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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 is becoming increasingly recognised, although remains underdiagnosed in many centres. It is characterised histologically by a significant eosinophilic infiltration of the oesophageal mucosa (>15 eosinophils per high powered field) differentiating EoE from other oesophageal disorders when other causes are excluded. Clinical features of EoE are 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 (Th) 2 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 increasing 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 linked paper]. 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.[1] This paper will describe the epidemiology, clinical presentation, diagnosis and pathophysiology of EoE.

EPIDEMIOLOGY

EoE was first described in 1978[2], 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 (see table 1).[3] EoE is now recognised in up to 1 in 2,500 individuals [4, 5] with a prevalence in some centres as high as 15% of patients presenting with dysphagia to endoscopy units.[6, 7] 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 to 2011.[4] 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. suggests that the incidence is indeed rising.[4]

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, male: female ratio of 3:1.[8] A recent study indicated that African American males may present with a more aggressive form of EoE earlier than Caucasians [9] however further studies are necessary to support this observation and investigate whether the increased prevalence in males and earlier presentation of African-American is due to the pathogenesis of EoE or related to social or environmental factors. The current consensus is that there is inconclusive evidence for

significant socioeconomic geographical and/or ethnic variations [11, 12]. 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.[10, 11]

CLINICAL PRESENTATION AND DIAGNOSIS

Eosinophilic oesophagitis 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).[12] The following section will detail the clinical, endoscopic and histological features of EO.

CLINICAL FEATURES AND ASSESSMENT FOR ALLERGY

The clinical presentation of EoE varies according to age of patient and severity of disease (see table 2). In children failure to thrive, choking, regurgitation or vomiting after eating or food refusal is seen.[13] Adolescents and adults classically present with retrosternal discomfort, dysphagia to solids (70%)[8], food bolus impaction (33-54%),[14] and intractable dyspepsia (38%) which is typically not, or only partially, responsive to 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 (i.e. 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 nineteen cases of perforation had occurred world wide by 2011, seven needed surgical intervention but none were fatal.[12, 15, 16]

Up to three quarters of patients may have a personal or family history of allergy; allergic rhino-conjunctivitis, eczema and asthma.[17, 18, 19] Approximately 50% of patients have peripheral eosinophilia (>300-350/mm^2) [12] or increased level of serum of IgE [20, 21] and 75% have a positive skin prick test to at least one food allergen – most commonly dairy, eggs, peanuts, fish, wheat, soy or aero-allergen – such as dust mite, pollen, grass.[22] In

general children with EoE tend to have a concomitant allergy to foods and adults to aero allergens This observed difference in allergen sensitivity between adults and children is consistent with the 'allergic or atopic march hypothesis'[13] whereby the atopic phenotype presents early in life as skin rashes (e.g. 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.[23, 24] The importance of taking a through 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 [25] and children [26] with EoE. Sufficient evidence is not available to support routine allergy testing in all patients with EoE however and it is generally agreed that these tests should be reserved for individuals in whom the history suggests a food allergen trigger [see linked review]. 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.

On clinical history alone it is impossible to diagnose EoE and examination is usually unremarkable in particular there are no identified oral pharyngeal manifestations. Many other oesophageal disorders including Gastric Oesophageal Reflex 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 table 1 in [the linked review] 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 [27], endoscopic signs associated with EoE are well documented and a recent grading system has been validated to score the endoscopic assessment [28] (see table 3 [this review] and endoscopic views in [linked paper]). Features include a narrow calibre oesophagus (9%), which maybe characterless (41%) or display longitudinal ridges/furrows (48%), fixed concentric 'corrugated' rings/ trachealisation (44%) giving the impression of a trachea, strictures (21-40%), Schatzki rings, linear superficial mucosal tears and 'crepe paper' effect due to mucosal fragility (59%), and eosinophilic abscesses (white speckled exudates, 1-2mm in diameter, that resemble oesophageal candidiasis) (27%).[29] Adults generally present with more subepithelial fibrosis and oesophageal narrowing than children and fibrosis increases

over time.[1, 13] Although endoscopy is vital for the diagnosis of EoE, none of above mentioned findings are pathognomonic.

