Eosinophilic oesophagitis

Eosinophilic oesophagitis is a chronic immune-mediated inflammatory disorder of the oesophagus, characterized by symptoms of dysphagia or food bolus obstruction. Diagnosis is supported by typical histological findings. This article covers pertinent aspects of the disease, pathogenic explanations and treatment options.

Eosinophilic oesophagitis is a chronic immune-mediated inflammatory disorder of the oesophagus that has become increasingly recognized over the last 15 years (Bystrom and O'Shea, 2014). It was first described as a distinct clinical condition in 1993 after 12 patients with dysphagia were identified as having dense eosinophilic infiltration in oesophageal biopsies (Attwood et al, 1993).

The allergic inflammatory response is triggered by food or aero antigens in genetically predisposed individuals (Sherrill and Rothenberg, 2014) and characterized by symptoms such as dysphagia and food bolus obstruction (Desai et al, 2005).

Epidemiology

The incidence of eosinophilic oesophagitis in the UK is unknown, and estimates vary considerably. A study performed in an adult Swedish population found that eosinophilic oesophagitis was present in 4 out of 1000 subjects (0.4%, 95% confidence interval 0.01–0.8%, mean age 51 years, 75% men) (Ronkainen et al, 2007). However, the reported incidence and prevalence of eosinophilic oesophagitis in western populations has increased over the last decade (Straumann and Simon, 2005; Chehade and Sampson, 2008; Prasad et al, 2009; Hruz et al, 2011). This may be the result of an increased awareness of the disease as suggested by a retrospective study which looked at oesophageal biopsy specimens between 1982 and 1999 and found no increase in incidence of eosinophilic oesophagitis (DeBrosse et al, 2010).

It occurs more commonly in males (Dellon et al, 2014) and in patients with a history of atopy (Simon et al, 2014).

Pathophysiology

The pathogenesis of eosinophilic oesophagitis is not fully understood, but is thought to be multifactorial, and caused by a combination of environmental, genetic and immune factors.

Genetic factors

As mentioned, patients with a history of atopy are more likely to develop eosinophilic oesophagitis. This supports a hypothesis that there may be a genetic predisposition to developing eosinophilic oesophagitis.

A familial study looked at recurrence risk ratios in family members, while also looking at monozygotic and dizygotic twins. They found that the rate of eosinophilic oesophagitis in proband siblings was 2.4% (sex adjusted). In the twins cohort, they found genetic heritability was 14.5±4.0% ($P<0.001$) while common family environment contributed 81.0±4% ($P<0.001$), suggesting that the environment plays a role (Alexander et al, 2014).

There is also an increased prevalence of eosinophilic oesophagitis in some patients with connective tissue disorders of Mendelian inheritance such as Loeys–Dietz and Marfan syndromes (which are both caused by mutations in the tumour growth factor-β (TGF-β) signalling pathway), and Ehlers–Danlos syndrome, which has been reported to show interactions with the protein COL5A1 and the TGF-β signalling pathway (Kahai et al, 2004). These patients have a reported eight-fold risk of developing eosinophilic oesophagitis (Abonia et al, 2013).

Other pro-allergenic disorders have also been associated with eosinophilic oesophagitis such as hyper-IgE syndrome and SAM syndrome (a disorder characterized by desmoglein-1 deficiency which results in severe dermatitis, multiple allergies and muscle wasting) (Rothenberg, 2009; Samuelov et al, 2013).

