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# Eosinophilic oesophagitis: clinical presentation and pathogenesis

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## ABSTRACT

Eosinophilic oesophagitis (EoE) is an inflammatory disorder of the oesophagus which has become increasingly recognised over recent years, although it remains underdiagnosed in many centres. It is characterised histologically by a significant eosinophilic infiltration of the oesophageal mucosa (>15 eosinophils per high powered field), and clinically with features of oesophageal dysfunction such as dysphagia, food impaction, and proton pump inhibitor (PPI) resistant dyspepsia. Fibrosis and oesophageal remodelling may occur and lead to oesophageal strictures. An allergic predisposition is common in the EoE population, which appears to be primarily food antigen driven in children and aeroallergen driven in adults. Evidence suggests that the pathogenesis of EoE is due to a dysregulated immunological response to an environmental allergen, resulting in a T helper type 2 (Th2) inflammatory disease and remodelling of the oesophagus in genetically susceptible individuals. Allergen elimination and anti-inflammatory therapy with corticosteroids are currently the mainstay of treatment; however, an increasing number of studies are now focused on targeting different stages in the disease pathogenesis. A greater understanding of the underlying mechanisms resulting in EoE will allow us to improve the therapeutic options available.

## INTRODUCTION

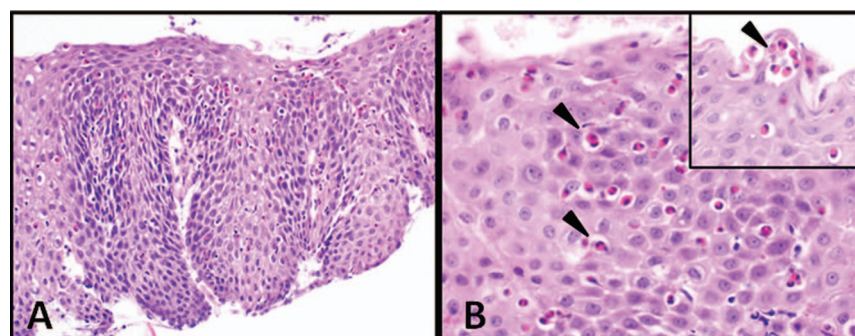
Eosinophilic oesophagitis (EoE) is an inflammatory disorder of the oesophagus which has become increasingly recognised over recent years. The cardinal feature of this disease is a significant infiltration of eosinophils into the epithelial layer of the oesophagus (figure 1). The resulting oesophageal inflammation is accompanied by basal layer hyperplasia and dilated intracellular spaces with

progression to lamina propria fibrosis over time, resulting in narrowing of the oesophagus and stricture formation (see companion article by Kumar *et al*)<sup>1</sup>. EoE is associated with considerable morbidity, and symptoms of dysphagia and food impaction are common. In rare cases rupture of the oesophagus may occur. Despite the significant impact on quality of life, EoE is not associated with an increased mortality and there is no evidence to suggest progression to oesophageal cancer.<sup>2</sup> This paper will describe the epidemiology, clinical presentation, diagnosis, and pathophysiology of EoE. The article by Kumar *et al*<sup>1</sup> will address the investigations and management of EoE.

## EPIDEMIOLOGY

EoE was first described in 1978,<sup>3</sup> but it was not until 1993 that it was acknowledged as a distinct clinicopathological entity separate from other gastrointestinal disorders in which an oesophageal eosinophilia is observed (box 1).<sup>4</sup> EoE is now recognised in up to 1 in 2500 individuals<sup>5 6</sup> with a prevalence in some centres as high as 15% of patients presenting with dysphagia to endoscopy units.<sup>7 8</sup> A significant increase in the number of cases has been reported in recent years, with one study quoting an incidence rise of 4.4–7.4 cases per 100 000 individuals during the period 2005–2011.<sup>5</sup> Whether this observation is due to a true increase in incidence or improved recognition and diagnosis remains under debate, but a study by Hruz *et al*<sup>5</sup> suggests that the incidence is indeed rising.

The onset of EoE has two peaks, one in childhood and the second in the third to fourth decade, although it may present at any age. There is a male preponderance, with a male:female ratio of 3:1.<sup>9</sup>



**Figure 1** Histology images of oesophageal epithelial eosinophilia. (A) Squamous mucosa showing basal cell hyperplasia, elongation of papillae, and numerous eosinophils in the epithelium (haematoxylin and eosin ×100). (B) Eosinophils in squamous epithelium (arrowhead, >30/high powered field). Detail upper right corner: eosinophilic micro abscess (arrow head, H&E ×400).



