

Eosinophilic Oesophagitis (EoE): An update

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ABSTRACT

EoE is a relatively newly recognised chronic immune mediated disease, which is increasing in incidence and prevalence in western populations. It frequently presents in Caucasian males between the third and fourth decade with a history of atopic disorders. Symptoms are related to oesophageal dysfunction and commonly include dysphagia and food bolus impaction. Recognition of food or aero allergens by the immune system triggers a Th2 response which is mediated by a number of cytokines including IL-5, IL-13 and eotaxins. The resulting eosinophil predominant chronic inflammation leads to oesophageal remodelling and is responsible for the clinicopathological features of the disease. The key histopathological feature of EoE is 15 eosinophils/high power field in the oesophageal mucosa. Endoscopic features, whilst not diagnostic, are nonetheless highly characteristic and include the loss of the normal vascular pattern, fragility of the mucosa and fixed oesophageal rings. Prompt diagnosis and treatment are important, as untreated disease leads to fibrostenotic complications. The mainstay of treatment for EoE is topical steroid therapy which has been proven to be effective in both reducing eosinophilic inflammation and improving symptoms. Long-term use may be needed however; as there is a high relapse rate on discontinuing therapy. Other pharmacological treatments such as sodium cromoglycate and thiopurines are either ineffective, of limited benefit or have insufficient evidence of efficacy. Some patients with

EoE respond to PPI therapy and may represent a distinct condition called PPI responsive oesophageal eosinophilia (PPI-REE). The six food elimination diet (SFED) is effective in improving histological appearances and symptoms.

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Key words: Eosinophilic oesophagitis; Immune mediated; Oesophageal dysfunction

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INTRODUCTION AND BACKGROUND

Eosinophilic oesophagitis (EoE) represents a 'chronic, immune-mediated oesophageal disease characterized clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation^[1]. The allergic inflammatory response is triggered by food or aero antigens in genetically predisposed individuals^[2]. EoE is characterised by symptoms of oesophageal dysfunction, such as dysphagia and food bolus obstruction^[3](Figure 1), in conjunction with typical endoscopic and histological appearances. This review is focussed on adult EoE as paediatric EoE is considered as a separate pathological entity.

Oesophageal eosinophilia was described in a patient with achalasia in 1978^[4] and subsequently in patients with gastro-oesophageal reflux disease (GORD) symptoms in 1982^[5]. The association with oesophageal dysfunction however was first described by Attwood *et al*^[6] in 1993. EoE has since become an increasingly recognised problem., indeed the most common cause of food bolus obstruction in young adults^[7]. There is associated dysphagia in over 90% of cases^[8]. Other symptoms of EoE include retrosternal discomfort and intractable dyspepsia which is not (or only partially) responsive to PPIs^[9].



Figure 1 A food bolus obstructing the oesophageal lumen of a patient with EoE (also seen are characteristic oesophageal rings).

EPIDEMIOLOGY

The incidence and prevalence of EoE in the UK is unknown and estimates elsewhere vary considerably. A Swedish study found EoE in four out of 1000 normal subjects^[10], whilst in the United States of America (USA) the incidence has been estimated at 1/10,000 new cases per year, with the prevalence estimated at 0.5-1 in 1000^[7].

The reported incidence and prevalence of EoE in western populations has greatly increased over the last decade^[8,11-13]. This may in part be due to an increased awareness of the disease, but a true increase in incidence remains likely.

EoE is more common in males^[7] and often occurs in individuals with a history of other allergic disorders such as asthma, allergic rhinitis, eczema, or hay fever^[14].

PATHOPHYSIOLOGY

Recognition of food or aero antigens by the immune system leads to cytokine-mediated T helper type 2 (Th2) inflammatory response resulting in eosinophilic infiltration and inflammation of the oesophagus^[15].

