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## Eosinophilic esophagitis: A clinicopathological review

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### ABSTRACT

Eosinophilic esophagitis (EoE) is considered to be a chronic antigen-driven disease whereby food and/or aeroallergens induce a chronic inflammatory infiltrate in the esophagus, resulting in pathological hyperplasia of the epithelia and muscular layers, and fibrosis of the lamina propria (referred to collectively as remodelling) and the symptoms of dysphagia and food impaction. EoE shares features with other atopic conditions of asthma and atopic dermatitis, such as a TH2 cytokine milieu and a mixed inflammatory infiltrate of eosinophils, mast cells and lymphocytes. Relatively distinct features include the strong male predominance amongst adult patients, and the expression of the eosinophil chemokine eotaxin 3. Current first line treatments such as strict dietary modification and corticosteroids fail many patients. Looking forward, clarification of distinct genotype/phenotype associations, determining the reversibility of remodelling following treatment, and the development of new pharmacotherapies that target fibrotic pathways (as opposed to eosinophilic inflammation per se) or specifically improve barrier integrity appear relevant.

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## 1. Introduction

Eosinophilic esophagitis (EoE) presents in adults as dysphagia and food impaction. The pathophysiological correlates of these symptoms are thought to comprise (1) acute narrowing of the esophageal lumen by inflammation and oedema, (2) fixed narrowing and limited

distensibility of the lumen by remodelling and (3) dynamic and variable narrowing caused by muscular contraction or spasm (Fontillon & Lucendo, 2012; Liacouras et al., 1998; Read & Pandolfino, 2012). The relative contribution of these three pathological processes to the clinical syndrome is not known, although the focus of research and treatment relates to remodelling. (See Figs. 1 and 2) (See Tables 1 and 2.)

Eosinophilic esophagitis (EoE) is considered to be a chronic antigen-driven disease, whereby food and/or aeroallergens induce an eosinophilic infiltration in the esophagus (Mulder & Justinich, 2011). Remodelling refers to the structural changes caused by acute and chronic inflammation, namely epithelial hyperplasia, fibrosis of the lamina propria and muscular hypertrophy (smooth and longitudinal) of the esophagus resulting from an inflammatory infiltrate typical of a TH2-mediated milieu (Cheng et al., 2012). The mechanism of injury has been demonstrated using

**Abbreviations:** EoE, eosinophilic esophagitis; TSLP, thymic stromal lymphopoietin; IL (e.g. IL-3), interleukin; AD, atopic dermatitis; VCAM-1, vascular cell adhesion protein 1; APC, antigen presenting cell; MBP, major basic protein; TGF- $\beta$ , transforming growth factor beta; ICAM, intracellular adhesion molecule; IFN, interferon; VEGF, vascular endothelial growth factor; EMT, epithelial mesenchymal transition.

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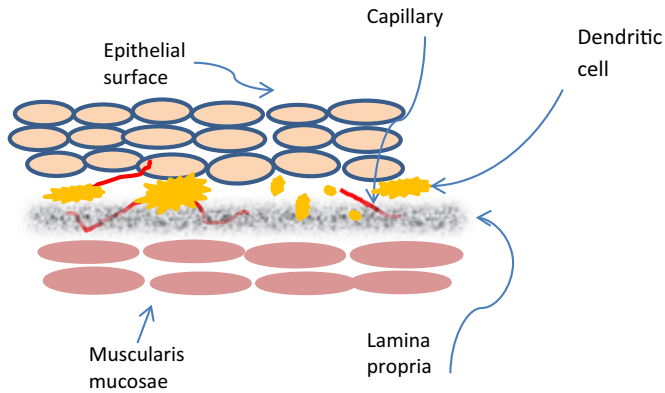


**Fig. 1.** Normal esophagus. Esophageal barrier function is maintained by an orderly arrangement of epithelial cells maintained by gap junction proteins. The muscularis is striated (upper 1/3 of the esophagus) and smooth (lower 2/3) of the esophagus. Antigen presentation may occur by dendritic cells or possibly epithelial cells.

animal models and in vivo human studies (before and after disease-modifying treatments) and may be conceptualised to involve cells (e.g., eosinophils, mast cells, epithelial cells and fibroblasts) cytokines (e.g., interleukins IL-4,5 and 13, and the chemokine eotaxin 3) and adhesion molecules (e.g., integrins and vascular cell adhesion protein 1 (VCAM-1)) (Akei et al., 2005; Liacouras et al., 2011). The precise sequence of events and the dominant cellular signalling or adhesion molecules involved are not yet fully elucidated. Importantly, however, treatments such as topical corticosteroids and dietary modification may at least partially reverse the pathological changes in a significant number of patients, with resultant improvements in swallowing reported in some studies (Aceves et al., 2010; Lieberman et al., 2012). Other atopic conditions, such as asthma and atopic dermatitis (AD) manifest tissue remodelling, again typified by cellular infiltration and fibrosis, and the significant body of research in these fields provides valuable potential clues to the pathogenesis of EoE, and may direct future research (Boguniewicz & Leung, 2011; Royce et al., 2012). The role of epithelial barrier function, epithelial defence, and repair and bacterial colonisation (both crucial in the pathogenesis of AD) are neglected areas of research. The genetic and racial predilection of EoE as a disease predominantly

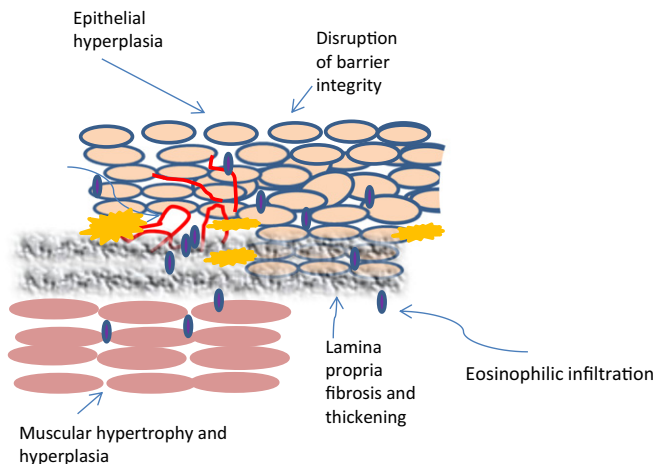


**Fig. 2.** Eosinophilic esophagitis. Epithelial barrier integrity is disrupted, allowing greater contact between antigens and dendritic cells. The epithelial layer is thickened and disordered, and an inflammatory infiltrate rich in eosinophils extends throughout all layers, and may contribute to dysmotility. Angiogenesis is present; the esophagus is friable and bleeds easily at endoscopy. The lamina propria is thickened and fibrotic. The clinical sequelae of the pathological changes are dysphagia and food bolus obstruction due to luminal narrowing, limited distensibility and disturbance of peristalsis.

Gastroscopy confirms Eosinophilic  
Esophagitis with biopsy  
( $>15$  eosinophils per high power field)

PPI commenced BD  
for 8 weeks

No response

Either or

Commence 6  
food elimination  
diet

Budesonide 1mg  
BD

Repeat  
gastroscopy  
after 6 weeks

Repeat  
gastroscopy  
after 6 weeks

**Fig. 3.** There are significant shortcomings in the current treatment options.

of white male Caucasians also deserves careful consideration (Spergel et al., 2009).

The natural history of EoE in the era of disease-modifying treatments (elimination diets and corticosteroids), and the clinicopathological correlations between remodelling, acute inflammation and esophageal dysmotility remain to be determined (Dellon et al., 2013; Gonsalves et al., 2012). The clinical and research tools that determine symptoms (such as dysphagia scores) and esophageal function (manometry) and structure (endoscopic biopsy) have limitations. Improvements in technical utilisation (such as measuring esophageal distensibility instead

1. Wheat
2. Egg
3. Milk
4. Soy
5. Nuts
6. Seafood

**Fig. 4.** The 6 food elimination diet.

**Table 1**  
Pharmacological treatments for EoE.

| Agent                      | Pharmacological targets | Evidence Base                                        | Efficacy        |
|----------------------------|-------------------------|------------------------------------------------------|-----------------|
| Corticosteroids            | Multiple                | Randomised controlled trial (Straumann et al., 2010) | 50–90% response |
| Montelukast                | Leukotriene receptor    | Open label trial (Attwood et al., 2003)              | Ineffective     |
| Sodium cromoglycate        | Mast cell               | Case report (Spergel et al., 2009)                   | Ineffective     |
| Thiopurines (azathioprine) |                         | Case report (Netzer et al., 2007)                    | Effective       |
| Mepolizumab                | IL-5                    | Randomised controlled trial (Straumann et al., 2010) | Ineffective     |
| Reslizumab                 | IL-5                    | Randomised controlled trial (Walsh, 2013)            | Ineffective     |
| Omalizumab                 | IgE                     | Randomised controlled trial (Rocha et al., 2011)     | Ineffective     |
| Infliximab                 | TNF                     | Case report (99)                                     | Ineffective     |
| OC00459                    | CRTH2 receptor          | Randomised controlled trial (Straumann et al., 2013) | Ineffective     |
| Losartan                   | AT-2 receptor           | Under study                                          | ?               |

of contractility and obtaining deeper endoscopic specimens including the lamina propria and muscularis) hold considerable promise (Lucendo et al., 2011; Read & Pandolfino, 2012). Clarifying the relationship between mucosal inflammation, esophageal motility, esophageal distensibility and the symptoms of dysphagia and food bolus obstruction will enable useful treatment end-points to be determined and potentially drive therapeutic innovation.