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**Box 1 Diseases other than eosinophilic oesophagitis associated with an oesophageal eosinophilia**

Gastro-oesophageal reflux disease (GORD)  
 Proton pump inhibitor (PPI) responsive oesophageal eosinophilia  
 Eosinophilic gastrointestinal diseases not isolated to the oesophagus  
 Crohn's disease  
 Coeliac diseases  
 Atopic disorders  
 Infection  
 Hypereosinophilic syndrome  
 Drug hypersensitivity  
 Churg-Strauss syndrome and other vasculitides  
 Graft versus host disease

A recent study indicated that African American males may present with a more aggressive form of EoE earlier than Caucasians<sup>10</sup>; however, further studies are necessary to support this observation and investigate whether the increased prevalence in males and earlier presentation in African Americans is due to the pathogenesis of EoE or is related to social or environmental factors. The current consensus is that there is inconclusive evidence for significant socioeconomic, geographical, and/or ethnic variations.<sup>11–12</sup> A seasonal variation is well documented, with exacerbations and an increased number of new diagnoses of EoE in the spring (33%) compared with winter (16%), which would support an environmental or allergen association.<sup>11–13</sup>

**CLINICAL PRESENTATION AND DIAGNOSIS**

EoE has been defined as 'a chronic, immune-antigen-mediated oesophageal disease characterised *clinically* by symptoms of oesophageal dysfunction and *histologically* by eosinophil-predominant inflammation' (updated consensus on EoE, 2011).<sup>12</sup> The following section will detail the clinical, endoscopic, and histological features of EoE.

**Clinical features and assessment for allergy**

The clinical presentation of EoE varies according to the age of the patient and the severity of the disease (box 2). In children, failure to thrive, choking, regurgitation or vomiting after eating or food refusal is seen.<sup>14</sup> Adolescents and adults classically

**Box 2 Clinical symptoms of eosinophilic oesophagitis in paediatric and adult patients**

Paediatrics  
 Failure to thrive  
 Vomiting/regurgitation  
 Choking  
 Food refusal  
 Adults  
 Dysphagia  
 Food impaction  
 Vomiting  
 Intractable dyspepsia; un/partially responsive to proton pump inhibitor (PPI)

present with retrosternal discomfort, dysphagia to solids (70%),<sup>9</sup> food bolus impaction (33–54%),<sup>15</sup> and intractable dyspepsia (38%) which is typically not, or only partially, responsive to proton pump inhibitors (PPIs). Patients may develop abnormal eating habits to compensate for symptoms, such as eating small pieces of food (taking little bites, cutting up food into manageable pieces), chewing excessively, avoiding foods which are likely to be difficult to swallow (ie, pieces of meat), eating only a soft diet or softening food with sauces and fluid, or vomiting after eating. Symptoms are most frequently chronic and may be intermittent; however, it is not uncommon for patients to present following a short history or even an acute event, especially if food impaction is the predominant feature. A rare but well recognised complication of EoE in adults and children is spontaneous oesophageal perforation. A total of 19 cases of perforation had occurred worldwide by 2011; seven needed surgical intervention but none was fatal.<sup>12–16–17</sup>

Up to three quarters of patients may have a personal or family history of allergy—allergic rhinoconjunctivitis, eczema, and asthma.<sup>18–20</sup> Approximately 50% of patients have peripheral eosinophilia ( $>300\text{--}350/\text{mm}^2$ )<sup>12</sup> or increased levels of serum IgE,<sup>21–22</sup> and 75% have a positive skin prick test to at least one food allergen—most commonly dairy, eggs, peanuts, fish, wheat, soy—or aeroallergens such as dust mite, pollen, and grass.<sup>23</sup> In general, children with EoE tend to have a concomitant allergy to foods, and adults to aeroallergens. This observed difference in allergen sensitivity between adults and children is consistent with the 'allergic or atopic march hypothesis'<sup>14</sup> whereby the atopic phenotype presents early in life as skin rashes (eg, eczema) secondary to food allergens, and progresses with age to upper and lower respiratory tract conditions such as allergic rhinitis and asthma, with a reaction-switch to airborne allergens.<sup>24–25</sup> The importance of taking a thorough allergy history in patients with suspected EoE is highlighted by the finding that elimination of common food allergens has been shown to be of benefit to a proportion of adults<sup>26</sup> and children<sup>27</sup> with EoE. Sufficient evidence is not available to support routine allergy testing in all patients with EoE, and it is generally agreed that these tests should be reserved for individuals in whom the history suggests a food allergen trigger (see article by Kumar *et al*).<sup>1</sup> It is important here to note that the presence of allergy in a patient with dysphagia is not diagnostic of EoE and may be a coincidental finding.