The Th2 response is characterized by the activation of B cells by antigen exposure, with the production of neutralizing non-cytolytic antibodies and activation of eosinophils and mast cells. Th2 cells mediate these functions by producing various cytokines such as Interleukin 13 (IL-13), Interleukin 15 (IL-15), eotaxin-3^[16] and transforming growth factor β (TGF- β)^[17]. IL-5 and IL-13 recruit and activate eosinophils; IL-13 is additionally able to activate epithelial cells to secrete eotaxins, which are eosinophil chemo-attractants^[18].

Oesophageal remodelling

Chronic oesophageal eosinophilia leads to tissue damage and alterations in oesophageal wall structure, including epithelial hyperplasia, sub-epithelial fibrosis, smooth muscle hyperplasia and angiogenesis. These are referred to collectively as “oesophageal remodelling”^[19].

Epithelial mesenchymal transition (EMT) is thought to play a pivotal role in the fibrosis seen in EoE and is mediated in part by TGF- β ^[20]. EMT is the process whereby epithelial cells lose their

characteristic histological and immunohistochemical properties (such as apical-basal polarity, surface markers and tight junctions) to transform into cells with the characteristic properties of mesenchymal cells. Oesophageal EMT has been demonstrated to regress with treatments for EoE that are able to decrease oesophageal eosinophilia^[20].

Microscopic oesophageal mucosal structure and permeability

Allergens are recognised by the immune system after they have permeated deep within the oesophageal mucosa. Allergens may be able to gain such deep-seated access to the mucosa in EoE due to an increase in oesophageal permeability (also referred to as reduced mucosal integrity). Histologically, the widening of the gap between epithelial cells (known as dilated intercellular spaces or spongiosis) may allow the paracellular transport of allergens into the mucosa and underlies the increase in permeability; indeed, spongiosis is a recognised feature of EoE^[21].

Furthermore, spongiosis is regulated by tight junction proteins which interconnect cell membranes; treatment of EoE with topical steroids has been found to not only decrease the amount of spongiosis, but also to increase levels of tight junction proteins^[22].

In conjunction with increased intercellular spaces, decreased oesophageal transepithelial electrical resistance (TER) and increased transepithelial small-molecule flux have been found in EoE, compared to healthy controls^[23]. TER and transepithelial small-molecule flux are both *in vitro* measures of mucosal permeability and indicate that this is indeed impaired in EoE.

Oesophageal permeability can also be determined *in vivo*. Electrical tissue impedance spectroscopy (ETIS)^[24] is measured endoscopically and is known to correlate with *in vitro* measures of permeability^[23]. Baseline electrical impedance of the mucosa (using a trans-nasal pH-impedance catheter) has also been used to assess permeability and has been demonstrated to be significantly lower in EoE patients, in comparison to healthy controls^[25].

Oesophageal permeability: cause or effect?

There is an increase in mucosal permeability in EoE and one possibility is that this phenomenon may be a primary or inherent defect which allows allergens to gain access to the mucosa. The temporal sequence of events in EoE is however not entirely clear and it may be that chronic eosinophilic oesophageal infiltration and inflammation are in fact precursors to increased permeability. This perspective is supported by evidence to suggest that treating EoE improves mucosal structural integrity^[22,26]. Furthermore, in rat models, gastric acid exposure to oesophageal mucosa first results in sub-mucosal inflammation and only later spreads to the mucosal surface, causing loss of integrity^[27].

OESOPHAGEAL REMODELLING AND BIOMECHANICS OF SWALLOWING

Oesophageal remodelling in EoE is likely to be the key process which underlies the functional consequences of dysphagia and food bolus obstruction. Numerous studies have examined either macroscopic oesophageal structure or the biomechanics of peristalsis and food bolus propulsion in EoE. A number of abnormalities have been demonstrated which may help to explain the clinical features of EoE.