## 2. Antigen presentation

EoE is viewed as an antigen-driven disease. The striking success of dietary therapy (up to 65% of patients improve on a 6 food elimination diet and 95% improve on an elemental diet) suggests that direct contact with the esophageal mucosa leads to antigen presentation and a localised inflammatory infiltration (Gonsalves et al., 2012; Lieberman et al., 2012). It is also possible that the exposure of the small bowel, which is rich in lymphoid follicles and is immunologically active, may lead to immune activation and subsequent migration of the eosinophils to the esophagus. This is the implication of a recent study, that demonstrated increased intestinal permeability in patients with EoE, that was reversible with treatment (using diet or corticosteroids) (Katzka et al., 2014). Another hypothesis, suggested by the observation that there is a seasonal peak of patients presenting with clinical symptoms of EoE (correlating with high aeroallergen levels in the atmosphere) is that distant contact with the respiratory epithelium of the nose or airways leads to trafficking of eosinophils to the esophagus (Moawad et al., 2010). This hypothesis is supported directly by a murine model, in which antigenic exposure of the nasal and not the esophageal mucosa leads to esophageal infiltration with eosinophils in ovalbumin sensitised mice, and indirectly by human studies of asthma and rhinitis, where stimulation of the nasal or distal airway mucosa leads to an infiltration in the opposing mucosal surface respectively (Braunstaal et al., 2001; Mishra et al., 2001).

If it is assumed that direct exposure of the esophageal epithelial surface to ingested food leads to the eosinophilic infiltration, the question remains as to how the inflammatory cascade then proceeds. The esophageal mucosa is stratified squamous and partially-keratinising in type, whereby up to 30 layers of epithelium separate the luminal contents and, therefore, potential food antigens from the lamina propria, where mast cells and (transiently) eosinophils may reside. There is only

secretion of mucus from submucosal glands in the lower esophagus. This contrasts with the airway epithelium, where a layer of ciliated epithelial cells are interposed with goblet cells that secrete mucus and thereby potentially trap antigen. It is hence apparent that, in health, the physical interaction of the food antigen with inflammatory cells such as mast cells residing in the lamina propria will be limited. Several alternative mechanisms may facilitate the interaction of antigen with inflammatory cells, including the potential of the esophageal epithelium and/or the eosinophils themselves to function as antigen presenting cell (APCs) (Akuthota et al., 2010; Mulder et al., 2011). It is interesting to note that the same physical barrier – multiple layers, lack of mucus to trap antigen – exists in the skin, yet the exposure to aeroallergens such as dust mite is thought to play a role in the pathogenesis of atopic dermatitis (AD dendritic cells, lying within the epithelial layers present antigen in the skin of patients with AD), potentially explaining the immune activation in spite of the barrier function mentioned (Boguniewicz & Leung, 2011). Dendritic cells that are present in the lamina propria of the normal esophagus, are found in increased numbers in patients with Barretts esophagus and esophageal adenocarcinoma but are not found in increased number in patients with EoE, suggesting a role for non-professional APCs such as epithelial cells (Lucendo et al., 2007). Abnormalities in the barrier function of the skin have been proposed as factors in the pathogenesis of AD, both predisposing and perpetuating the condition by enabling increased antigen exposure (Boguniewicz & Leung, 2011). The barrier function of the esophagus is discussed below.

## 3. Inflammatory cell infiltration

### 3.1. Eosinophils

Eosinophils define EoE, in name, diagnosis (>15 eosinophils per high power field following endoscopic biopsy is required to confirm the condition) and response to treatment (Odze, 2012). Furthermore, eosinophils are key players in the process of remodelling. The normal esophagus does not contain eosinophils, although a non-specific eosinophilic inflammatory reaction may occur, for example, in patients with gastroesophageal reflux disease (GORD) and viral esophagitis (Odze, 2012). Eosinophils are derived from myeloid precursors in the bone marrow and mature in response to IL-5, subsequently circulating in

**Table 2**  
Potential future pharmacotherapies for EoE.

| Agent                  | Pharmacological targets | Evidence base                                                               |
|------------------------|-------------------------|-----------------------------------------------------------------------------|
| Anti TSLP antibody     | TSLP or TSLP receptor   | Monkey (Cheng et al., 2013)                                                 |
| Siglec 8               | Siglec receptor         | Mouse (Kiwamoto et al., 2012)                                               |
| Relaxin                | Relaxin receptor        | Mouse (Royce et al., 2009)                                                  |
| Sphingosine kinase     | Sphingosine kinase      | Mouse (Price et al., 2013)                                                  |
| Antibiotics            | Multiple                | Human studies of atopic dermatitis – RCT (Huang et al., 2009)               |
| Methotrexate           | Multiple                | Human studies of atopic dermatitis – case series (Weatherhead et al., 2007) |
| Calcineurin inhibitors | IL-1, multiple          | Human studies of atopic dermatitis – RCT (Reitamo et al., 2000)             |

the blood for up to 20 h and residing in the tissues for between 2–14 days. Eosinophils remain increased in number in the esophagus of patients with EoE (who are untreated), but the absolute density or numbers may fluctuate over time (Mishra, 2009).

Cytokines and chemokines drive the migration of eosinophils into the esophagus. Cytokines such as IL-5, IL-9 and IL-13 and the chemokines, eotaxins 1, 2, and 3, are of central importance, as determined by elevated circulating levels and mRNA expression of esophageal tissue in human patients with EoE, and as demonstrated in murine knockout models (see below) (Blanchard et al., 2007; Konikoff et al., 2006; Niranjan et al., 2013). Studies in vitro of human lung and endobronchiolar tissues suggest a role for vascular adhesion mediated by VCAM-1 and P-selectin on the endothelial surface along with P-selectin glycoprotein and very late protein-4 on eosinophils in facilitating eosinophil attachment and migration into tissues, a process governed by integrins (Aceves et al., 2007).

Once in the esophagus, eosinophils may reside in the intraepithelial spaces where they can form microabscesses when clustered, in the lamina propria and, in some cases, muscular layers although the prevalence of the last two locations is difficult to determine given the limited sampling capability of standard endoscopic biopsies (Lucendo et al., 2011; Odze, 2009). Eosinophils release a range of mediators stored in secondary granules. These include major basic protein (MBP), eosinophil peroxidase, eosinophil cationic protein and eosinophil-derived neurotoxin the release of which causes local tissue damage and esophageal dysmotility, and may secondarily activate mast cells (Kephart et al., 2010; Mavi et al., 2012; Mueller et al., 2006). MBP comprises a major component by volume of the secondary granules and putatively plays a significant role in causing fibrotic remodelling of the esophagus (Cheng et al., 2012; Rothenberg, 2009). MBP may act on esophageal epithelial cells, leading to production of fibroblast growth factor-9 (FGF-9) that in turn promotes epithelial hyperplasia (Mulder et al., 2009). Transforming growth factor- $\beta$  (TGF- $\beta$ ) is also produced by eosinophils. This growth factor promotes activation of quiescent fibroblasts to myofibroblasts and, in turn, the production of fibrotic tissue in the lamina propria (Abonia et al., 2010). TGF- $\beta$  also may contribute to smooth muscle contraction, hyperplasia and hypertrophy.

Eosinophils are both attracted and activated by cytokines and interleukins secreted by other cell types. They are capable of cytokine secretion themselves, which influences the inflammatory process, as demonstrated by studies in vitro of human cells (Hogan & Rothenberg, 2006). Recently, the importance of IL-9 production by eosinophils in patients with EoE and of the ability of this cytokine to attract mast cells were demonstrated (Otani et al., 2013). Further clarification of the role of eosinophils in EoE appears warranted. Eosinophils have, for instance been demonstrated in vivo to have an immunoregulatory role, eosinophil granule proteins decreasing the proliferation of lymphocytes (using donor eosinophils from healthy controls) and have also been shown to influence T cells, skewing development toward a Th 2-like profile (Odemuyiwa et al., 2004; Peterson et al., 1986).