It is impossible to diagnose EoE on clinical history alone, and the examination is usually unremarkable—in particular, there are no identified oral pharyngeal manifestations. Many other oesophageal disorders, including gastro-oesophageal reflux disease (GORD), achalasia, and oesophageal cancer, can present in a similar manner and must be excluded. The diagnosis of EoE is made histologically from oesophageal biopsies taken during endoscopy (see box 1 in article by Kumar *et al*<sup>1</sup> for a complete list of diagnostic criteria for EoE).

**Endoscopic features of EoE**

Endoscopy is an essential tool to aid in the diagnosis of EoE. Although the upper gastrointestinal tract of patients with EoE often look macroscopically normal at endoscopy,<sup>28</sup> endoscopic signs associated with EoE are well documented and a recent grading system has been validated to score the endoscopic assessment<sup>29</sup> (see table 1 in this article and endoscopic views in Kumar *et al*).<sup>1</sup> Features include a narrow calibre oesophagus (9%), which may be characterless (41%) or display longitudinal ridges/furrows (48%), fixed concentric 'corrugated' rings/trachealisation (44%) giving the impression of a trachea, strictures

**Table 1** Endoscopic features of eosinophilic oesophagitis, classification and grading

	Grade 0	Grade 1	Grade 2	Grade 3
<i>Major features</i>				
Oedema (decreased vascular markings, mucosal pallor)	Absent; distinct vascularity present	Loss of clarity or absence of vascular markings		
Fixed rings (concentric rings, corrugated oesophagus, corrugated rings, ringed oesophagus, trachealisation)	None	Mild—subtle circumferential ridges	Moderate—distinct rings that do not impair passage of a standard diagnostic adult endoscope (outer diameter 8–9.5 mm)	Severe—distinct rings that do not permit passage of a diagnostic endoscope
Exudates (white spots, plaques)	None	Mild—lesions involving <10% of the oesophageal surface area	Severe—lesions involving >10% of the oesophageal surface area	
Furrows (vertical lines, longitudinal furrows)	Absent	Present		
Stricture	Absent	Present (specify estimated luminal diameter)		
<i>Minor features</i>				
Crepe paper oesophagus (mucosal fragility or laceration upon passage of diagnostic endoscope but not after oesophageal dilation)	Absent	Present		
Narrow calibre oesophagus (reduced luminal diameter of the majority of the tubular oesophagus)	Absent	Present		

Adapted from Hirano *et al*, 2013.<sup>29</sup>

(21–40%), Schatzki rings, linear superficial mucosal tears and ‘crepe paper’ effect due to mucosal fragility (59%), and eosinophilic abscesses (white speckled exudates, 1–2 mm in diameter, that resemble oesophageal candidiasis) (27%).<sup>30</sup> Adults generally present with more subepithelial fibrosis and oesophageal narrowing than children, and fibrosis increases over time.<sup>2 14</sup> Although endoscopy is vital for the diagnosis of EoE, none of above mentioned findings is pathognomonic.

### Histological features of EoE

Clinical assessment and endoscopic findings may support a diagnosis of EoE, but oesophageal biopsy and histological analysis of tissue sections are required for the definitive diagnosis. In practice the diagnosis of EoE may be missed as oesophageal biopsies are not routinely carried out unless the indication is clear, the clinical suspicion is high, or they are particularly requested by the referring doctor. At least 2–4 biopsies are recommended, taken from both the distal and proximal oesophagus,<sup>14</sup> although some authors have shown that up to 5–6 biopsies are required for >99.9% sensitivity.<sup>27</sup> A definitive diagnosis is made if >15 eosinophils in at least one high powered field (hpf) are seen (figure 1) and this eosinophilia is

isolated to the oesophagus (ie, not present in gastric and duodenal biopsies). Eosinophils stain brightly red with haematoxylin and eosin stain (figure 1). They may be found in clusters called micro abscesses (see inset, figure 1B) and can be found in the squamous oesophageal epithelium or deeper oesophageal tissue layers.