Oesophageal luminal diameter

Oesophageal luminal narrowing on barium studies^[28] and at

gastroscopy^[29] has been observed in EoE which may thus (according to Poiseuille's law) underlie a degree of oesophageal dysfunction. Such narrowing may in part be due to mucosal inflammation and oedema which improves with topical steroid therapy^[28]. Fibrosis and strictures which are seen in up to 30% of patients^[30] cause a fixed luminal narrowing and must play an important role in symptoms, particularly food bolus impaction^[31]. Indeed endoscopic treatment of strictures significantly improves dysphagia but has no impact on the underlying inflammatory process^[32].

Oesophageal circular muscle and lower oesophageal sphincter (LOS)

High-resolution oesophageal manometry (HRM) in EoE has demonstrated a number of abnormalities such as an increased frequency of bolus pressurisation and weak (or absent) peristalsis when compared to normal controls, there was however no significant difference when compared to patients with GORD^[33]. LOS and distal oesophageal dysfunction have also been described in a sub-set of patients with EoE^[29], but HRM is frequently normal and there is no evidence to suggest that there are any pathognomonic HRM findings.

Oesophageal longitudinal muscle

Oesophageal longitudinal muscle (LM) contraction can be assessed by intraluminal ultrasound imaging. A study using simultaneous HRM and intraluminal ultrasound found that there was selective dysfunction of the LM in EoE^[34]. Such dysfunction may contribute to dysphagia and is either mediated by inflammation targeting the LM specifically or by fibrosis in the mucosa and submucosa.

Oesophageal distensibility and compliance

Oesophageal distensibility (expandability) is measured using the Endoscopic functional luminal imaging probe (EndoFLIPTM). In a study of 33 EoE patients and normal controls using EndoFLIPTM it was demonstrated that oesophageal distensibility is reduced in EoE^[35]. Such reduction in distensibility has been proposed to be secondary to fibrosis and would affect bolus propulsion during peristalsis.

DIAGNOSING EOE

The diagnosis of EoE requires the demonstration of oesophageal dysfunction as well as compatible histological findings, sometimes supported by characteristic endoscopic appearances.

In EoE eosinophil infiltration is limited to the oesophagus. Other conditions where oesophageal eosinophilia is a feature (e.g. GORD, coeliac disease, Crohn's disease, achalasia, connective tissue disease and hypereosinophilic syndrome) should be excluded before the diagnosis is made^[1]. Furthermore EoE should remit with dietary exclusion, topical corticosteroids, or both.

Endoscopic appearances

Upper gastrointestinal endoscopy often shows loss of the normal vascular pattern (due to oedema), fragility of the mucosa, exudates (also referred to as white spots or plaques), fixed oesophageal rings (trachealization; Figure 2), longitudinal furrows or strictures^[30]. However, endoscopy is completely normal in over 40% of cases^[36]; endoscopic changes can be subtle and liable to be missed by the novice endoscopist^[30]. Endoscopic findings suggestive of EoE (e.g. rings, furrows or plaques) have a high specificity (approaching 90%) even though sensitivity may be low^[37].

Two to four biopsy specimens from both the distal and proximal

oesophagus should be obtained^[1]. Taking biopsies of gastric and duodenal mucosa is not however routinely recommended, but should be done when the clinician feels it is indicated. When done, such biopsies may demonstrate the absence of eosinophilic infiltration or help rule out other conditions where oesophageal eosinophilia is a feature.

Histopathological appearances

One or more oesophageal biopsy specimens must show eosinophil-predominant inflammation (Figure 3). 15 eosinophils/high power field (HPF) is considered a minimum threshold for a diagnosis of EoE^[1]. There may be endoscopic sampling error however; it has been reported that over one third of patients who have fewer than 15 eosinophils/high power field (HPF) found initially, will reach the diagnostic criteria on repeat biopsy^[38]. This phenomenon may also

