8]

In addition to GORD, further differential diagnoses for a finding of oesophageal eosinophilia include eosinophilic gastroenteritis, Crohn's disease, parasitic infections, hypereosinophilic syndrome, achalasia, connective tissue diseases and drug hypersensitivity.[9]

TREATMENT

There is no role for empirical therapy in EoE and a histological diagnosis is required before treatment. Once EoE has been diagnosed on clinicopathological grounds, the aims of treatment are:

- to facilitate symptom control and histological improvement
- to correct or prevent potential complications, including oesophageal strictures, food impaction and secondary oesophageal rupture.

Treatment options for EoE are summarised in Box 2. They can be regarded as the three 'Ds': drugs, diet and dilatation.[10] Initial treatment involves the use of a PPI. Following this, the choice lies between further medical therapy or an elimination

2. TREATMENT OPTIONS FOR EOSINOPHILIC OESOPHAGITIS

Medication

- A proton pump inhibitor trial should be first-line therapy
- Topical corticosteroids are the mainstay of current drug treatment

Diet

- Potential role for:
  - Elemental diet
  - Six-food elimination diet
  - Targeted elimination diet

Dilatation

- Consider oesophageal dilatation if there is significant luminal narrowing that does not respond to medical therapy

diet. Thorough evaluation by an allergist or immunologist may also be necessary when EoE is diagnosed to identify and control concurrent atopic diseases.

Medications

Proton pump inhibitors. Given the potential for PPI-responsive eosinophilic oesophageal infiltration, a trial of a PPI is recommended in the first instance when EoE is suspected. Potential explanations for the benefits of PPI use in EoE include the postulated anti-inflammatory effects of PPIs, as well as healing of the disrupted epithelial barrier, preventing further immune activation.[6] The recommended dose is 20 to 40 mg, once or twice daily for eight to 12 weeks. If there is no clinicopathological response to PPI therapy despite patient adherence, with either persistence of symptoms or no reduction in the degree of eosinophilia on repeat oesophageal biopsy, then the diagnosis of EoE is more certain. Nonetheless, PPIs may be useful as conjunctive therapy in patients with EoE, given their potential to improve symptoms secondary to coexisting GORD.

Topical corticosteroids. Notwithstanding the role of PPIs, topical corticosteroids are the current predominant pharmacological therapy used for EoE. Corticosteroids improve histological and endoscopic appearance of the oesophagus and, to a lesser extent, symptoms.[11] The formulation and duration of corticosteroid therapy depend on disease severity and the patient's lifestyle and compliance with medication. Although systemic and topical corticosteroids have equal efficacy, topical formulations are preferred to minimise adverse events. Prescription of topical corticosteroids for EoE remains an off-label indication.

Currently, topical administration involves swallowing a corticosteroid that is usually inhaled for asthma therapy, such as fluticasone (250 μg, three puffs swallowed twice daily) or budesonide (400 to 800 μg swallowed twice daily) in either multidose inhalers or nebuliser solutions. Patients should be advised to rinse their mouths following each use of a topical corticosteroid to prevent oral candidiasis. Oral viscous budesonide has shown impressive outcomes in clinical trials but is currently not available commercially.[9]

Follow-up endoscopy is recommended after six to eight weeks of topical corticosteroid therapy. If symptoms and eosinophilia have improved then maintenance treatment can be considered; however, if clinical response has been inadequate then alternative options could be trialled. These include a longer course or higher dose of topical corticosteroids, systemic corticosteroids, dietary therapy or dilatation. Novel medical therapies such as anti-interleukin-5 therapy with mepolizumab are currently being investigated.

The optimum duration of therapy is yet to be determined. Cessation of inhaled corticosteroids is associated with symptom recurrence, occurring in up to 91% of patients at a mean of 8.8 months.[12] A recommendation to try to prevent recurrence includes initial regular therapy for four to eight weeks, followed by on-demand therapy.[13]

Dietary therapy

Dietary therapy is of particular interest in the treatment of children, and can lead to near complete resolution of symptoms as well as histological improvement. General strategies for food elimination in EoE include an elemental diet, the six-food elimination diet and a targeted elimination diet.

Elemental diet. An elemental formula consisting of amino acids, basic carbohydrates and medium chain triglycerides has been shown to be effective in children. This diet has also been examined in adults, with only a 50% partial response being demonstrated, possibly reflecting limited compliance.[14] Wider use of an elemental diet is compromised by expense, poor palatability and frequent need for nasogastric tube delivery.

Six-food elimination diet. The focus has now turned to the six-food elimination diet, which involves avoiding milk, soy, wheat, eggs, peanuts/tree nuts and fish/shellfish, although wheat and milk have been found to have the strongest association with EoE. This diet has been shown to significantly improve symptoms and reduce the endoscopic and histopathological features of EoE in adults.[15]

Targeted elimination diet. The third approach to diet is the targeted elimination diet, in which food allergens identified by allergy testing are eliminated. The best approach to food allergen identification remains uncertain, and the utility of this diet in adults is questionable.

The current recommendation is that dietary therapy should be considered in all children with a diagnosis of EoE and also in motivated adult patients. The involvement of a dietitian is recommended.[6]

Oesophageal dilatation

Until recently, there were many reservations about the use of endoscopic dilatation of the oesophagus in EoE because of concerns about the increased risk of oesophageal perforation. However, several studies have recently suggested that dilatation in EoE is safer than originally thought.[16] Nevertheless, given the potential for mucosal tears following dilatation, patients should be warned about the possibility of post-procedure pain, which may be a clue to this complication.

Currently, in the absence of high-grade oesophageal stenosis, an initial trial of medical or dietary therapy is suggested, whereas dilatation should be considered if high-grade strictures are present. The use of dilatation alone does not, however, address the underlying issue of inflammation.

CONCLUSION

EoE is an increasingly recognised cause of dysphagia and often presents with food impaction. Other presenting symptoms include chest pain, dyspepsia and refractory heartburn, and the condition can result in significant morbidity in both adults and children. The diagnosis is based on the finding of more than 15 eosinophils per HPF on histological examination of oesophageal biopsy specimens in patients with suggestive symptoms. Treatment options include medications (PPIs and ingested topical corticosteroids), dietary therapy and endoscopic dilatation when complicating high-grade oesophageal strictures are present.

Despite significant progress in the past 20 years, continuing research is required to further characterise the pathogenesis and natural history of EoE, as well as to determine the most reliable diagnostic methods and effective management pathways. MT

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