Genome-wide microarray analysis performed on patients with eosinophilic oesophagitis found that the gene eotaxin-3 was the most commonly induced gene compared to healthy individuals. Furthermore a single nucleotide polymorphism of eotaxin-3 was associated with disease susceptibility. In a murine study, mice that were deficient in the eotaxin-3 receptor were protected from developing experimental eosinophilic oesophagitis. These findings

Dr Aaron S Bancil is Core Medical Trainee in the Department of Hepatology, King's College Hospital, London SE5 9RS

Dr Rhys Hewett is Clinical Research Fellow in the Department of Gastroenterology, St George's Hospital, London

Dr Jamal O Hayat is Consultant in the Department of Gastroenterology, St George's Hospital, London

Dr Andrew Poullis is Consultant in the Department of Gastroenterology, St George's Hospital, London

Correspondence to: Dr AS Bancil (asbancil@gmail.com)

> Early diagnosis of eosinophilic oesophagitis is imperative. If left untreated, irreversible oesophageal remodelling, fibrosis and stenotic strictures may occur, the risk of which increases with age

implicate eotaxin-3 as a key receptor in the pathogenesis of eosinophilic oesophagitis (Blanchard et al, 2006). A single nucleotide polymorphism in the protein filaggrin (a structural membrane protein) has also been implicated (Blanchard et al, 2010).

Immune factors

Recognition of food antigens or aero-antigens leads to a T-helper type-2 (Th2) mediated response, causing eosinophilic infiltration of the lamina propria and sub-mucosa of the oesophagus. The exact mechanism is not fully recognized at present but it is thought that there is a complex interplay between various cytokines (D'Alessandro et al, 2015).

The Th2 response leads to activation of various cytokines such as interleukin-13 (IL-13), interleukin-5 (IL-5) (Blanchard et al, 2011) and TGF-β (Rothenberg, 2009), which recruit and activate eosinophils. IL-13 also has a role in eosinophil chemoattraction, and in a murine model, was able to induce eosinophilic oesophagitis when delivered intratracheally. This further establishes the intimate connection between respiratory and oesophageal inflammation (Mishra and Rothenberg, 2003).

Oesophageal remodelling

Chronic oesophageal infiltration leads to epithelial hyperplasia, thickening of the muscularis propria and oesophageal wall as well as deposition of constituents of the extracellular matrix such as sub-epithelial collagen. These lead to the endoscopic findings of oesophageal thickening, stricture formation, furrowing, and thus the clinical manifestations of dysphagia and food bolus obstruction (Aceves and Ackerman, 2009).

Diagnosis

Early diagnosis of eosinophilic oesophagitis is imperative. If left untreated, irreversible oesophageal remodelling, fibrosis and stenotic strictures may occur, the risk of which increases with age (Dellon et al, 2014) and disease duration (Schoepfer et al, 2013).

Diagnosing eosinophilic oesophagitis requires evidence of oesophageal dysfunction along with characteristic histological findings. Other diseases that have eosinophilic infiltration of the oesophagus such as Crohn's disease, gastro-oesophageal reflux disease, proton pump inhibitor-responsive eosinophilia, connective tissue diseases and achalasia must also be ruled out. The diagnosis of eosinophilic oesophagitis is further supported by characteristic endoscopic appearances of the oesophagus.

Endoscopy

Two to four biopsies of the proximal and distal oesophagus should be obtained (Liacouras et al, 2011). Characteristic features include loss of the normal vascular pattern secondary to oedema, mucosal fragility, the appearance of exudates (which will look like white spots or plaques), rings, longitudinal furrows or strictures. Additional features include a narrow calibre oesophagus, 'trachealisation' of the oesophagus and crepe paper oesophagus (Hirano et al, 2013).