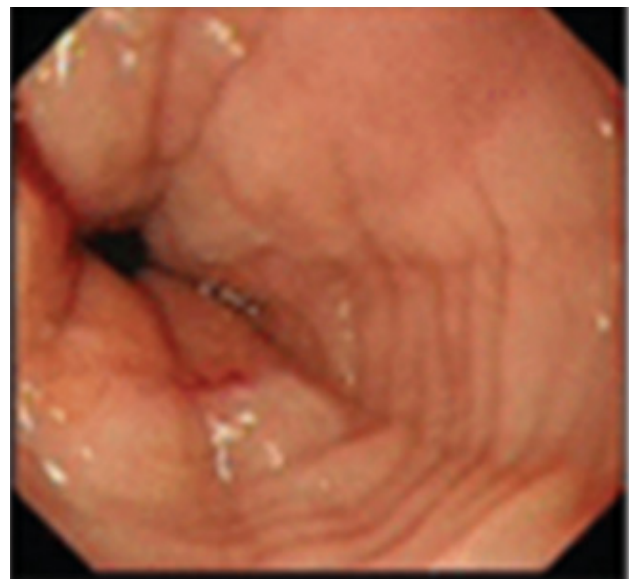


Figure 2 Characteristic ringed appearance seen in the oesophagus of an EoE patient.

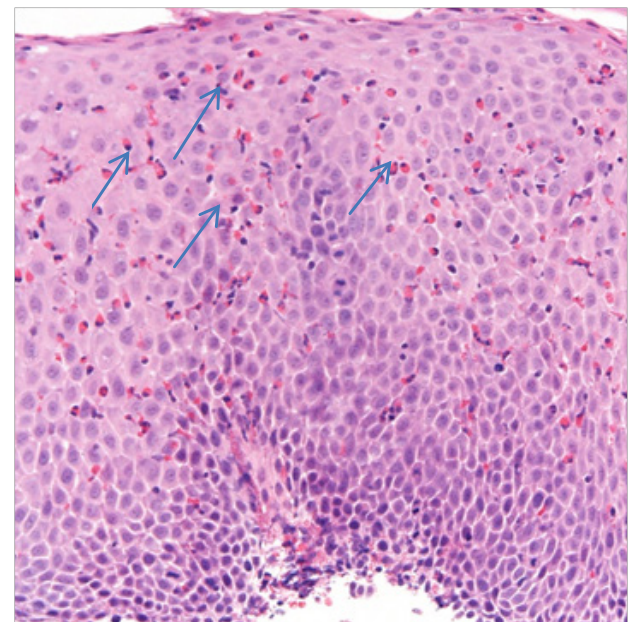


Figure 3 High power photomicrograph of oesophageal squamous epithelium with large numbers of eosinophils throughout (arrows).

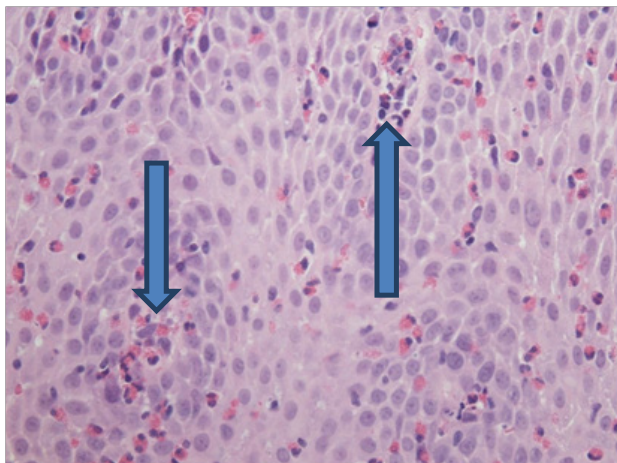


Figure 4 High magnification view of the squamous epithelium of the oesophagus showing numerous eosinophils, some aggregated to form eosinophil microabscesses (arrows).

be due to a partial treatment response. Other histological features of EoE (which may support the diagnosis in those with less than 15 eosinophils/HPF) include eosinophilic microabscesses (intraepithelial cluster of four or more eosinophils) (Figure 4), superficial layering of eosinophils and extracellular eosinophil granules^[1]. Lamina propria fibrosis and basal cell hyperplasia are also seen^[39].