HISTOLOGICAL FEATURES OF EO

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 maybe 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 distal and proximal oesophagus [13] although some authors have shown that up to 5-6 biopsies are required for >99.9% sensitivity.[26] A definitive diagnosis is made if >15 eosinophils in at least one high powered field (HPF) are seen (see figure 1) and this eosinophilia is isolated to the oesophagus (i.e. not present in gastric and duodenal biopsies). Eosinophils stain brightly red with haematoxylin and eosin stain (see 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 (see table 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 PPI and/or pH studies, to exclude GORD and PPI-responsive oesophageal eosinophilia, prior to reporting a histological diagnosis of EoE.[see linked paper]. 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.[12] 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 (see table 3). 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, see table 4.[30, 31] Furthermore, some studies have reported increased numbers of mast cells and

immunoglobulin E (IgE) positive cells [32] indicating an allergic-type process in the mucosa that differentiates EoE from GORD. Table 5 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 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 Th2 inflammatory cascade, seen in EoE are not completely understood. (see 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[33, 34] - 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 localized to this region.[1,2] 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.[35] 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 Th 2 lymphocytes are prominent in the oesophagus of EoE patients (see the histology section and figure 2).[36] Furthermore a wealth of literature has documented the benefit of allergen elimination through strict exclusion diets, particularly in children with EoE, which strongly supports a role of allergy in EoE. Almost complete resolution of both clinical and histological abnormalities have been described following exclusion diets [37] and a reversal of oesophageal fibrosis have even been demonstrated in some studies.[26, 38] The

results in adults are less conclusive, perhaps as the culprit is more likely to be an aero allergen, 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 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 [39]. Th2 lymphocytes produce interleukin (IL-) 4, IL-13 and IL-5 and the mRNA for these cytokines have been found up-regulated in the oesophagus of EoE patients.[32, 34, 40]

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.[32] 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.[41] In line with these findings studies using animal models have demonstrated that antibody-producing B lymphocytes are not necessary for EoE pathogenesis (see below).[42]

IL-13 shares a common signal transduction pathway with IL-4, via the signalling molecule signal transducer of activator of transcription (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.[34] IL-13 also induces TSLP which is an IL-7-like cytokine associated with paediatric EoE in GWAS [1]. Epithelium derived TSLP stimulates dendritic cells inducing a Th2 response.[43] mRNA for eotaxin-3 and TSLP was found up-regulated in oesophageal biopsies from EoE patients.[44, 45] These finding 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 5 for other markers that differentiate EoE from GORD).[45] Inhibitors of IL13, such as the anti-IL-13

antibodies Lebrikizumab or QAX576, maybe a potential therapeutic option.[46, 47] 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 [48], 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.[49] 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 (see table 6). However the clinical response to IL-5 antibodies is variable and as such they are not recommended for routine use at the present time.[12]

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 [42] but not T and B-lymphocyte deficient mice [50] and the disease development in murine models has been shown to be critically dependent on IL-5 and eotaxin.[51] Furthermore IL-13 have been shown to promote IL-5 dependent oesophageal eosinophilia in mice.[52] However the importance of IL-4 and IL-13 in the pathogenesis of EoE has recently been challenged [52]; 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 may in EoE result from 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.[53] and 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.[45, 54, 55, 56] 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.[45, 57, 58] The finding that MBP induces the release of mediators from mast cells and ECP increases

the secretion of transforming growth factor beta (TGF-β) from fibroblasts [57, 59] supports the suggestion that the presence of oesophageal eosinophils in EoE is pathogenic. TGF-β is a cytokine known to stimulate fibrosis and influence smooth muscle contractility.[60] Elevated levels of TGF-β have been found in EoE biopsies but not in GORD [30] which may account for, or contribute to, the pathologic, endoscopic and histological changes seen in EoE. Long-term removal of TGF-β has been proposed as a regimen for treatment of tissue fibrosis.[60] Increased numbers of mast cells, which also produce TGF- β, are seen in the oesophagus of EoE patients but not of GORD patients.[61] The number of mast cells in the oesophagus and level of degranulation correlate with severity of disease.[62] If left untreated, fibrosis may cause permanent damage to the oesophagus and potentially lead to structuring and debilitating dysphagia. Further research is however needed to determine whether all patients with EoE are at the same risk for tissue remodelling, how long it takes, and under what circumstances.[63]

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 however entirely conceivable 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, others may exert a protective effect.

Proton Pump Inhibitors:

PPI resistant dyspepsia is a well-recognised feature of EoE. However a group of patients do respond positively to PPI treatment which is not completely understood.[64] 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 have been shown in squamous epithelial cells from EoE patients [65] or up-regulate heme oyxgenase

1.[66] 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 recruitment of eosinophils to the oesophagus.[67]

COX-2 Inhibitors:

The expression of COX-2 in epithelial cells is increased in GORD, but reduced in EoE.[68] 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), commonly used in the general population, influence disease development is not currently known. Prostaglandin D_2 (PGD_2) is however produced and released from activated mast cells (see figure 2). By attenuating the response of PGD_2 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.[69]

ROLE OF ANTIBIOTICS:

A recent study reported that antibiotic use in the first year of infancy was associated with 6 times the odds of developing EoE.[70] Incidentally the usage of antibiotics has been linked to allergy development in mice.[71] Interestingly the presence of *H. pylori* in gastric biopsies is also inversely correlated with oesophageal eosinophilia.[72] 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- and aero-allergens (see 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

Eosinophilic oesophagitis 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.