Other diseases, in particular GORD, can be associated with oesophageal eosinophilia (box 1), and should be excluded, although it is rare for oesophageal eosinophil levels in these conditions to exceed 10/hpf. Ideally patients with dyspepsia should have an 8 week empirical trial of a PPI and/or pH studies, to exclude GORD and PPI responsive oesophageal eosinophilia, before reporting a histological diagnosis of EoE (see Kumar *et al*)<sup>1</sup>. If, however, dysphagia is the presenting complaint, patients should proceed directly to endoscopy in order to exclude a more sinister cause such as oesophageal tumour/ulceration.

The only marker currently universally accepted to diagnose EoE is the ‘eosinophil count’ in oesophageal biopsies.<sup>12</sup> In a few cases, however, patients with EoE may have a strong clinical picture of EoE with <15 eosinophils/hpf but have other histological features indicative of eosinophilic inflammation (table 1). Markers such as lamina propria fibrosis (determined by trichrome staining) and basal zone hyperplasia (defined as a percentage of oesophageal epithelial height; moderate 51–75% or severe >75%) have been reported to be more prevalent in adults and children with EoE than in individuals with GORD, and can be used to assess for EoE in conjunction with the eosinophil counts (box 3).<sup>31 32</sup> Furthermore, some studies have reported increased numbers of mast cells and immunoglobulin E (IgE) positive cells,<sup>33</sup> indicating an allergic-type process in the mucosa that differentiates EoE from GORD. Table 2 contains a list of histological markers which differentiate EoE from GORD. The contribution of these markers to the pathology of EoE is discussed further in the pathophysiology section. It is important to note that immunosuppressive medication (in particular steroids) taken at the time of endoscopy may alter the

### Box 3 Oesophageal histological features of eosinophilic oesophagitis

- >15 eosinophils per high powered field
- Micro abscesses
- Surface layering eosinophils
- Extracellular eosinophil granules
- Basal layer hyperplasia
- Dilated intracellular spaces
- Lamina propria fibrosis



**Table 2** Studies that have evaluated histological markers that discriminate eosinophilic oesophagitis from GORD

	Eosinophilic oesophagitis	GORD	Adult/child	Correlation	Reference
Intraepithelial eosinophils*	55 (±27.5)	6.9 (±9.7)	Children	p<0.0001	62
MBP†	1479 (±1290)	59 (±103)	Adult	p<0.001	46
Eotaxin-3‡	2219 (±1782)	479 (±777)	Adult	p=0.01	46
Intraepithelial mast cells*	26.3 (±12.7)	7.8 (±8.9)	Children	p<0.0001	62
TGF-β positive cells in LP*	126 (61–191)	9 (2–24)	Children	p=0.002	31
COX-2‡	0	0.5**	Adult	p<0.01	69

The table summarises studies that have assessed potential laboratory markers to discriminate eosinophil oesophagitis from GORD.

\*Per high powered field

†Maximum staining density, cells/mm<sup>2</sup> (±SD)

‡Monoclonal antibody uptake grading.

\*\*Faint stain in basal layer of epithelium.

COX, cyclo-oxygenase; GORD, gastric oesophageal reflux disease; LP, lamina propria; MBP, major basic protein; TGF-β, transforming growth factor β.

immune cells resident in the biopsy sections and lead to a false negative result when assessing histologically for EoE.