It is apparent that eosinophils contribute to the key pathological processes of tissue remodelling, namely epithelial hyperplasia, subepithelial fibrosis, and muscular hypertrophy and hyperplasia. Eosinophil density may be decreased by administering corticosteroids or instituting dietary therapy, and this reduction has been found in some studies to correlate with a reduction in remodelling or a return to a more histologically normal esophagus (Aceves, Newbury, et al., 2010; Lieberman et al., 2012). Determining if the eosinophil count following endoscopic biopsy is a reliable marker of successful treatment and correlates closely with the reversal of pathological remodelling and symptom resolution needs clarification.

### 3.2. Mast cells

Mast cells (MCs) are found in small numbers in the normal esophagus, residing only in the lamina propria (Odze, 2012). In EoE, increased

density of MCs is found, both in the connective tissues and also within the intraepithelial and muscular layers (Fontillon & Lucendo, 2012). These cells are derived from CD34<sup>+</sup> progenitors in the bone marrow, but mature in the tissues and do not circulate in the bloodstream (E. Cheng et al., 2012).

Mast cells are classically associated with the type 1 hypersensitivity reaction, whereby an antigen comes into contact with specific IgE bound to mast cells leading to activation, degranulation and release of a range of mediators such as histamine, eicosanoids and cytokines (Lucendo et al., 2009). Mast cells bearing IgE have been demonstrated in the esophagus of patients with EoE in a human study, as well as in animal models of disease (Konikoff et al., 2006; Vicario et al., 2010). The evidence that mast cells are important in disease pathogenesis is furthered by the correlation between successful treatment with corticosteroid therapy, dietary therapy and mast cell density (Konikoff et al., 2006; Peterson et al., 2013). Some have suggested that 'mastocytic esophagitis' would be a better term for EoE, given the relatively greater specificity of histological techniques such as mast cell tryptase in determining the diagnosis of EoE, as compared to eosinophil density, which is non-specific (Abonia et al., 2010). Mast cells may modulate remodelling via the production of TGF- $\beta$ , which in turn governs connective tissue production and also possibly smooth muscle contractility (Aceves et al., 2010). Importantly, mast cells, but not eosinophils, may cause smooth muscle spasm (Aceves et al., 2010). In models of asthma, mast cells may release TGF- $\beta$  and, in turn, increase the expression of adhesion molecules, intercellular adhesion molecule (ICAM) and VCAM (Chai et al., 2011). The role of mast cells in inflammation, remodelling and esophageal dysmotility is an area worthy of further research.

### 3.3. B-lymphocytes and IgE antibodies

B cells, identified by staining for CD-20 (human B cell lymphocyte restricted differentiation antigen), are found in the esophageal mucosa of patients with EoE. IgE is also demonstrable, suggesting, along with the observation that skin prick tests and serum-specific IgE to food and/or aeroallergens are frequently positive, that class switching to IgE antibody production by B cells occurs in response to TH2 cytokines (Vicario et al., 2010). Furthermore, a growing body of literature suggests that the removal of the putative food allergens by, for example, elemental or six-food elimination diets, reverses the eosinophilic infiltration and remodelling in these patients (Gonsalves et al., 2012; Lieberman et al., 2012; Spergel et al., 2012).

Whilst EoE is considered an antigen-driven disease, the significance of IgE antibodies in the pathogenesis is debatable. The variably reported positive and negative predictive values of skin prick and patch tests, and antigen-specific IgE antibodies in determining a response to food elimination diets, and the heterogeneity of the responses to food or environmental allergens despite a florid infiltrate of eosinophils, hamper a definitive assertion to this regard (Gonsalves et al., 2012; Lieberman et al., 2012; Spergel et al., 2002). Binding and removing IgE from the circulation with the monoclonal antibody, omalizumab, may greatly decrease IgE levels (Steiss et al., 2012) which has had limited success in EoE (Rocha et al., 2011). The failure of this medication to deliver universally positive results also supports the suggestion that a TH2-mediated cytokine production, rather than B cell antibody production is of greater importance in the pathogenesis of EoE.

### 3.4. T lymphocytes

Patients with EoE have an increased density of T cells (CD8<sup>+</sup>, CD4<sup>+</sup> and CD3<sup>+</sup>) compared to the normal esophagus (Rajavelu et al., 2012). The assertion that EoE is a TH2-mediated disease is upheld by the finding that the cytokines, IL-4, IL-5 and IL-13, are produced in greater quantities by monocytes following antigen exposures in the peripheral blood of patients with EoE compared to healthy controls, and that mRNA for these cytokines is overexpressed in esophageal biopsies. Furthermore,

the mRNA levels decrease following corticosteroid therapy (Blanchard et al., 2007; Yamazaki et al., 2006). It is interesting to note that TH-1 cytokines, TNF- $\alpha$  and IFN- $\gamma$  are also increased following antigen exposure of monocytes and are found in increased quantities in esophageal mucosal biopsies, and that skin patch tests (generally considered a measure of cellular or delayed hypersensitivity) are often positive to common food and aeroallergens (Spergel et al., 2002; Yamazaki et al., 2006).

The cytokines IL-4, IL-5, IL-13 and possibly IL-9 are produced by TH2 and TH-9 cells, and drive the eosinophilic and mastocytic infiltrates characteristic of EoE (Otani et al., 2013). It has been proposed that the expression of eotaxin-3 by the esophageal epithelium, VEGF by the endothelium and integrins by the interstitium attracts these cells to the esophagus, whereby activation and degranulation occur, modulating local tissue damage by MBP, histamine and other mediators (Cheng et al., 2012; Rothenberg, 2009). Furthermore, growth factors such as TGF- $\beta$  and FGF-9 (fibroblast growth factor 9) are released by eosinophils and mast cells that activate quiescent fibroblasts to myofibroblasts, and drive hyperplasia of epithelium and smooth muscle that complete the cycle of remodelling (Fuentebella et al., 2010). It can hence be appreciated that T helper cells are central to the pathogenesis of EoE and the resultant esophageal remodelling. Accordingly, murine T helper deficient mice do not develop EoE (Rajavelu et al., 2012).

Given the role of T helper cells in EoE, some focus of research has been directed at T-regulatory cells that express immunomodulatory cytokines such as IL-2 and IL-10. A small study of paediatric patients with EoE or GORD revealed an increase number of T regulatory cells compared with those of control patients, but no difference between those with different forms of esophageal inflammation (Fuentebella et al., 2010). Murine models have suggested a reduction of regulatory T cells, and a reduction in the esophageal eosinophilia with the infusion of T regulatory cells. Further research appears warranted in humans (Tantibhaedhyangkul et al., 2009).

### 3.5. Basophils and the TSLP basophil axis (see also gender differences)

An exciting recent hypothesis, supported by a murine model and a single human study is that basophils and the epithelial cytokine thymic stromal lymphopoietin (TSLP) are integral to the development of EoE, and that disease development can occur in the absence of IgE and IL-5. Noti et al., in a landmark paper demonstrated that mice that were sensitised to ovalbumin and then re-exposed would develop changes representative of EoE, whereas mice that were treated in addition with antibodies to basophils and TSLP respectively did not develop esophageal eosinophilia (Noti et al., 2013). Remarkably, mice did develop disease even when IgE antibodies were administered, strongly supporting a non-IgE mediated, TSLP/basophil mediated pathogenesis. A further human study demonstrated increased expression of TSLP (immunohistochemistry of esophageal biopsies) and cells resembling activated basophils in these biopsy specimens (flow cytometry) (Noti et al., 2013). This alternative disease model would appear to offer great promise in understanding and potentially treating at least a subset of patients with EoE in the future, with monoclonal antibodies against TSLP representing one possible option (Kim et al., 2013).

## 4. Remodelling

### 4.1. Epithelial cells

The esophagus is lined by squamous partially keratinised epithelium. Patients with EoE develop epithelial hyperplasia, possibly in response to MBP and TGF- $\beta$  produced by eosinophils. A complex positive feedback loop has been proposed to explain the recruitment and maintenance of eosinophilic and mastocytic infiltration and epithelial hyperplasia (Abonia et al., 2010). Eotaxin 3 is produced by esophageal epithelium in response to IL-13, which in turn attracts eosinophils expressing the CCR-3 (eotaxin 3) receptor, promoting the remodelling

described. Finally, it has been proposed that mast cells may produce IL-9 in turn causing increased IL-13 production by TH2 cells, thus completing the loop (see Figs. 1 and 2) (Abonia et al., 2010). Eotaxin 3 appears to be of central importance in the pathogenesis of EoE, with histological and mRNA studies of biopsy specimens demonstrating a specificity of this chemokine in patients with EoE compared to those with GERD, and some (but not all) studies demonstrating a correlation between disease activity, successful treatment and eotaxin 3 levels (Bhattacharya et al., 2007; Cheng et al., 2012). Furthermore, a single nucleotide polymorphism in the gene encoding eotaxin 3 has been demonstrated in some patients with EoE (Abdulnour-Nakhoul et al., 2013; Spergel, 2010).