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COMPETING INTERESTS

None

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TABLES

Table 1: Diseases other that Eosinophilic Oesophagitis associated with an oesophageal eosinophilia

Diseases other that EoE associated with an oesophageal eosinophilia:
Gastric oesophageal Reflux disease (GORD)
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

Table 2: Clinical symptoms of Eosinophilic Oesophagitis in paediatric and adult patients

Clinical Symptoms:
Paediatics:
Failure to thrive
Vomiting/regurgitation
Choking
Food refusal
Adults:
Dysphagia
Food impaction
Vomiting
Intractable dyspepsia; un/partially responsive to PPI

Table 3: Endoscopic features of Eosinophilic Oesophagitis, classification and grading adapted from Hirano et al, 2013.[28]

MAJOR FEATURES	GRADE 0	GRADE 1	GRADE 2	GRADE 3
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, trachealization)	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 less than 10% of the oesophageal surface area	Severe-lesions involving greater than 10% of the oesophageal surface area	
Furrows (vertical lines, longitudinal furrows)	Absent	Present		
Stricture	Absent	Present (specify estimated luminal diameter)		
MINOR FEATURES				
Crepe paper oesophagus (mucosal fragility or laceration upon passage of diagnostic endoscope but not after oesophageal dilation)	Absent	Present		
Narrow-caliber oesophagus (reduced luminal diameter of the majority of the tubular oesophagus)	Absent	Present		

Table 4: Oesophageal histological features of Eosinophilic Oesophagitis

Histological findings:
> 15 Eo/HPF
Micro abscesses
Surface layering eosinophils
Extracellular eosinophil granules
Basal layer hyperplasia
Dilated intracellular spaces
Lamina propria fibrosis

Table 5. Studies that have evaluated histological markers that discriminate Eosinophilic Oesophagitis from GORD

	EoE	GORD	Adult/Child	Correlation	Reference
Intraepithelial eosinophils *	55 +/- 27.5	6.9 +/- 9.7	Children	P < 0.0001	[61]
MBP **	1479 (+/-1290)	59 (+/- 103)	Adult	p<0.001	[45]
Eotaxin-3 **	2219 (+/-1782)	479 (+/- 777)	Adult	p=0.01	[45]
Intraepithelial mast cells *	26.3 +/- 12.7	7.8 +/- 8.9	Children	p < 0.0001	[61]
TGF beta positive cells in LP *	126 (61-191)	9	Children	p=0.002	[30]
COX-2 ***	0	0.5 (Faint stain in basal layer of epithelium)	Adult	p<0.01	[68]

The table summarises studies that have assessed potential laboratory markers to discriminate eosinophil oesophagitis from gastro-oesophageal reflux disease. * per hpf ** maximum staining density, cells / mm2 (+/-s.d.) *** monoclonal antibody uptake grading, LP: lamina propria

Table 6: Trials using anti IL-5 antibody in Eosinophilic Oesophagitis

Authors	Study design	Anti IL5	Adult/ Child	N	Primary objective(s)	Outcome(s)
Stein *et al.*, 2006 [73]	Case series	Mepolizumab 3 infusions	Adult	4		Marked reduction in blood and oesophageal eosinophils
Straumann et al, 2010 [74]	Randomised placebo controlled	Mepolizumab 2 infusions 750mg IV 1 week apart. After 2 months histological non responders given a further 2 infusions 1500mg 1 month apart	Adults with ≥20EoE/hpf)	11	Complete histological remission (<5 peak eosinophil number/hpf)	1. 4 weeks after starting treatment, 54% reduction of mean oesophageal eosinophils in patients receiving active therapy compared with the placebo group (5%) ($p<0.05$) 2. Reduced expression of tenascin C ($p=0.033$) and TGFβ ($p=0.05$) genes associated with oesophageal remodelling 3. Trend towards clinical improvement observed after 4 and 13 weeks
Assa'ad *et al.* 2011 [75]	Randomised non placebo controlled	Mepolizumab monthly infusion 0.55, 2.5, or 10 mg/kg for 3 months	Children with ≥20EoE/hpf)	59	Histological improvement	Peak and mean oesophageal intraepithelial eosinophil counts decreased significantly ($p<0.0001$). Symptoms were not recorded
Spergel *et al.*, 2012)[76]	Randomised placebo controlled	Reslizumab , 1, 2 or 3 mg/kg IV (monthly intervals for 3 months)	Children/ adolescent; symptom severity scores > moderate >24EoE/hpf	262	Histological and clinical improvement	1. Peak oesophageal eosinophil counts significantly reduced in the groups receiving reslizumab compared with placebo group ($p<0.001$). 2. No significant difference between physician's global assessment scores