PPI responsive oesophageal eosinophilia

Both spongiosis^[40] and reduced extracellular impedance^[24] are found in patients with oesophageal injury due to gastro-oesophageal reflux. This has raised the question of whether gastro-oesophageal reflux may play a role in the pathophysiology of EoE. Indeed it has been proposed that acid reflux into the oesophagus causes injury which leads to eosinophilic infiltration^[41]. Certainly oesophageal eosinophilia has been found in GORD and there is an overlap in symptoms of GORD and EoE such as dysphagia and chest pain^[5].

Gastric acid suppression with proton pump inhibitors (PPIs) is a mainstay of treatment for GORD. Despite non-responsiveness to acid suppression being amongst the initial diagnostic criteria for EoE^[1], PPIs have been shown to lead to a clinical and histological improvement in a sub-set of patients with symptomatic oesophageal eosinophilic infiltration^[42,43]. Such patients with clinicopathologic features of EoE, but who respond to PPIs, may thus be diagnosed as PPI responsive oesophageal eosinophilia (PPI-REE).

It is not clear if PPI-REE represents a completely distinct disease to EoE. PPI therapy in patients with PPI-REE was found (unlike those with true EoE) to partially restore mucosal integrity^[23]. This improvement may be independent of acid suppression and relates to the ability of PPIs to block Th2 mediated eotaxin-3 (a potent eosinophil chemoattractant) expression in oesophageal squamous cells^[44].

IMPORTANCE OF DIAGNOSIS AND TREATMENT

Patients with EoE have been shown to remain symptomatic for at least 10 years^[45], their symptoms impacting significantly on quality of life. Without effective therapy, chronic, uncontrolled inflammation may evoke irreversible oesophageal remodelling and fibrosis^[46]. Indeed the odds of EoE transforming from an inflammatory to fibrostenotic disease increase significantly with age^[47] and the prevalence of strictures increases with disease duration^[48].

Treatment for EoE has been proven to reverse both microscopic structural integrity^[22], EMT^[20] and oesophageal remodelling in general^[49]. Promptly diagnosing EoE and instigating treatment are therefore imperative.

TREATMENT

Pharmacological: topical steroids

Topical steroid therapy is currently the mainstay of treatment for EoE. Although systemic steroids are effective in EoE^[50] their use is limited by significant adverse effects. Fluticasone propionate and budesonide can be sprayed into the mouth without a spacer and dry-swallowed to provide topical anti-inflammatory effect to the oesophageal body^[51]. Only very small amounts are absorbed, thereby minimising systemic side effects.

There have been numerous trials of topical steroid therapy in EoE, but many are limited by relatively small numbers^[43] and lack of a control group^[52,51]. Other studies which have a control group were not randomised^[53] or blinded^[43]. Despite these disadvantages, most studies have shown topical steroids have generally favourable outcomes in both symptoms and/or histological appearances.

Disadvantages of topical steroids include a high symptomatic relapse rate on stopping the medication^[54] which implies a necessity of recurrent courses and/or long term therapy. Potential side effects of topical steroids include oral candidiasis and although only small amounts are absorbed, there have been case reports of Cushing's syndrome secondary to topical steroid use, although not for EoE^[55].

Pharmacological: other therapies

Leukotriene D4 is a chemotactic factor for eosinophils and thus Montelukast (a leukotriene receptor antagonist used for asthma) was thought to have been of promise in EoE treatment. Although it was reported to be symptomatically beneficial in a small number of EoE patients in an open label trial^[56], large doses were required and it did not produce an improvement in oesophageal eosinophil infiltration. More recently, standard dose (10 mg/day) montelukast was found to be ineffective for maintaining a topical steroid induced symptomatic and histological remission of EoE^[57].