As well as participating in the process of inflammation and remodelling characteristic of EoE, it is possible that inherited or acquired defects in esophageal epithelial barrier function may contribute to the development and/or perpetuation of EoE. Filaggrin is a structural protein of critical importance in the development of dermatitis. In health, filaggrin is found in the stratum corneum and binds keratin and intermediate filaments (De Benedetto et al., 2008). The gene for profilaggrin, which is subsequently phosphorylated to filaggrin, is located on chromosome 1. Specific mutations within this locus have been described to cause or greatly increase the risk of ichthyosis vulgaris and, of great relevance to EoE, atopic dermatitis (De Benedetto et al., 2008). Since human skin is composed of stratified squamous keratinising epithelium, the importance of filaggrin in keratin attachment is apparent. However, the squamous epithelium of the esophagus doesn't undergo keratinisation to a significant extent. Yet both of these conditions, along with asthma correlate with the filaggrin genetic loci albeit to a lesser extent in the case of asthma and EoE (Boguniewicz & Leung, 2011). It remains to be seen if the association between filaggrin and EoE is more than a confounding factor, simply demonstrating the co-existence of EoE with atopic dermatitis, or if instead there is a hitherto unknown role for filaggrin in the esophagus that contributes to the pathogenesis of EoE. The evidence thus far suggests that filaggrin is not of central importance in EoE, as immunohistochemical staining of the esophagus failed to reveal filaggrin expression (De Benedetto et al., 2008).

Proteins aside from filaggrin, such as occludins and claudins, may be important in EoE. Patients with atopic dermatitis have demonstrable decreases in the production of tight junction proteins, claudin-1 and claudin-23 (De Benedetto et al., 2011). Furthermore single nucleotide polymorphisms in claudin-1 have been demonstrated in patients with AD, implying that decreased protein expression results in disease, rather than being a result of the dermatitis (De Benedetto et al., 2011). It is interesting to note that disruption of tight junction proteins is thought to contribute to the increase in size of intracellular spaces in patients with GERD, and that treating patients with EoE using proton pump inhibitors improves the histology in many patients, and is considered a first line therapy (Molina-Infante et al., 2011; Tobey et al., 1996). Abnormalities in tight junction protein and hence barrier function may precipitate and perpetuate EoE and warrant further study.

### 4.2. Esophageal muscle

The esophageal muscle layer is predominantly striated in the cervical esophagus (the upper third), a mixture of striated and smooth muscle in the middle third and smooth muscle alone in the lower third. The muscle layers themselves are oriented in a circular (inner) and longitudinal (outer) fashion (Mittal, 2013).

The inflammatory infiltrate of EoE that involves the muscular layer includes both mast cells and eosinophils, the former predominating in one study (Aceves et al., 2010). The availability of muscle tissue for study has hampered research as standard gastroscopy forceps will sample muscle tissue in <20% (Lieberman et al., 2012). It is possible that both structural alterations (myocyte hypertrophy and hyperplasia along with inflammatory infiltration) and dynamic changes (muscular contraction) contribute to the clinical syndrome of dysphagia and food

bolus obstruction. Mediators released from mast cells, including histamine, have the ability to cause muscle contraction and hyperplasia according to animal studies and one study of humans, and a correlation between the number of mast cells and the expression of TGF- $\beta$  in the esophageal muscle layer has been demonstrated (Aceves et al., 2010), suggesting a role for mast cells in driving remodelling. Future studies aiming for systematic sampling of the muscular layer across a range of patients with variable disease severity seem necessary. It is yet to be determined, for example, whether the refractory dysphagia typical of some patients with EoE represents ongoing inflammation in the muscle layer or muscular dysmotility, or simply subepithelial fibrosis.

#### 4.3. Epithelial mesenchymal transition

Epithelial mesenchymal transition (EMT) refers to the process whereby epithelial cells may lose their typical histological and immunohistochemical appearance, and functional properties to instead acquire the structure and function of mesenchymal cells, such as motility (instead of adherent tight junctions) and depolarised cytoskeletal arrangements (vimentin instead of cytokeratin in epithelial cells) (Kagalwalla et al., 2012). Myofibroblasts, the quintessential mesenchymal cells characteristic of the remodelling process in asthma, can both synthesise extracellular matrix such as collagen and express  $\alpha$ -smooth muscle actin ( $\alpha$ SMA), possessing contractile properties relevant to airway narrowing (Doerner & Zuraw, 2009). Furthermore myofibroblasts may differentiate to smooth muscle cells and contribute to the muscle thickening typical of chronic asthma (Doerner & Zuraw, 2009).

The same process of EMT, and the resultant fibrosis and smooth muscle hyperplasia observed in asthma may occur in EoE (Kagalwalla et al., 2012). Histological as well as sonographic endoscopic assessments demonstrate thickening of the lamina propria and esophageal muscular layer (Stevoff et al., 2001). Immunohistochemistry and mRNA of tissue in studies of patients with EoE pre- and post-treatment with corticosteroids demonstrate reversible EMT as defined by expression of mRNA or cell surface protein of cytokeratin or vimentin (Kagalwalla et al., 2012). These changes correlated with a reduction in eosinophil number and immunohistochemical stains for TGF- $\beta$  (Kagalwalla et al., 2012). It is hence apparent that the EMT of EoE is an important step in the remodelling of EoE, and that this area warrants further study in line with asthma research (Muir et al., 2013).

#### 4.4. Production of extracellular matrix (ECM) – the process of subepithelial fibrosis

Subepithelial fibrosis is characterised by an increase in the thickness and density of collagen bundles, and an increase in fibroblast density (E. Cheng et al., 2012). Several studies have employed a three-point scoring system to denote the severity of fibrosis according to these three indices (Lieberman et al., 2012; Lucendo et al., 2011). The production of the ECM by myofibroblasts that have been activated by TGF $\beta$  secreted by a range of cells (e.g., eosinophils, mast cells, epithelial cells) leads to SMAD-dependent signalling, upregulating fibrogenic genes such as collagen,  $\alpha$ -SMA and periostin (Bhattacharya et al., 2007). Indeed mRNA studies have found that patients with EoE express SMAD-2 and -3 and periostin at high levels in the esophageal tissues compared to patients with GERD (Aceves et al., 2007). Subepithelial fibrosis is dynamic and does respond in some patients who receive either dietary restriction (the six-food elimination diet or the elemental diet) or corticosteroid therapy (Abu-Sultaneh et al., 2011; Gonsalves et al., 2012; Lieberman et al., 2012; Spergel et al., 2012). The reversal of the fibrous remodelling appears to correlate with the disappearance of eosinophils (Abu-Sultaneh et al., 2011). Determining which patients will respond to therapy remains a research question worthy of consideration. Periostin is traditionally viewed as a cell adhesion molecule regulating extracellular matrix deposition. However, considerable research focus on its role in mediating a range of biological processes involved in the fibrous

remodelling of EoE, such as binding and facilitating cross-linking of collagen, potentially functioning to increase eosinophil adhesion to integrins and inducing epithelial mesenchymal transition, is ongoing (Sherrill & Rothenberg, 2011). Intriguingly, the upregulation of periostin is only partially reversed by corticosteroid administration, suggesting a causative role for this protein in EoE, and reinforcing the potential importance in disease pathogenesis (Sherrill & Rothenberg, 2011).

#### 4.5. Angiogenesis

Angiogenesis, the formation and development of new blood vessels, is a feature of eosinophilic esophagitis. The angiogenic factor vascular endothelial growth factor alpha (VEGF-A), angiogenin and IL-8 have been implicated in promoting this pathological process, and it is notable that eosinophil-depleted mice have decreased angiogenesis (Persad et al., 2012; Rubinstein et al., 2011). The abnormal vascularisation of the diseased esophagus typical of EoE may contribute to the friability and propensity to bleed at the time of endoscopy, and circulating inflammatory cells including eosinophils would have ready access to the site due to the angiogenesis, potentially perpetuating the disease process. A decrease in VEGF has been demonstrated following treatment with corticosteroids and dietary therapy respectively (Lieberman et al., 2012; Lucendo et al., 2011). It is interesting that Siglec F, sialic acid immunoglobulin-like lectin, a protein that is highly expressed on eosinophils, may facilitate eosinophil adhesion and contribute to angiogenesis according to a murine model. Anti-Siglec F was shown in a mouse model to reverse remodelling, eosinophilia and angiogenesis, raising the possibility of the use of this agent as a novel therapy in EoE (Rubinstein et al., 2011).