### Pathophysiology of EoE

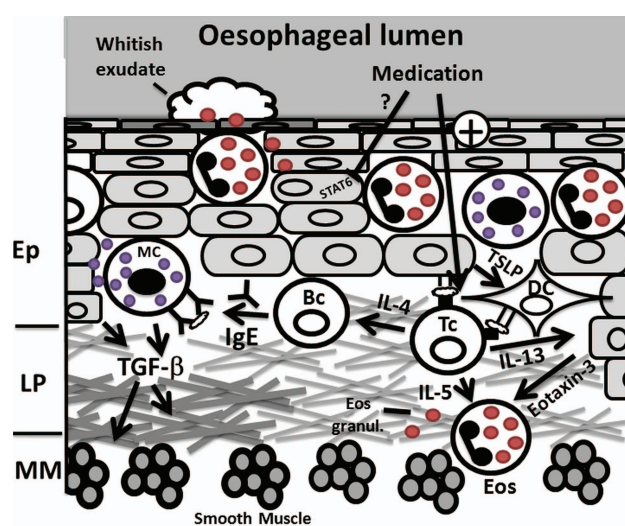
The aberrant processes which trigger and maintain an increased infiltration of eosinophils and other inflammatory cells to the oesophageal epithelium, and the subsequent T helper type 2 (Th2) inflammatory cascade seen in EoE, are not completely understood (figure 2). Both clinical and histological features support a role for allergens in the onset and/or maintenance of the disease. Recent advances in technologies have helped to improve our understanding of the pathophysiology of EoE. In particular, genome-wide analysis studies (GWAS) and mRNA profiling have highlighted candidate genes which may provide an insight into the mechanism of the disease development<sup>34 35</sup>—EoE has been associated with a region on chromosome 5q22 in a paediatric cohort, and the gene for thymic stromal lymphopoietin (TSLP), whose protein product is found overexpressed in atopic disease, is localised to this region.<sup>2 3</sup> The following section will discuss our current understanding of the pathological processes involved in EoE and the evidence supporting the role of each in the pathophysiology of the disease.

### Role of allergens

EoE is strongly associated with allergy. Most patients (70%) with EoE are found to react to either airborne or food allergens.<sup>36</sup> Patients with EoE, who are negative to allergen testing, also have classic cellular markers of allergy in the oesophagus; eosinophils, IgE bearing mast cells, and Th2 lymphocytes are prominent in the oesophagus of EoE patients (see the histology section and figure 2).<sup>37</sup> Furthermore a wealth of literature has documented the benefit of allergen elimination through strict exclusion diets, particularly in children with EoE, which strongly supports the role of allergy in EoE. Almost complete resolution of both clinical and histological abnormalities has been described following exclusion diets<sup>38</sup> and a reversal of oesophageal fibrosis has even been demonstrated in some studies.<sup>27 39</sup> The results in adults are less conclusive, perhaps as the culprit is more likely to be an aeroallergen, rather than food.

### Th2 type inflammation

EoE has been described as an ‘allergen induced disorder’ with a Th2 type inflammatory response. Such a response is



**Figure 2** Mechanism of eosinophilic oesophagitis (EoE). Simplified diagram showing epithelial and immune cells in the oesophageal mucosa during EoE. The mucosa is subdivided into a stratified epithelial layer (Ep), lamina propria (LP) and the smooth muscle layer, mucosa muscularis (MM). Inflammatory cells infiltrating the epithelial layer are eosinophils (Eos, bilobar nuclei, red intracellular granules), and mast cells (MC with blue histamine containing granules). Eosinophils release granules (red stain). B cells (Bc), T cells (Tc) and dendritic cells (Dc) are present in the LP (the cells have been reported to be present in Ep and MM as well). T cells release IL-13 which induces eotaxin-3 production by epithelial cells. Eotaxin-3 is a specific chemoattractant for eosinophils attracting the cells from the peripheral blood. T helper type 2 (Th2) lymphocytes release IL-4 inducing an antibody isotype switch to IgE isotype in B cells. IgE binds to mucosal resident MC's facilitating granule release. Th2 lymphocyte derived IL-5 promotes survival of eosinophils. The epithelium produces thymic stromal lymphopoietin (TSLP) and stimulates Dc's to present allergens for Th2 Lymphocytes. Whitish exudates are present at the epithelium surface due to accumulation of eosinophils. Medications such as proton pump inhibitors (PPIs) may act in an anti-inflammatory capacity through inhibition of the allergy associated transcription factor signal transducer of activator of transcription 6 (STAT-6) or by altering epithelial permeability. Medications such as antibiotics may additionally promote EoE by skewing the immune response from a Th1 to Th2 type. Transforming growth factor β (TGF-β) released by epithelial cells, MC, and Eos induces activation of fibroblasts augmenting fibrosis in the LP and contraction of the mucosa muscularis (MM), the combination of which may lead to pathological features such as strictures.

characteristically induced during allergic reactions and by helminthic infections, and this reaction is also present in the oesophageal mucosa of patients with EoE. The Th2 type inflammation is distinguished by T helper and B lymphocytes, mast cells, eosinophils, and a specific cytokine profile from stromal and epithelial cells.<sup>40</sup> Th2 lymphocytes produce interleukin 4 (IL-4), IL-13, and IL-5, and the mRNA for these cytokines have been found upregulated in the oesophagus of EoE patients.<sup>33 35 41</sup>