Interleukin 5 (IL-5) plays a key role in regulating the inflammatory cascade in EoE and therefore led to an interest in IL-5 inhibitors (Reslizumab, Mepolizumab) for treatment. Randomised trials of IL-5 inhibitors in EoE have shown reduction in oesophageal eosinophil counts, but have not demonstrated any clear improvement in symptoms^[58,59,60].

Thiopurines have long been used as steroid sparing agents in inflammatory bowel disease. A case report of three patients with steroid dependent EoE showed that thiopurine therapy (azathioprine or 6-mercaptopurine) had a steroid sparing effect^[61].

The mast cell stabiliser sodium cromoglycate has been used in a small number of male paediatric patients with EoE with no improvement found in either eosinophil counts or symptoms^[62].

An open label trial of three patients with EoE found infliximab (anti TNF- α blocker) to be of no benefit^[63].

Monteleukast, sodium cromoglycate, IL-5 inhibitors, infliximab and thiopurines are not considered standard therapy for EoE.

Dietary

Dietary manipulation for EoE is an attractive alternative to pharmacological therapy, particularly when patients are concerned about the effects of long-term medication use. The concept of food allergens playing a role in EoE was demonstrated by an elemental

formula diet being helpful in children who had oesophageal eosinophilia that was not responsive to standard treatment^[64]. Elemental diets are not palatable and are expensive; thus interest led to elimination diets in the treatment of EoE.

The six food elimination diet (SFED) is where six most common food allergens (wheat, egg, milk, soy, nuts and seafood) are initially excluded from the diet and then subsequently reintroduced in a stepwise fashion to assess any causative triggers. SFED is of proven efficacy for adults with EoE for both improving symptoms and reducing eosinophil counts^[65,66].

The disadvantage of the SFED diet is that it may be difficult to follow. Furthermore caution is advised when restrictive diets are followed without proper diagnosis or appropriate supervision by a dietician, particularly in children as they have led to severe nutrient deficiencies in extreme cases^[67].

Endoscopic

Oesophageal strictures are a manifestation of later-stage fibrostenotic disease. Strictures can be dilated endoscopically using balloons or bougies. Despite concerns about the fragility of the oesophagus in EoE with the reported high rates of oesophageal perforation in removing food boluses from such patients^[31], stricture dilatation has been found to be both safe and effective in the long-term^[32].

SUMMARY

EoE is a relatively newly recognised chronic immune mediated disease, which is increasing in incidence and prevalence in western populations.

Frequently presents in Caucasian males between the third and fourth decade with a history of atopic disorders.

Symptoms are related to oesophageal dysfunction and commonly include dysphagia and food bolus impaction.

Recognition of food or aero allergens by the immune system triggers a Th2 response which is mediated by a number of cytokines including IL-5, IL-13 and eotaxins. The resulting eosinophil predominant chronic inflammation leads to oesophageal remodelling and is responsible for the clinicopathological features of the disease.

The key histopathological feature of EoE is 15 eosinophils/HPF in the oesophageal mucosa. Other supporting features include eosinophil microabscesses and basal cell hyperplasia.

Endoscopic features, whilst not diagnostic, are nonetheless highly characteristic and include the loss of the normal vascular pattern, fragility of the mucosa and fixed oesophageal rings.

Prompt diagnosis and treatment are important, as untreated disease leads to fibrostenotic complications.

The mainstay of treatment for EoE is topical steroid therapy which has been proven to be effective in both reducing eosinophilic inflammation and improving symptoms. Long-term use may be needed however; as there is a high relapse rate on discontinuing therapy.

Other pharmacological treatments such as sodium cromoglycate and thiopurines are either ineffective, of limited benefit or have insufficient evidence of efficacy.

Some patients with EoE respond to PPI therapy and may represent a distinct condition called PPI responsive oesophageal eosinophilia (PPI-REE).

Exclusion diets are also used in the treatment of EoE especially when there is concern over long-term use of steroids. The six food elimination diet (SFED) is effective in improving histological appearances and symptoms.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to this review.

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