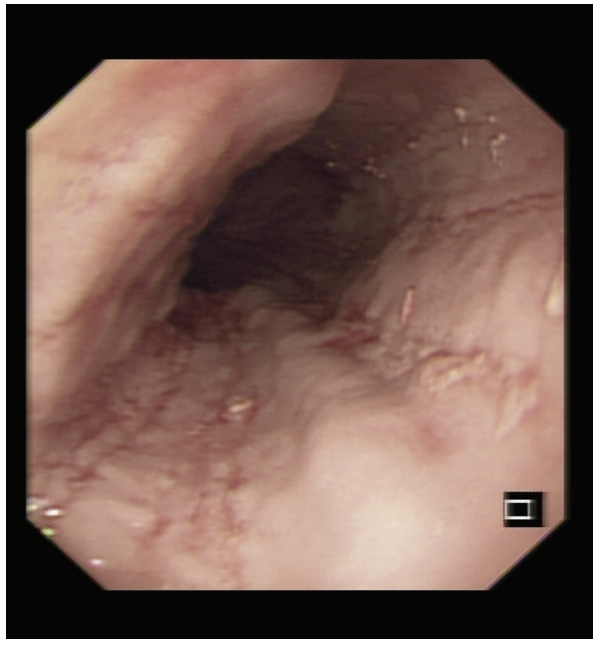
The presence of four classical endoscopic findings of eosinophilic oesophagitis (plaques, rings, furrows, strictures) (*Figure 1*) can strongly predict the presence of eosinophilic oesophagitis (sensitivity 72%, specificity 89%, negative predictive value 98%) (Veerappan et al, 2009).

Histology

The minimum criteria for diagnosing eosinophilic oesophagitis is 15 eosinophils per high-powered field. This eosinophilic inflammation must be on at least one or more biopsies (Liacouras et al, 2011). Patients who do not have the minimum criteria might be missed initially, but they should fit the criteria for a repeat biopsy (Ravi et al, 2011). The minimum criteria may also be missed as a result of partially treated eosinophilic oesophagitis.

Other histological features that may be seen include the presence of an intraepithelial cluster of four or more eosinophils (eosinophilic micro-abscesses), a superficial layering of eosinophils and extracellular eosinophilc granules (Liacouras et al, 2011). One may also see fibrosis of the lamina propria and basal cell hyperplasia (Ali et al, 2012).

Figure 1. An example of linear furrowing and tramlining in eosinophilic oesophagitis.



Treatment

Diet

The concept of food allergens being involved in the pathogenesis of eosinophilic oesophagitis offers a potential treatment through dietary modification. A small paediatric study of 10 children showed that after being fed with an elemental formula for 6 weeks, eight patients showed resolution of symptoms, while two patients showed improvement with significant decreases in intraepithelial eosinophil counts (P=0.005). Symptoms returned in all patients after re-introduction of normal diets (Kelly et al, 1995).

The Six Food Elimination Diet is another modification that has been trialled. The diet involves the removal of the six most common food allergens (egg, nuts, milk, seafood, soya and wheat), with a slow re-introduction of each food to ascertain which food group may be contributing to symptoms. This diet shows a decrease in eosinophil counts and an improvement in symptoms in adults (Gonsalves et al, 2012; Lucendo et al, 2013). Foods most commonly associated with eosinophilic oesophagitis were wheat (60% of patients) and milk (50% of patients) (Gonsalves et al, 2012). However, the diet can be difficult to enforce, especially in children, and caution is required to avoid nutrient deficiencies (Alvares et al, 2013).

Another study looked at diet modification based on skin-prick and patch testing. A total of 146 patients diagnosed with eosinophilic oesophagitis had diets restricted based upon their test results, with 39 patients showing unequivocally that food was the causative factor of eosinophilic oesophagitis. Seventy three patients had biopsy-proven resolution of eosinophilic oesophagitis, while only 15 were non-responders (Spergel et al, 2005). However, the study by Gonsalves et al (2012) showed that skin prick testing only predicted 13% of foods associated with eosinophilic oesophagitis.

The above studies suggest that use of dietary modification in eosinophilic oesophagitis significantly improves symptoms.

Pharmacological therapies

Topical steroids are the current mainstay of treatment for eosinophilic oesophagitis. Systemic steroids are an effective treatment for eosinophilic oesophagitis, but their use is limited because of their side effects (Schaefer et al, 2008).

Topical treatment is achieved through budesonide and fluticasone propionate sprayed into the mouth and dry-swallowed. There is minimal systemic absorption, thus limiting systemic side effects (Remedios et al, 2006; Straumann et al, 2011).

Studies have generally shown a positive effect of topical steroids, although these have been limited by the lack of a control group (Liacouras et al, 1998; Remedios et al, 2006), not randomizing the control group, not being blinded (Francis et al, 2012) and small numbers (Peterson et al, 2010).