IL-4 influences B lymphocytes facilitating antibody class switching to IgE subclass. A recent study demonstrated that the increased expression of IL-4 seen in EoE patients, unrelated to a history of other allergies, was associated with a local immunoglobulin class switching to IgE and IgE production in the oesophageal mucosa of EoE patients.<sup>33</sup> This finding suggests that sensitisation and activation of mast cells involving local IgE may contribute to the pathogenesis of EoE. Unfortunately, a small trial of EoE using a specific anti-IgE antibody (omalizumab) did not reduce oesophageal inflammation.<sup>42</sup> In line with these findings, studies using animal models have demonstrated that antibody-producing B lymphocytes are not necessary for EoE pathogenesis (see below).<sup>43</sup>

IL-13 shares a common signal transduction pathway with IL-4, via the signalling molecule signal transducer of activator of transcription 6 (STAT-6). When primary oesophageal epithelial cell cultures were stimulated with IL-13 an RNA transcript expression profile emerged, similar to that seen in oesophageal biopsies from humans with EoE. IL-13 stimulates the production of the chemokine eotaxin-3, a specific attractant of eosinophils from epithelial cells and from fibroblasts.<sup>35</sup> IL-13 also induces TSLP which is an IL-7-like cytokine associated with paediatric EoE in GWAS.<sup>2</sup> Epithelium derived TSLP stimulates dendritic cells inducing a Th2 response.<sup>44</sup> mRNA for eotaxin-3 and TSLP was found upregulated in oesophageal biopsies from

EoE patients.<sup>45 46</sup> These findings are unlikely to be a consequence of inflammation per se as the expression of eotaxin-3 is not increased in GORD and can be used as a biomarker to differentiate EoE from GORD (see table 2 for other markers that differentiate EoE from GORD).<sup>46</sup> Inhibitors of IL-13, such as the anti-IL-13 antibodies lebrikizumab or QAX576, may be a potential therapeutic option.<sup>47 48</sup> Lebrikizumab has shown promising effects in patients with asthma and a high Th2 response, and QAX576 is currently under investigation as a treatment option for EoE.

IL-5, which is induced by IL-13,<sup>49</sup> is known to play a significant role in eosinophil differentiation and activation, and levels of IL-5 are significantly elevated in oesophageal biopsies of patients with EoE.<sup>50</sup> A number of IL-5 antagonists have subsequently been trialled as a treatment for EoE, and studies to date demonstrate a significant reduction in oesophageal eosinophil numbers and minor improvements in a few parameters of oesophageal remodelling (table 3). However, the clinical response to IL-5 antibodies is variable and as such they are not recommended for routine use at the present time.<sup>12</sup>

Animal studies provide further support that allergens and Th2 cytokines play key roles in the pathogenesis of EoE: the disorder can be induced by allergens in B lymphocyte deficient mice<sup>43</sup> but not T and B lymphocyte deficient mice,<sup>51</sup> and the disease development in murine models has been shown to be critically dependent on IL-5 and eotaxin.<sup>52</sup> Furthermore, IL-13 have been shown to promote IL-5 dependent oesophageal eosinophilia in mice.<sup>53</sup> However, the importance of IL-4 and IL-13 in the pathogenesis of EoE has recently been challenged<sup>53</sup>; allergen induced experimental EoE, in contrast to lung eosinophilia, was not found to be impaired in IL-13 deficient, STAT-6 deficient, or IL-13/IL4 double deficient mice. Animal models may not, however, truly replicate the disease processes occurring in humans, which in EoE may result from