#### 4.6. Microbiota

Microbiota of the esophagus and possible effects on barrier function may be important in the pathogenesis of EoE. Limited studies in patients with GERD, Barrett's esophagus and esophageal adenocarcinoma (Blackett et al., 2013) have reported a decrease in the microbial diversity in these diseases, with a propensity to be colonised with *Clostridium consisus* in one study (Fillon et al., 2012). It is not known if the difference in microbial diversity represents a causal role for some bacteria, or rather a secondary change to altered local condition. Little is known about the microbial profile in patients with EoE. This is arguably an important area given the ability of skin infection to modulate the severity of atopic dermatitis and for antibiotics to improve the condition. Defensins are proteins that are secreted at the mucosal surface and play a role in maintaining microbial homeostasis, being considered part of the innate immune system. It has been noted that patients with atopic dermatitis and, more recently, those with EoE have a decreased expression of defensins (using techniques *in vitro*) (Schroeder et al., 2013). Further, studies *in vivo* appear warranted.

#### 4.7. Gender differences

There is a male predominance of EoE with a male:female ratio of 3 or 4:1, but this remains unexplained. This differs from asthma where a bimodal gender distribution pattern occurs where asthma is more common in young male children, but adult females are more likely to suffer from asthma (DunnGalvin et al., 2006; Furuta, 2011). Interestingly sensitisation to common food and environmental allergens as determined by skin prick or serum-specific IgE tests shows no sex difference (DunnGalvin et al., 2006). It could be hypothesised that a further factor may then modulate the response to allergen exposure.

TSLP is a protein product mainly of epithelial cells that closely resembles IL-7 in structure and function, and promotes a characteristic TH2-mediated milieu via the activation of dendritic cells in AD and asthma (Zhang et al., 2012). Single nucleotide polymorphisms in the gene

coding for TSLP at 5q22 are associated with predisposition to asthma, AD and EoE (Zhang & Zhou, 2012). Intriguingly, the gene coding for the TSLP receptor is located at Xp22.3/Yp11.3, and polymorphisms at both sex linked loci may predispose male but not female patients to EoE (Sherrill et al., 2010). Recently, the 'TSLP–basophil axis' was studied and found to play a central role in eosinophilic inflammation of the esophagus in both mouse and human models, whereby disease did not develop in the absence of TSLP, and single nucleotide polymorphisms associated with gain of function correlated with increased disease activity (Noti et al., 2013). Further clarification concerning the role of TSLP is clearly warranted.

Nitrous oxide-mediated relaxation of smooth muscle in the bladder is reduced in the presence of testosterone in a rodent model. Effects of TGF $\beta$  in causing cardiac fibrosis and mediating adverse outcomes following myocardial infarction in males are attributed to testosterone (Chung et al., 2013; Vignozzi et al., 2012). Relaxin is a hormone present in large amounts in pregnancy, small amounts in non-pregnant females of reproductive age and also in males. It may have the potential to decrease fibrosis in a range of organs, as demonstrated by animal models (Mookerjee et al., 2006; Royce et al., 2009). A study of relaxin in human bronchial biopsies suggests an association with the remodelling process in asthma, whilst a greater expression of relaxin receptors in female compared with male cruciate ligament tissue has been cited as an explanation for greater tissue laxity in females (Galey et al., 2003; Royce et al., 2012). Further research may allow the therapeutic use of relaxin in the future.

## 5. Alterations in esophageal function (biomechanics)

From a theoretical standpoint, it is apparent that the dysphagia and the food bolus obstruction events that occur in EoE may be caused by fixed narrowing (remodelling), acute narrowing (inflammation and oedema) and esophageal dysmotility or spasm, alone or in combination. As fixed narrowing is demonstrable as focal strictures at endoscopy or barium swallow, the emphasis in research has been on remodelling. Routine esophageal manometry has not uniformly demonstrated abnormalities in patients with EoE, although high-amplitude abnormal distal contractions have been reported in some patients and findings consistent with nutcracker esophagus found in a subset of patients with a high eosinophil count (Lucendo et al., 2007; Moawad et al., 2011; Read & Pandolfino, 2012). Manometry findings in another study were similar in patients with EoE to those with GORD, both having limited peristaltic activity, perhaps demonstrating the importance of a control group (Roman et al., 2011). Research methodologies utilising the barostat or planimetry, which assess esophageal distensibility, however, have defined abnormalities in a significant percentage of patients, with decreased distensibility and pan-esophageal pressurisation characteristic (Compare et al., 2004; Roman et al., 2011). Further research, particularly delineating the change in distensibility with treatment, and correlation with traditional measures of treatment success such as patient reports of dysphagia and eosinophil count at gastroscopy are needed.

Acute or subacute infiltration by inflammatory cells may also explain the dysphagia and food bolus obstruction events. Significant improvement in these features has been demonstrated within six weeks of the commencement of dietary modification, inhaled corticosteroids and even oral corticosteroid therapy. It remains to be determined if complete symptom resolution can be achieved using these treatments and many patients notably do not respond. The presence of eosinophils and mast cells may contribute to the esophageal dysfunction via the production of products of degranulation such as tryptase, major basic protein and eosinophil derived neurotoxin (see below), as well as causing inflammation and oedema (Kephart et al., 2010). Correlations between eosinophil and mast cell densities and dysphagia have been noted, and future definition of this potential pathophysiological

phenomenon appears important in establishing valid treatment goals (Gonsalves et al., 2012).

### 5.1. Treatment

There are compelling reasons to advocate aggressive early treatment of EoE, and there are significant shortcomings in the current treatment options. It is now apparent that EoE is a chronic fibro-stenosing disease that likely benefits from prompt recognition and therapy (Dellon et al., 2014; Schoepfer et al., 2013). It is possible that broadening the treatment goals to include measurable changes and return of normal esophageal distensibility may guide treatment type, duration and potentially define a need for additional agents to address not just eosinophilic inflammation (the current sole focus of treatment) but also lamina propria and muscular thickening and disturbances in physiological peristalsis. It should be noted that it is not clearly established that controlling the eosinophilic inflammation will correct all of the pathological changes and return the esophagus to normal structure and function, although some studies are suggestive (admittedly hampered by the lack of lamina propria and muscularis sampling).

Existing guidelines advocate the use of dietary therapy such as the six-food elimination diet or corticosteroids as first line in the management of EoE, and suggest esophageal dilatation at endoscopy as an alternative in refractory cases (see Figs. 3 and 4) (Dellon et al., 2013). Unfortunately, many patients do not respond or have an inadequate response to either or both therapies, as determined by symptoms and/or subsequent endoscopy and biopsy. The response to a six-food elimination diet in adult and paediatric patients approaches 65%, albeit in a controlled trial situation, whilst swallowed corticosteroids as dry powder or gel solutions result in histological improvement in 50% to 90% of patients (Gonsalves et al., 2012; Straumann et al., 2010). Dietary therapy is by definition restrictive and hence potentially cumbersome. Neither strategy is curative. Patients rapidly relapse following cessation of treatment. Basic scientific research supports this – that is after treatment with corticosteroids eosinophils do not revert to a normal phenotype, rather the capacity of eosinophils to adhere to epithelium is diminished (Lingblom et al., 2014). Corticosteroids may also cause oral candidiasis and a hoarse voice in up to 25% of patients' long term, whilst suppression of the hypothalamopituitary axis and reduction of bone mineral density are potential issues (Lipworth, 1999).

Immunotherapy (subcutaneous or oral/sublingual) could be used as treatment for EoE, and one case series supports this approach (Ramirez & Jacobs, 2013). However the fact that immunotherapy for seasonal rhinitis has potentially caused EoE suggests great caution should be exercised, and further research occurs before such therapy can be advocated (Miehlke et al., 2013). Furthermore immunotherapy for classical food allergy (anaphylactic) is not an established treatment, and the efficacy of the elimination or elemental diets in EoE suggests that food antigens are the likely trigger, again raising questions about the rationale of this approach.

The mast cell stabiliser (sodium cromoglycate) and the leukotriene receptor antagonist (monteleukast) have both been used to treat EoE but without success. Monteleukast does not result in a reduction in esophageal eosinophil count, nor does it sustain histological remission in those treated with corticosteroids (Attwood et al., 2003). Sodium cromoglycate has been used in a number of paediatric patients and found to be ineffective (Spergel et al., 2009). Extrapolating from other gastrointestinal diseases characterised by chronic inflammation (e.g. Crohn's disease and ulcerative colitis) the thiopurines have been used successfully in a case series of 3 patients, with relapse of the condition following the cessation of this medication supporting a treatment effect (Netzer et al., 2007). Nonetheless, the potential side effects of this medication class (increased risk of non-melanomatous skin cancer, increased risk of lymphoma, immunosuppression) make this an unattractive option, given that EoE is not in itself associated with a decreased life expectancy.