“Topical steroids are the current mainstay of treatment for eosinophilic oesophagitis. Systemic steroids are effective treatment for eosinophilic oesophagitis, but their use is limited because of their side effects”

The disadvantage of topical steroids is the potential for developing oral candida infection and the high relapse rate on cessation of steroids. In one study, 91% of patients had disease recurrence with a mean time of 8.8 months after treatment cessation (Helou et al, 2008).

An alternative treatment which has been studied is the use of montelukast (a leukotriene receptor antagonist used in asthma). Leukotriene D4 is a chemotactic factor for eosinophils, thus its inhibition offered an attractive potential treatment for eosinophilic oesophagitis. One study looked at the treatment of eosinophilic oesophagitis with montelukast in eight patients. Of these, six reported complete improvement after treatment and five patients remained symptom free after starting maintenance therapy. It must be noted that this study used high doses of montelukast and also showed no improvement in eosinophil counts (Attwood et al, 2003).

However, a further study looking at treatment with montelukast after an initial 6-month treatment with fluticasone found that eosinophil density in the oesophageal epithelium and lamina propria was significantly reduced after a 6-month treatment with topical steroids (P=0.003). After 3 months of montelukast, eosinophil density increased to levels similar to baseline (Lucendo et al, 2011).

Further studies have looked at other immunomodulators of the inflammatory cascade, such as IL-5 inhibition with medications such as reslizumab and mepolizumab. These have been trialled in eosinophilic oesophagitis, and found a significant reduction in eosinophil counts but no significant change in symptoms (Assa'ad et al, 2011; Spergel et al, 2012).

Infliximab has also been trialled in an open label study, with no benefit found (Straumann et al, 2008a). A study analysing the effect of thiopurines on eosinophilic oesophagitis showed some promise, with clinical and histological remission with azathioprine or 6-mercaptopurine. In all patients, blood eosinophilia levels disappeared with azathioprine. Patients did experience relapses after cessation of azathioprine, but remission was restored once starting corticosteroid therapy (Netzer et al, 2007). However, these studies are limited by small patient numbers.

Proton pump inhibitor-responsive eosinophilic oesophagitis

Some patients respond to proton pump inhibitor therapy, with clinical and histological improvement seen. In a study of 35 patients with oesophageal eosinophilic infiltration,

KEY POINTS

- Eosinophilic oesophagitis is more common in males and those with a history of atopy.
- The pathogenesis is multifactorial but is thought to be the result of a combination of genetics, the environment and immune factors.
- Diagnosis of eosinophilic oesophagitis is through the combination of clinical and endoscopic findings.
- The mainstay of treatment remains topical corticosteroids, alongside dietary modification and proton pump inhibitors.
- Endoscopy remains a safe and effective way of treating food bolus obstruction secondary to eosinophilic oesophagitis. A gentle approach is necessary.

75% achieved clinical and pathological remission with proton pump inhibitor therapy (Molina-Infante et al, 2011).

It is possible that proton pump inhibitor-responsive eosinophilic oesophagitis may be a distinct disease altogether. Those with true eosinophilic oesophagitis do not tend to have restored mucosal integrity unlike patients with proton pump inhibitor-responsive eosinophilic oesophagitis (van Rhijn et al, 2014). The improvement in mucosal integrity may not be related to acid suppression but to proton pump inhibitor action on Th2-mediated eotaxin-3, which is a chemo-attractant to eosinophils that is also expressed in oesophageal squamous epithelium (Zhang et al, 2012).

Endoscopic therapies

Later stages of eosinophilic oesophagitis may develop fibrostenotic strictures. These can be dilated endoscopically using balloons or bougies. There has been concern about oesophageal perforation when removing food boluses endoscopically. A Swiss study found that in 134 episodes of food impaction, using rigid endoscopy resulted in a perforation rate of 20%. Thus bolus removal in patients with eosinophilic oesophagitis is a high-risk procedure, so should take a more delicate approach (Straumann et al, 2008b), as the oesophageal mucosa may be more fragile. However, endoscopic removal remains an effective and safe method (Schoepfer et al, 2010).