**Table 3** Trials using anti IL-5 antibody in eosinophilic oesophagitis

Authors	Study design	Anti IL5	Adult/ Child	N	Primary objective(s)	Outcome(s)
Stein <i>et al</i> <sup>74</sup>	Case series	Mepolizumab 3 infusions	Adult	4		Pronounced reduction in blood and oesophageal eosinophils
Straumann <i>et al</i> <sup>75</sup>	Randomised placebo controlled	Mepolizumab 2 infusions 750 mg IV 1 week apart. After 2 months histological non-responders given a further 2 infusions 1500 mg 1 month apart	Adults with $\geq 20$ Eos/hpf	11	Complete histological remission (<5 peak eosinophil number/hpf)	<ol style="list-style-type: none"> <li>4 weeks after starting treatment, 54% reduction of mean oesophageal eosinophils in patients receiving active therapy compared with the placebo group (5%) (<math>p &lt; 0.05</math>)</li> <li>Reduced expression of tenascin C (<math>p = 0.033</math>) and TGF-<math>\beta</math> (<math>p = 0.05</math>) genes associated with oesophageal remodelling</li> <li>Trend towards clinical improvement observed after 4 and 13 weeks</li> </ol>
Assa'ad <i>et al</i> <sup>76</sup>	Randomised non-placebo controlled	Mepolizumab monthly infusion 0.55, 2.5, or 10 mg/kg for 3 months	Children with $\geq 20$ Eos/hpf)	59	Histological improvement	Peak and mean oesophageal intraepithelial eosinophil counts decreased significantly ( $p < 0.0001$ ). Symptoms were not recorded
Spergel <i>et al</i> <sup>77</sup>	Randomised placebo controlled	Reslizumab, 1, 2 or 3 mg/kg IV (monthly intervals for 3 months)	Children/ adolescent; symptom severity scores > moderate >24 Eos/hpf	262	Histological and clinical improvement	<ol style="list-style-type: none"> <li>Peak oesophageal eosinophil counts significantly reduced in the groups receiving reslizumab compared with placebo group (<math>p &lt; 0.001</math>)</li> <li>No significant difference between physician's global assessment scores</li> </ol>

Eos, eosinophils; hpf, high powered field; IV, intravenous; TGF- $\beta$ , transforming growth factor  $\beta$ .

a complex interaction between environmental factors and host.

#### Eosinophils, mast cells, and fibrosis

Eosinophils are not usually found in the squamous epithelium lined oesophagus of healthy individuals.<sup>54</sup> The presence of the eosinophil granulocyte in the oesophageal lamina propria is the hallmark of EoE. But how important is the cell in the aetiology of the disease?

Intraepithelial eosinophils in oesophageal biopsies from EoE patients have been shown to be activated, releasing proteins and entire eosinophil granules correlating with disease activity.<sup>46 55–57</sup> Two of these granule proteins—the major basic protein (MBP), which can be used to discriminate EoE from GORD, and the eosinophil cationic protein (ECP)—can both be used to monitor response to treatment in EoE and in other allergic diseases.<sup>46 58 59</sup> The finding that MBP induces the release of mediators from mast cells, and ECP increases the secretion of transforming growth factor  $\beta$  (TGF- $\beta$ ) from fibroblasts,<sup>58 60</sup> supports the suggestion that the presence of oesophageal eosinophils in EoE is pathogenic. TGF- $\beta$  is a cytokine known to stimulate fibrosis and influence smooth muscle contractility.<sup>61</sup> Elevated levels of TGF- $\beta$  have been found in EoE biopsies but not in GORD,<sup>31</sup> which may account for, or contribute to, the pathologic, endoscopic, and histological changes seen in EoE. Long term removal of TGF- $\beta$  has been proposed as a regimen for treatment of tissue fibrosis.<sup>61</sup> Increased numbers of mast cells, which also produce TGF- $\beta$ , are seen in the oesophagus of EoE patients but not of GORD patients.<sup>62</sup> The number of mast cells in the oesophagus and the level of degranulation correlate with severity of disease.<sup>63</sup> If left untreated, fibrosis may cause permanent damage to the oesophagus and potentially lead to structuring and debilitating dysphagia. Further research is needed, however, to determine whether all patients with EoE are at the same risk for tissue remodelling, how long it takes, and under what circumstances.<sup>64</sup>

Although the literature suggests eosinophils do play a pathogenic role in EoE, the clinical trials of medications which reduce eosinophil numbers have proved disappointing to date—results have been variable and improvements minimal. It is entirely conceivable, however, that once the inflammatory cascade has been triggered, removing the causative cell may have a limited effect.

#### Role of concomitant medications

A combination of factors, such as concomitant medication or changes in bacterial flora, may contribute to the aetiology of EoE, resulting in a dysregulated immune response to an allergen with pathological consequences. Whether, and how, allergens penetrate the oesophagus to stimulate the atopic response is an interesting question. It has been proposed that medications may affect oesophageal permeability—some may lead or contribute to a ‘leaky mucosa’ which could allow allergens to penetrate, while others may exert a protective effect.