Esophageal dilatation at endoscopy is an effective treatment in some patients, providing immediate relief of dysphagia. Initial safety concerns relating to the potential to cause esophageal perforation have been moderated by the publication of a retrospective cohort of 207 adult patients, in which there were no reported perforations although significant chest discomfort and odynophagia occurred in 45% (Schoepfer et al., 2010). In this same study, swallowing was normalised in 50% of patients. Other smaller and prospective studies have suggested clinical remission of dysphagia in up to 90% of patients, which is durable in 50% of these patients at 24 months (Bohm et al., 2010).

It is hence apparent that current treatments have variable and suboptimal success rates, and may be poorly tolerated. The need for alternative management approaches is evident. Biological agents have been trialled in EoE, although to date the efficacy has been disappointing and the cost remains prohibitive. Monoclonal antibodies to IL-5 (mepolizumab and reslizumab), have been trialled, with reslizumab demonstrating a dose related ability to decrease esophageal intraepithelial eosinophil counts in comparison to placebo in a large study of paediatric patients (Walsh, 2013). Unfortunately, even at maximal dose, reductions in the eosinophil count were modest (the study expressing the change in eosinophil count as a percentage, rather than the ability to decrease the eosinophil count to less than 5 per high power field as is customary). Furthermore all groups, including placebo demonstrated an improvement in symptoms, and the difference between groups was not significant. Mepolizumab was used in a small placebo controlled trial of adult patients, and like reslizumab achieved a significant reduction in eosinophils, but not symptoms with between 4 and 13 weeks of follow-up (Straumann et al., 2010).

The CRTH2 receptor antagonist OCO0459 has been trialled in a group of 26 adult patients with EoE. After 26 weeks of therapy, there was a modest decrease in the eosinophil count, but with the mean eosinophil count at the conclusion of therapy in this group of patients with severe EoE decreasing only to 75 per hpf, the utility must be questioned, despite an improvement in the physician rated disease activity index (Straumann et al., 2013). Omalizumab, a monoclonal anti-IgE antibody has been trialled, and has not proven successful according to a randomised controlled trial, as well as case reports (Rocha et al., 2011). Neither histology nor clinical symptoms were improved. Similarly, infliximab (an anti-TNF agent) was studied in a single series of adult patients with EoE, and was not effective (Straumann et al., 2008).

Borrowing from established treatments of other related conditions (asthma and atopic dermatitis) may potentially be extended to EoE, with likely benefit. The calcineurin inhibitors (tacrolimus and the related pimecrolimus) have been used topically in atopic dermatitis, as well as orally in refractory cases (including with cyclosporine) (Reitamo et al., 2000). It is foreseeable that a gel suspension of pimecrolimus or tacrolimus could be used (these agents are fortunately free of the side effect of gum hyperplasia that occurs with cyclosporine). Methotrexate is another option, case reports indicating potential efficacy in atopic dermatitis (Weatherhead et al., 2007). Disturbances in the esophageal microbiota have not been characterised in EoE, but potential abnormalities could be treated with antibiotics, once again an established treatment in AD (Huang et al., 2009).

TSLP may activate basophils and drive a TH2 like mediated disease milieu independent of IgE antibodies (see below). A trial of a monoclonal antibody against TSLP in allergic airways disease in cynomolgus monkeys was successful (Cheng et al., 2013). This is particularly pertinent to EoE, given the SNP coding for TSLP and TSLP receptor that correlate with EoE in particular (Sherrill et al., 2010). Siglecs are cell surface proteins expressed on eosinophils, basophils and mast cells. Siglec F, and the related Siglec 8 in humans govern eosinophil apoptosis, and hence the observation that Siglec F may decrease eosinophilic inflammation in murine airways may lead to human trials in the future (Kiwamoto et al., 2012). Finally sphingosine kinase is an enzyme implicated in IgE mediated mast cell responses. Inhibition of

sphingosine kinase-1 decreases airway hyper-responsiveness and allergic inflammation in murine inflammatory airways disease models (Price et al., 2013). Again EoE, as a mast cell rich inflammatory disease, may foreseeably be helped by this approach and research appears warranted.

All of the pharmacological treatments discussed work by reducing the (mainly) eosinophilic infiltrate. Thinking more broadly, agents that may modulate barrier membrane integrity, and thus minimise antigen exposure, or those that address the end result of eosinophilic infiltration, namely subepithelial fibrosis can be considered. Barrier integrity is a considerable focus of treatment for atopic dermatitis, where factors that denude the epithelium of the protective moisture retaining lipid surface layer, such as harsh soaps, are minimised, and moisturisers and emollients are used extensively. Furthermore, using antibiotics may improve barrier integrity (Boguniewicz & Leung, 2011). One existing treatment for eosinophilic esophagitis, namely PPIs, may act by improving barrier function of the esophagus (Dohil et al., 2012). Patients with coeliac disease have impairments in intestinal permeability and barrier function, and the agent lazerotide, that promotes tight junction assembly has been shown to return epithelial integrity to a more normal phenotype (Gopalakrishnan et al., 2012). As antigen presentation may occur in the duodenum as opposed to the esophagus in EoE, targeting intestinal barrier function may have a role in reducing antigen presentation. It remains to be seen if this agent will have a similar effect in the duodenum of patients with EoE.

Treatments that address fibrosis of the lamina propria are needed. Borrowing from research in cardiovascular medicine and hepatology, angiotensin 2 receptor blockers inhibit TGF- $\beta$  production, that is significantly expressed in EoE (see above). For example ACE inhibitors and AT 2 blockers have been demonstrated to influence myocardial remodelling positively post-myocardial infarction (Uh et al., 2013). A trial has been commenced examining the role of losartan in paediatric EoE patients. Relaxin has been used and demonstrated positive effect in murine asthma models of bronchiolar remodelling (Royce et al., 2009). As expert clinical commentators suggest that the fibrosis and hence dysphagia induced by EoE may persist long after the resolution of inflammation, and currently only responds to dilatation at endoscopy, further therapeutic agents are needed.

## 6. Conclusion

EoE is a chronic antigen-driven disease characterised clinically by dysphagia and recurrent food bolus obstruction events. Despite a great deal of recent research interest, many questions remain. Apparently related conditions such as asthma and atopic dermatitis provide clues as to the likely mechanisms and promising research and therapeutic targets for the future. It is likely that both inherited (gender and individual genes) and acquired factors (e.g. dietary allergens, microbiota) are significant. Clarifying the relationship between the cessation of inflammation, and potential improvements in symptoms and reversal of remodelling will enable treatment end-points to be established and guide therapeutic advances.

## Conflict of interest statement

The author states there are no conflicts of interest to declare.

## References

- Abdulnour-Nakhoul, S. M., Al-Tawil, Y., Gyftopoulos, A. A., Brown, K. L., Hansen, M., Butcher, K. F., et al. (2013). Alterations in junctional proteins, inflammatory mediators and extracellular matrix molecules in eosinophilic esophagitis. *Clin Immunol* 148(2), 265–278, <http://dx.doi.org/10.1016/j.clim.2013.05.004>.
- Abonia, J. P., Franciosi, J. P., & Rothenberg, M. E. (2010). TGF- $\beta$ 1: Mediator of a feedback loop in eosinophilic esophagitis—or should we really say mastocytic esophagitis? *J Allergy Clin Immunol* 126(6), 1205–1207, <http://dx.doi.org/10.1016/j.jaci.2010.10.031>.