Figures

Figure 1: Histology images of oesophageal epithelial eosinophilia

A. Squamous mucosa showing basal cell hyperplasia, elongation of papillae and numerous eosinophils in the epithelium (Hematoxilin & eosin x100). B. Eosinophils in squamous epithelium (arrow head, >30/high power field). Detail upper right corner: eosinophilic micro abscess (arrow head, Hematoxilin & eosin x400).

Figure 2: Mechanism of Eosinophilic Oesophagitis

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, bi-lobar 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 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. 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 TSLP 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 PPI's may act in an anti-inflammatory capacity through inhibition of the allergy associated transcription factor STAT-6 or altering epithelial permeability. Medications such as antibiotics may additionally promote EoE by skewing the immune-response from a Th1 to Th2 type. TGF-β released by epithelial cells, MC and Eos induces activation of fibroblasts augmenting fibrosis in LP and contraction of MM, the combination of which may lead to pathological features such as strictures.

RESEARCH QUESTIONS

- Research and development of novel non-invasive biomarkers in diagnosis of EO needed
- Study the influence and effect of environmental influences and medication such as PPI's and antibiotics on the incidence of EO
- Ascertain role of proton pump inhibitors (PPI) in management of EO
- Identify effective steroid sparing agents in the management of EO

MAIN MESSAGES

- The incidence of EO is increasing
- EO is characterised *clinically* by symptoms of dysphagia, food impaction and proton pump inhibitor resistant dyspepsia and *histologically* by a significant eosinophilic infiltration of the oesophageal mucosa
- A minimum of two to four oesophageal biopsies should be taken from proximal and distal oesophagus to diagnose EO
- All endoscopy units should initiate a standard biopsy protocol for all patients presenting with unexplained dysphagia and food bolus impaction
- High resolution manometry and pH monitoring study are useful adjuncts to distinguish EO from GORD.
- EO is associated with atopy and a T helper type 2 response. A thorough allergy history must be taken before testing for food and aeroallergens in EO patients
- GWAS have found EO to be associated with a region on chromosome 5q22 in a paediatric cohort. The gene for thymic stromal lymphopoietin (TSLP) is localized to this region
- Dietary therapy and topical corticosteroids are the mainstay of the therapy once diagnosis is confirmed. Immunosuppressants and biologics may have a role in

management of refractory cases. Endoscopic dilatation of strictures, secondary to EO, is safe and effective.

Quiz Questions:

1. Updated 2011 consensus guidelines recommend that
   a. A minimum of 2-4 biopsies from the distal oesophagus alone is required for diagnosis of EO
   b. >15 eosinophils/hpf is a diagnostic criterion for EO
   c. Allergy assessment is useful in management of EO
   d. pH study is required for all patients with suspected EO
   e. Systemic corticosteroids should be avoided in patients diagnosed with EO

2. Eosinophilic oesophagitis
   a. Is more common in patients over the age of 50
   b. Is frequently associated with atopy
   c. Presents in children with severe reflux symptoms and growth failure
   d. Is an immune/antigen mediated disease
   e. Has characteristic endoscopic features in majority of patients

3. Dietary therapy
   a. Is the mainstay of therapy for EO in adults
   b. Elemental diet is an effective therapy in EO
   c. SFED has been shown to induce both histological and symptomatic response
   d. Relapse is not common on reintroduction of normal diet after successful dietary therapy
   e. Elimination diet based on allergy testing is not beneficial in patients with EO

4. Pharmacotherapy for EO.
   a. High dose proton pump inhibitor therapy should be tried in all patients with suspected EO
   b. Topical corticosteroids are the most effective therapy for induction and maintenance of remission in EO
   c. Systemic steroids should be used to treat all patients diagnosed with EO
   d. Budesonide should be inhaled to be effective in EO
   e. Immunosuppressants are a treatment of choice in patients diagnosed with EO