Conclusions

As research continues, so does further understanding of eosinophilic oesophagitis. The epidemiology has become clearer, and laboratory techniques allow further elucidation of the exact pathophysiological mechanisms. However, much further work is needed.

Eosinophilic oesophagitis is an increasingly recognized immune-mediated disorder with patients often presenting with dysphagia and food bolus obstruction. Diagnosis is often delayed and can be associated with complications such as oesophageal stricture formation. The use of steroids remains the mainstay of treatment, with endoscopy a safe and effective treatment for the later manifestations of eosinophilic oesophagitis. Dietary manipulation has also been shown to be effective but can be restrictive. Further research is needed to elucidate the underlying pathophysiology and improve treatment options.

Eosinophilic oesophagitis remains an important diagnosis that must not be missed, and increasing awareness may prevent patients from developing the complications such as fibrosis and stricture formation. **BJHM**

Conflict of interest: none.

Abonia JP, Wen T, Stucke EM et al (2013) High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. *J Allergy Clin Immunol* **132**(2): 378–86 (doi: 10.1016/j.jaci.2013.02.030)

Aceves SS, Ackerman SJ (2009) Relationships between eosinophilic inflammation, tissue remodeling, and fibrosis in eosinophilic esophagitis. *Immunol Allergy Clin North Am* **29**(1): 197–211, xiii–xiv (doi: 10.1016/j.iac.2008.10.003)

Alexander ES, Martin LJ, Collins MH et al (2014) Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. *J Allergy Clin Immunol* **134**(5): 1084–92.e1 (doi: 10.1016/j.jaci.2014.07.021)

Ali MA, Lam-Himlin D, Voltaggio L (2012) Eosinophilic esophagitis: a clinical, endoscopic, and histopathologic review. *Gastrointest Endosc* **76**(6): 1224–37 (doi: 10.1016/j.gie.2012.08.023)

Alvares M, Kao L, Mittal V, Wuu A, Clark A, Bird JA (2013) Misdiagnosed food allergy resulting in severe malnutrition in an infant. *Pediatrics* **132**(1): e229–32 (doi: 10.1542/peds.2012-2362)

Assa'ad AH, Gupta SK, Collins MH et al (2011) An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology* **141**(5): 1593–604 (doi: 10.1053/j.gastro.2011.07.044)

Attwood SE, Smyrk TC, Demeester TR, Jones JB (1993) Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* **38**(1): 109–16

Attwood SE, Lewis CJ, Bronder CS, Morris CD, Armstrong GR, Whittam J (2003) Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut* **52**(2): 181–5 (doi: 10.1136/gut.52.2.181)

Blanchard C, Wang N, Stringer KF et al (2006) Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* **116**(2): 536–47 (doi: 10.1172/JCI26679)

Blanchard C, Stucke EM, Burwinkel K et al (2010) Coordinate interaction between IL-13 and epithelial differentiation cluster genes in eosinophilic esophagitis. *J Immunol* **184**(7): 4033–41 (doi: 10.4049/jimmunol.0903069)

Blanchard C, Stucke EM, Rodriguez-Jimenez B et al (2011) A striking local esophageal cytokine expression profile in eosinophilic esophagitis. *J Allergy Clin Immunol* **127**(1): 208–17, 217.e1–7 (doi: 10.1016/j.jaci.2010.10.039)

Bystrom J, O'Shea NR (2014) Eosinophilic oesophagitis: clinical presentation and pathogenesis. *Postgrad Med J* **90**(1063): 282–9 (doi: 10.1136/postgradmedj-2012-131403)

Chehade M, Sampson HA (2008) Epidemiology and etiology of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* **18**(1): 33–44; viii (doi: 10.1016/j.giec.2007.09.002)