- Abu-Sultaneh, S. M., Durst, P., Maynard, V., & Elitsur, Y. (2011). Fluticasone and food allergen elimination reverse sub-epithelial fibrosis in children with eosinophilic esophagitis. *Dig Dis Sci* 56(1), 97–102, <http://dx.doi.org/10.1007/s10620-010-1259-5>.
- Aceves, S. S., Chen, D., Newbury, R. O., Dohil, R., Bastian, J. F., & Broide, D. H. (2010). Mast cells infiltrate the esophageal smooth muscle in patients with eosinophilic esophagitis, express TGF- $\beta$ 1, and increase esophageal smooth muscle contraction. *J Allergy Clin Immunol* 126(6), 1198–1204, <http://dx.doi.org/10.1016/j.jaci.2010.08.050> (e1194).
- Aceves, S. S., Newbury, R. O., Chen, D., Mueller, J., Dohil, R., Hoffman, H., et al. (2010). Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy* 65(1), 109–116, <http://dx.doi.org/10.1111/j.1398-9995.2009.02142.x>.
- Aceves, S. S., Newbury, R. O., Dohil, R., Bastian, J. F., & Broide, D. H. (2007). Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 119(1), 206–212, <http://dx.doi.org/10.1016/j.jaci.2006.10.016>.
- Akei, H. S., Mishra, A., Blanchard, C., & Rothenberg, M. E. (2005). Epicutaneous antigen exposure primes for experimental eosinophilic esophagitis in mice. *Gastroenterology* 129(3), 985–994, <http://dx.doi.org/10.1053/j.gastro.2005.06.027>.
- Akuthota, P., Wang, H., & Weller, P. F. (2010). Eosinophils as antigen-presenting cells in allergic upper airway disease. *Curr Opin Allergy Clin Immunol* 10(1), 14–19, <http://dx.doi.org/10.1097/ACI.0b013e328334f693>.
- Attwood, S. E., Lewis, C. J., Brondor, C. S., Morris, C. D., Armstrong, G. R., & Whittam, J. (2003). Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut* 52(2), 181–185.
- Bhattacharya, B., Carlsten, J., Sabo, E., Kethu, S., Meitner, P., Tavares, R., et al. (2007). Increased expression of eotaxin-3 distinguishes between eosinophilic esophagitis and gastroesophageal reflux disease. *Hum Pathol* 38(12), 1744–1753, <http://dx.doi.org/10.1016/j.humpath.2007.05.008>.
- Blackett, K. L., Siddhi, S. S., Cleary, S., Steed, H., Miller, M. H., Macfarlane, S., et al. (2013). Oesophageal bacterial biofilm changes in gastro-oesophageal reflux disease, Barrett's and oesophageal carcinoma: association or causality? *Aliment Pharmacol Ther* 37(11), 1084–1092, <http://dx.doi.org/10.1111/apt.12317>.
- Blanchard, C., Mingler, M. K., Vicario, M., Abonia, J. P., Wu, Y. Y., Lu, T. X., et al. (2007). IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol* 120(6), 1292–1300, <http://dx.doi.org/10.1016/j.jaci.2007.10.024>.
- Boguniewicz, M., & Leung, D. Y. (2011). Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev* 242(1), 233–246, <http://dx.doi.org/10.1111/j.1600-065X.2011.01027.x>.
- Bohm, M., Richter, J. E., Kelsen, S., & Thomas, R. (2010). Esophageal dilation: simple and effective treatment for adults with eosinophilic esophagitis and esophageal rings and narrowing. *Dis Esophagus* 23(5), 377–385, <http://dx.doi.org/10.1111/j.1442-2050.2010.01051.x>.
- Braunstaal, G. J., Overbeek, S. E., Kleijman, A., Prins, J. B., Hoogsteden, H. C., & Fokkens, W. J. (2001). Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 107(3), 469–476, <http://dx.doi.org/10.1067/mai.2001.113046>.
- Chai, O. H., Han, E. H., Lee, H. K., & Song, C. H. (2011). Mast cells play a key role in Th2 cytokine-dependent asthma model through production of adhesion molecules by liberation of TNF- $\alpha$ . *Exp Mol Med* 43(1), 35–43, <http://dx.doi.org/10.3858/emmm.2011.43.1.004>.
- Cheng, D. T., Ma, C., Niewoehner, J., Dahl, M., Tsai, A., Zhang, J., et al. (2013). Thymic stromal lymphopoietin receptor blockade reduces allergic inflammation in a cynomolgus monkey model of asthma. *J Allergy Clin Immunol* 132(2), 455–462, <http://dx.doi.org/10.1016/j.jaci.2013.05.011>.
- Cheng, E., Souza, R. F., & Spechler, S. J. (2012). Tissue remodeling in eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 303(11), G1175–G1187, <http://dx.doi.org/10.1152/ajpgi.00313.2012>.
- Chung, C. C., Kao, Y. H., & Chen, Y. J. (2013). Androgen modulates cardiac fibrosis contributing to gender differences on heart failure. *Aging Male* 16(1), 22–27, <http://dx.doi.org/10.3109/13685538.2012.754008>.
- Compare, D., Pica, L., Rocco, A., De Giorgi, F., Cuomo, R., Sarnelli, G., et al. (2004). Effects of long-term PPI treatment on producing bowel symptoms and SIBO. *Eur J Clin Invest* 34(4), 380–386.
- De Benedetto, A., Qualia, C. M., Baroody, F. M., & Beck, L. A. (2008). Filaggrin expression in oral, nasal, and esophageal mucosa. *J Invest Dermatol* 128(6), 1594–1597, <http://dx.doi.org/10.1038/sj.jid.5701208>.
- De Benedetto, A., Rafals, N. M., McGirt, L. Y., Ivanov, A. I., Georas, S. N., Cheadle, C., et al. (2011). Tight junction defects in patients with atopic dermatitis. *J Allergy Clin Immunol* 127(3), 773–786, <http://dx.doi.org/10.1016/j.jaci.2010.10.018> (e771–777).
- Dellon, E. S., Gonsalves, N., Hirano, I., Furuta, G. T., Liacouras, C. A., & Katzka, D. A. (2013). ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* 108(5), 679–692, <http://dx.doi.org/10.1038/ajg.2013.71> (quiz 693).
- Dellon, E. S., Kim, H. P., Sperry, S. L., Rybnicek, D. A., Woosley, J. T., & Shaheen, N. J. (2014). A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc* 79(4), 577–585, <http://dx.doi.org/10.1016/j.gie.2013.10.027> (e574).
- Doerner, A. M., & Zuraw, B. L. (2009). TGF- $\beta$ 1 induced epithelial to mesenchymal transition (EMT) in human bronchial epithelial cells is enhanced by IL-1 $\beta$  but not abrogated by corticosteroids. *Respir Res* 10, 100, <http://dx.doi.org/10.1186/1465-9921-10-100>.
- Dohil, R., Newbury, R. O., & Aceves, S. (2012). Transient PPI responsive esophageal eosinophilia may be a clinical sub-phenotype of pediatric eosinophilic esophagitis. *Dig Dis Sci* 57(5), 1413–1419, <http://dx.doi.org/10.1007/s10620-011-1991-5>.
- DunnGalvin, A., Hourihane, J. O., Frewer, L., Knibb, R. C., Oude Elberink, J. N., & Klinge, I. (2006). Incorporating a gender dimension in food allergy research: a review. *Allergy* 61(11), 1336–1343, <http://dx.doi.org/10.1111/j.1398-9995.2006.01181.x>.
- Fillon, S. A., Harris, J. K., Wagner, B. D., Kelly, C. J., Stevens, M. J., Moore, W., et al. (2012). Novel device to sample the esophageal microbiome—the esophageal string test. *PLoS One* 7(9), e42938, <http://dx.doi.org/10.1371/journal.pone.0042938>.
- Fontillon, M., & Lucendo, A. J. (2012). Transmural eosinophilic infiltration and fibrosis in a patient with non-traumatic Boerhaave's syndrome due to eosinophilic esophagitis. *Am J Gastroenterol* 107(11), 1762, <http://dx.doi.org/10.1038/ajg.2012.226>.
- Fuentebella, J., Patel, A., Nguyen, T., Sanjanwala, B., Berquist, W., Kerner, J. A., et al. (2010). Increased number of regulatory T cells in children with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 51(3), 283–289, <http://dx.doi.org/10.1097/MPG.0b013e318e0817b>.
- Furuta, G. T. (2011). Eosinophilic esophagitis: update on clinicopathological manifestations and pathophysiology. *Curr Opin Gastroenterol* 27(4), 383–388, <http://dx.doi.org/10.1097/MOG.0b013e328347bb10>.
- Galey, S., Konieczko, E. M., Arnold, C. A., & Cooney, T. E. (2003). Immunohistological detection of relaxin binding to anterior cruciate ligaments. *Orthopedics* 26(12), 1201–1204.
- Gonsalves, N., Yang, G. Y., Doerfler, B., Ritz, S., Ditto, A. M., & Hirano, I. (2012). Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 142(7), 1451–1459, <http://dx.doi.org/10.1053/j.gastro.2012.03.001> (e1451; quiz e1414–1455).
- Gopalakrishnan, S., Durai, M., Kitchens, K., Tamiz, A. P., Somerville, R., Ginski, M., et al. (2012). Larazotide acetate regulates epithelial tight junctions in vitro and in vivo. *Peptides* 35(1), 86–94, <http://dx.doi.org/10.1016/j.peptides.2012.02.015>.
- Hogan, S. P., & Rothenberg, M. E. (2006). Eosinophil function in eosinophil-associated gastrointestinal disorders. *Curr Allergy Asthma Rep* 6(1), 65–71.
- Huang, J. T., Abrams, M., Tlougan, B., Rademaker, A., & Paller, A. S. (2009). Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics* 123(5), e808–e814, <http://dx.doi.org/10.1542/peds.2008-2217>.
- Kagalwalla, A. F., Akhtar, N., Woodruff, S. A., Rea, B. A., Masterson, J. C., & Mukkada, V. (2012). Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodeling and reverses with treatment. *J Allergy Clin Immunol* 129(5), 1387–1396, <http://dx.doi.org/10.1016/j.jaci.2012.03.005> (e1387).
- Katzka, D. A., Geno, D. M., Blair, H. E., Lamsam, J. L., Alexander, J. A., & Camilleri, M. (2014). Small intestinal permeability in patients with eosinophilic esophagitis during active phase and remission. *Gut*, <http://dx.doi.org/10.1136/gutjnl-2013-305882>.
- Kephart, G. M., Alexander, J. A., Arora, A. S., Romero, Y., Smyrk, T. C., Talley, N. J., et al. (2010). Marked deposition of eosinophil-derived neurotoxin in adult patients with eosinophilic esophagitis. *Am J Gastroenterol* 105(2), 298–307, <http://dx.doi.org/10.1038/ajg.2009.584>.
- Kim, B. S., Siracusa, M. C., Saenz, S. A., Noti, M., Monticelli, L. A., & Sonnenberg, G. F. (2013). TSLP elicits IL-33-independent innate lymphoid cell responses to promote skin inflammation. *Sci Transl Med* 5(170), 170ra, <http://dx.doi.org/10.1126/scitranslmed.3005374> (116).
- Kiwamoto, T., Kawasaki, N., Paulson, J. C., & Bochner, B. S. (2012). Siglec-8 as a druggable target to treat eosinophil and mast cell-associated conditions. *Pharmacol Ther* 135(3), 327–336, <http://dx.doi.org/10.1016/j.pharmthera.2012.06.005>.
- Konikoff, M. R., Blanchard, C., Kirby, C., Buckmeier, B. K., Cohen, M. B., Heubi, J. E., et al. (2006). Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 4(11), 1328–1336, <http://dx.doi.org/10.1016/j.cgh.2006.08.013>.
- Konikoff, M. R., Noel, R. J., Blanchard, C., Kirby, C., Jameson, S. C., Buckmeier, B. K., et al. (2006). A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 131(5), 1381–1391, <http://dx.doi.org/10.1053/j.gastro.2006.08.033>.
- Liacouras, C. A., Furuta, G. T., Hirano, I., Atkins, D., Attwood, S. E., & Bonis, P. A. (2011). Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 128(1), 3–20, <http://dx.doi.org/10.1016/j.jaci.2011.02.040> (e26; quiz 21–22).
- Liacouras, C. A., Wenner, W. J., Brown, K., & Ruchelli, E. (1998). Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 26(4), 380–385.
- Lieberman, J. A., Morotti, R. A., Konstantinou, G. N., Yershov, O., & Chehade, M. (2012). Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. *Allergy* 67(10), 1299–1307, <http://dx.doi.org/10.1111/j.1398-9995.2012.02881.x>.
- Lingblom, C., Bergquist, H., Johnsson, M., Sundstrom, P., Quiding-Jarbrink, M., Bove, M., et al. (2014). Topical corticosteroids do not revert the activated phenotype of eosinophils in eosinophilic esophagitis but decrease surface levels of CD18 resulting in diminished adherence to ICAM-1, ICAM-2, and endothelial cells. *Inflammation*, <http://dx.doi.org/10.1007/s10753-014-9926-x>.
- Lipworth, B. J. (1999). Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 159(9), 941–955.
- Lucendo, A. J., Arias, A., De Rezende, L. C., Vague-Campadre, J. L., Mota-Huertas, T., Gonzalez-Castillo, S., et al. (2011). Subepithelial collagen deposition, profibrogenic cytokine gene expression, and changes after prolonged fluticasone propionate treatment in adult eosinophilic esophagitis: a prospective study. *J Allergy Clin Immunol* 128(5), 1037–1046, <http://dx.doi.org/10.1016/j.jaci.2011.08.007>.
- Lucendo, A. J., Bellon, T., & Lucendo, B. (2009). The role of mast cells in eosinophilic esophagitis. *Pediatr Allergy Immunol* 20(6), 512–518, <http://dx.doi.org/10.1111/j.1399-3038.2008.00798.x>.
- Lucendo, A. J., Castillo, P., Martin-Chavarri, S., Carrion, G., Pajares, R., Pascual, J. M., et al. (2007). Manometric findings in adult eosinophilic esophagitis: a study of 12 cases. *Eur J Gastroenterol Hepatol* 19(5), 417–424, <http://dx.doi.org/10.1097/MEG.0b013e328010bd69>.