5. Endoscopy in EO
   a. Can identify mucosal changes typically found in EO
   b. Patients with EO may have normal endoscopy
   c. Endoscopy and oesophageal biopsies should be repeated following an 8 week course of high dose PPI therapy to rule out GORD
   d. Endoscopic dilatation of strictures secondary to EO carry a high risk of oesophageal perforation
   e. Endoscopic dilatation of fixed oesophageal strictures alters the underlying pathophysiology of EO and prevents recurrence

Answers:

1. a-F, b-T, c-T, d-F, e-F
2. a-F, b-T, c-T, d-T, e-F
3. a-F, b-T, c-T, d-F, e-F
4. a-T, b-T, c-F, d-F, e-T
5. a-T, b-T, c-T, d-F, e-F

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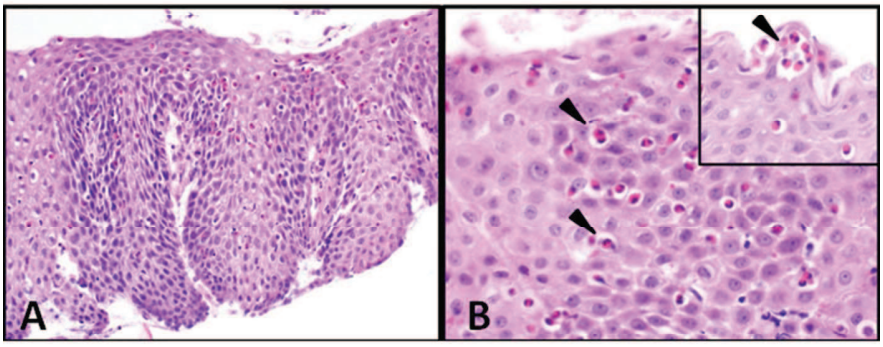
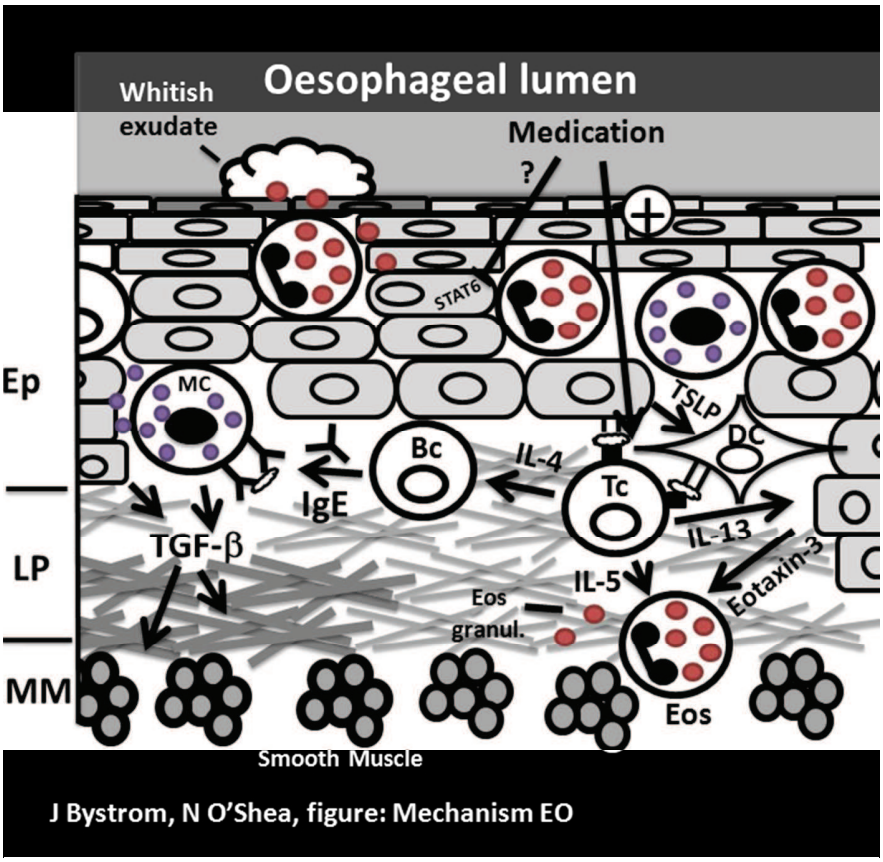


Figure1. J Bystrom et al. EOSINOPHILIC OESOPHAGITIS – AN OVERVIEW FOR CLINICIANS

Oesophageal epithelial eosinophilia
60x81mm (300 x 300 DPI)



190x254mm (96 x 96 DPI)