D'Alessandro A, Esposito D, Pesce M, Cuomo R, De Palma GD, Sarnelli G (2015) Eosinophilic esophagitis: From pathophysiology to treatment. *World J Gastrointest Pathophysiol* **6**(4): 150–8 (doi: 10.4291/wjgp.v6.i4.150)

DeBrosse CW, Collins MH, Buckmeier Butz BK et al (2010) Identification, epidemiology, and chronicity of pediatric esophageal eosinophilia, 1982-1999. *J Allergy Clin Immunol* **126**(1): 112–19 (doi: 10.1016/j.jaci.2010.05.027)

Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ (2014) A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc*

79(4): 577–85.e4 (doi: 10.1016/j.gie.2013.10.027)
Desai TK, Stecevic V, Chang CH, Goldstein NS, Badizadegan K, Furuta GT (2005) Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest Endosc* **61**(7): 795–801 (doi: 10.1016/S0016-5107(05)00313-5)
Francis DL, Foxx-Orenstein A, Arora AS et al (2012) Results of ambulatory pH monitoring do not reliably predict response to therapy in patients with eosinophilic oesophagitis. *Aliment Pharmacol Therap* **35**(2): 300–7 (doi: 10.1111/j.1365-2036.2011.04922.x)
Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I (2012) Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* **142**(7): 1451–9.e1; quiz e14–5 (doi: 10.1053/j.gastro.2012.03.001)
Helou EF, Simonson J, Arora AS (2008) 3-Yr-follow-up of topical corticosteroid treatment for eosinophilic esophagitis in adults. *Am J Gastroenterol* **103**(9): 2194–2199 (doi: 10.1111/j.1572-0241.2008.01989.x)
Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR (2013) Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut* **62**(4): 489–95 (doi: 10.1136/gutjnl-2011-301817)
Hruz P, Straumann A, Bussmann C et al; Swiss EoE study group (2011) Escalating incidence of eosinophilic esophagitis: a 20-year prospective, population-based study in Olten County, Switzerland. *J Allergy Clin Immunol* **128**(6): 1349–50.e5 (doi: 10.1016/j.jaci.2011.09.013)
Kahai S, Vary CP, Gao Y, Seth A (2004) Collagen, type V, alpha1(COL5A1) is regulated by TGF-beta in osteoblasts. *Matrix Biol* **23**(7): 445–55 (doi: 10.1016/j.matbio.2004.09.004)
Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA (1995) Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* **109**(5): 1503–12 (doi: 10.1016/0016-5085(95)90637-1)
Liacouras CA, Wenner WJ, Brown K, Ruchelli E (1998) Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* **26**(4): 380–5
Liacouras CA, Furuta GT, Hirano I et al (2011) Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* **128**(1): 3–20.e6; quiz 21–2 (doi: 10.1016/j.jaci.2011.02.040)
Lucendo AJ, De Rezende LC, Jimenez-Contreras S et al (2011) Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. *Dig Dis Sci* **56**(12): 3551–8 (doi: 10.1007/s10620-011-1775-y)
Lucendo AJ, Arias A, Gonzalez-Cervera J et al (2013) Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol* **131**(3): 797–804 (doi: 10.1016/j.jaci.2012.12.664)
Mishra A, Rothenberg ME (2003) Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology* **125**(5): 1419–27 (doi: 10.1016/j.gastro.2003.07.007)
Molina-Infante J, Ferrando-Lamana L, Ripoll C et al (2011) Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* **9**(2): 110–17 (doi: 10.1016/j.cgh.2010.09.019)
Netzer P, Gschossmann JM, Straumann A, Sendensky A, Weimann R, Schoepfer AM (2007) Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. *Eur J Gastroenterol Hepatol* **19**(10): 865–9 (doi: 10.1097/MEG.0b013e32825a6ab4)
Peterson KA, Thomas KL, Hilden K, Emerson LL, Wills JC, Fang JC (2010) Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. *Dig Dis Sci* **55**(5): 1313–19 (doi: 10.1007/s10620-009-0859-4)