#### Proton pump inhibitors

PPI resistant dyspepsia is a well recognised feature of EoE. However, some patients do respond positively to PPI treatment, but why this should occur is not completely understood.<sup>65</sup> It has been proposed that this phenomenon may relate to the drug’s anti-inflammatory properties. The drug may either inhibit the Th2 associated transcription factor STAT-6, which has been shown in squamous epithelial cells from EoE

patients,<sup>66</sup> or upregulate haem oxygenase 1.<sup>67</sup> An alternative explanation might be that PPIs reduce acid damage to the oesophageal epithelium, in undiagnosed GORD, which may otherwise result in dilated intercellular spaces and increased epithelial permeability. This would allow for allergens to penetrate and exacerbate the inflammatory load, leading to recruitment of eosinophils to the oesophagus.<sup>68</sup>

#### COX-2 inhibitors

The expression of cyclo-oxygenase 2 (COX-2) in epithelial cells is increased in GORD, but reduced in EoE.<sup>69</sup> IL-13, which is known to down-regulate COX-2 expression, could be responsible for this. Whether attenuated basal levels of COX-2 derived prostaglandins from epithelial cells or non-steroidal anti-inflammatory drugs (NSAIDs), which are commonly used in the general population, influence disease development is not currently known. Prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) is, however, produced and released from activated mast cells (figure 2). By attenuating the response of PGD<sub>2</sub> via antagonism of its receptor CRTH2, expressed on T lymphocytes, eosinophils and basophils, using the compound OC000459, a cohort of adults with severe, non-responsive EoE were found to have an improvement in symptoms.<sup>70</sup>

#### Role of antibiotics

A recent study reported that antibiotic use in the first year of infancy was associated with six times the odds of developing EoE.<sup>71</sup> Incidentally, the usage of antibiotics has been linked to allergy development in mice.<sup>72</sup> Interestingly the presence of *Helicobacter pylori* in gastric biopsies is also inversely correlated with oesophageal eosinophilia.<sup>73</sup> There is, however, no evidence to suggest that patients undergoing antibiotic induced *H pylori* eradication are at greater risk for EoE.

In summary, EoE is a polygenic disorder in which a dysregulated environment in the oesophageal mucosa appears to lead to inflammatory cell infiltration and disease development in response to food allergens and aeroallergens (figure 2). Both genetic and/or environmental factors appear to influence the production of mediators such as TSLP and eotaxin-3 by epithelial and other stromal cells. Eosinophils, Th2 lymphocytes, and mast cells are recruited to the mucosa. B lymphocytes may undergo local IgE class switching. Increasing evidence indicates that environmental factors, in particular medications such as antibiotics, particularly early in life, could contribute to disease development and may even account for the increased incidence of disease observed.

#### CONCLUSION

EoE has emerged over recent years as an increasingly common disease in both adults and children, with a significant associated morbidity. However, it still remains underdiagnosed in many centres. Substantial advances have been made during the last decades which have contributed to our understanding of EoE. A greater awareness and insight into the clinical presentation, pathological processes involved, and triggers of this complex disease will facilitate improved diagnostic criteria and enhance our management through earlier diagnosis and introduction of novel treatments.

## Review

## Main messages

- ▶ The incidence of eosinophilic oesophagitis (EoE) is increasing.
- ▶ EoE is characterised *clinically* by symptoms of dysphagia, food impaction and proton pump inhibitor resistant dyspepsia, and *histologically* by significant eosinophilic infiltration of the oesophageal mucosa.
- ▶ A minimum of 2–4 oesophageal biopsies should be taken from the proximal and distal oesophagus to diagnose EoE.
- ▶ EoE is associated with atopy and a T helper type 2 (Th2) response. A thorough allergy history must be taken before testing for food and aeroallergens in EoE patients.
- ▶ Genome-wide analysis studies (GWAS) have found EoE to be associated with a region on chromosome 5q22 in a paediatric cohort. The gene for thymic stromal lymphopoietin (TSLP) is localised to this region.

## Current research questions

- ▶ Research and development of novel non-invasive biomarkers in the diagnosis of EoE is needed.
- ▶ The influence and effect of environmental influences and medication such as proton pump inhibitors and antibiotics on the incidence of EoE should be studied.

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## Self assessment questions

For self assessment questions please see the companion article by Kumar *et al*<sup>1</sup>.

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