Prasad GA, Alexander JA, Schleck CD et al (2009) Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol* **7**(10): 1055–61 (doi: 10.1016/j.cgh.2009.06.023)
Ravi K, Talley NJ, Smyrk TC et al (2011) Low grade esophageal eosinophilia in adults: an unrecognized part of the spectrum of eosinophilic esophagitis? *Dig Dis Sci* **56**(7): 1981–6 (doi: 10.1007/s10620-011-1594-1)
Remedios M, Campbell C, Jones DM, Kerlin P (2006) Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest Endosc* **63**(1): 3–12 (doi: 10.1016/j.gie.2005.07.049)
Ronkainen J, Talley NJ, Aro P et al (2007) Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population–based Kalixanda study. *Gut* **56**(5): 615–20 (doi: 10.1136/gut.2006.107714)
Rothenberg ME (2009) Biology and treatment of eosinophilic esophagitis. *Gastroenterology* **137**(4): 1238–49 (doi: 10.1053/j.gastro.2009.07.007)
Samuelov L, Sarig O, Harmon RM et al (2013) Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat Genet* **45**(10): 1244–8 (doi: 10.1038/ng.2739)
Schaefer ET, Fitzgerald JF, Molleston JP et al (2008) Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clin Gastroenterol Hepatol* **6**(2): 165–73 (doi: 10.1016/j.cgh.2007.11.008)
Schoepfer AM, Gonsalves N, Bussmann C, Conus S, Simon HU, Straumann A, Hirano I (2010) Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. *Am J Gastroenterol* **105**(5): 1062–70 (doi: 10.1038/ajg.2009.657.)
Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU, Straumann A (2013) Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* **145**(6): 1230–6.e1-2 (doi: 10.1053/j.gastro.2013.08.015)
Sherrill JD, Rothenberg ME (2014) Genetic and epigenetic underpinnings of eosinophilic esophagitis. *Gastroenterol Clin North Am* **43**(2): 269–80 (doi: 10.1016/j.gtc.2014.02.003)
Simon D, Straumann A, Simon HU (2014) Eosinophilic esophagitis and allergy. *Dig Dis* **32**(1–2): 30–3 (doi: 10.1159/000357006)
Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA (2005) Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* **95**(4): 336–43 (doi: 10.1016/S1081-1206(10)61151-9)
Spergel JM, Rothenberg ME, Collins MH et al (2012) Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* **129**(2): 456–63, 463.e1–3 (doi: 10.1016/j.jaci.2011.11.044)
Straumann A, Bussmann C, Conus S, Beglinger C, Simon HU (2008a) Anti-TNF-alpha(infliximab) therapy for severe adult eosinophilic esophagitis. *J Allergy Clin Immunol* **122**(2): 425–7 (doi: 10.1016/j.jaci.2008.06.012)
Straumann A, Bussmann C, Zuber M, Vannini S, Simon HU, Schoepfer A (2008b) Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. *Clin Gastroenterol Hepatol* **6**(5): 598–600 (doi: 10.1016/j.cgh.2008.02.003)
Straumann A, Conus S, Degen L et al (2011) Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* **9**(5): 400–9.e1 (doi: 10.1016/j.cgh.2011.01.017)
Straumann A, Simon HU (2005) Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* **115**(2): 418–19 (doi: 10.1016/j.jaci.2004.11.006)
van Rhijn BD, Weijenborg PW, Verheij J et al (2014) Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. *Clin Gastroenterol Hepatol* **12**(11): 1815–23.e2 (doi: 10.1016/j.cgh.2014.02.037)
Veerappan GR, Perry JL, Duncan TJ et al (2009) Prevalence of eosinophilic esophagitis in an adult population undergoing upper endoscopy: a prospective study. *Clin Gastroenterol Hepatol* **7**(4): 420–6, 426e1–2 (doi: 10.1016/j.cgh.2008.10.009)
Zhang, X, Cheng, E, Huo, X et al (2012) Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. *PloS One* **7**(11): e50037 (doi: 10.1371/journal.pone.0050037)