- Lucendo, A. J., Navarro, M., Comas, C., Pascual, J. M., Burgos, E., Santamaria, L., et al. (2007). Immunophenotypic characterization and quantification of the epithelial inflammatory infiltrate in eosinophilic esophagitis through stereology: an analysis of the cellular mechanisms of the disease and the immunologic capacity of the esophagus. *Am J Surg Pathol* 31(4), 598–606, <http://dx.doi.org/10.1097/01.pas.0000213392.49698.8c>.
- Mavi, P., Rajavelu, P., Rayapudi, M., Paul, R. J., & Mishra, A. (2012). Esophageal functional impairments in experimental eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 302(11), G1347–G1355, <http://dx.doi.org/10.1152/ajpgi.00013.2012>.
- Miehlke, S., Alpan, O., Schroder, S., & Straumann, A. (2013). Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. *Case Rep Gastroenterol* 7(3), 363–368, <http://dx.doi.org/10.1159/000355161>.
- Mishra, A. (2009). Mechanism of eosinophilic esophagitis. *Immunol Allergy Clin North Am* 29(1), 29–40, <http://dx.doi.org/10.1016/j.jiac.2008.09.010> (viii).
- Mishra, A., Hogan, S. P., Brandt, E. B., & Rothenberg, M. E. (2001). An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 107(1), 83–90, <http://dx.doi.org/10.1172/JCI10224>.
- Mittal, R. K. (2013). Longitudinal muscle of the esophagus: its role in esophageal health and disease. *Curr Opin Gastroenterol* 29(4), 421–430, <http://dx.doi.org/10.1097/MOG.0b013e3283622b57>.
- Moawad, F. J., Maydonovitch, C. L., Veerappan, G. R., Bassett, J. T., Lake, J. M., & Wong, R. K. (2011). Esophageal motor disorders in adults with eosinophilic esophagitis. *Dig Dis Sci* 56(5), 1427–1431, <http://dx.doi.org/10.1007/s10620-011-1655-5>.
- Moawad, F. J., Veerappan, G. R., Lake, J. M., Maydonovitch, C. L., Haymore, B. R., Kosisky, S. E., et al. (2010). Correlation between eosinophilic esophagitis and aeroallergens. *Aliment Pharmacol Ther* 31(4), 509–515, <http://dx.doi.org/10.1111/j.1365-2036.2009.04199.x>.
- Molina-Infante, J., Ferrando-Lamana, L., Ripoll, C., Hernandez-Alonso, M., Mateos, J. M., Fernandez-Bermejo, M., et al. (2011). Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 9(2), 110–117, <http://dx.doi.org/10.1016/j.cgh.2010.09.019>.
- Moore, J. E., Solly, N. R., Royce, S. G., Tregear, G. W., Samuel, C. S., & Tang, M. L. (2006). Endogenous relaxin regulates collagen deposition in an animal model of allergic airway disease. *Endocrinology* 147(2), 754–761, <http://dx.doi.org/10.1210/en.2005-1006>.
- Mueller, S., Aigner, T., Neureiter, D., & Stolte, M. (2006). Eosinophil infiltration and degranulation in oesophageal mucosa from adult patients with eosinophilic oesophagitis: a retrospective and comparative study on pathological biopsy. *J Clin Pathol* 59(11), 1175–1180, <http://dx.doi.org/10.1136/jcp.2005.031922>.
- Muir, A. B., Lim, D. M., Benitez, A. J., Modayur Chandramouleeswaran, P., Lee, A. J., Ruchelli, E. D., et al. (2013). Esophageal epithelial and mesenchymal cross-talk leads to features of epithelial to mesenchymal transition in vitro. *Exp Cell Res* 319(6), 850–859, <http://dx.doi.org/10.1016/j.yexcr.2012.12.002>.
- Mulder, D. J., & Justinich, C. J. (2011). Understanding eosinophilic esophagitis: the cellular and molecular mechanisms of an emerging disease. *Mucosal Immunol* 4(2), 139–147, <http://dx.doi.org/10.1038/mi.2010.88>.
- Mulder, D. J., Pacheco, I., Hurlbut, D. J., Mak, N., Furuta, G. T., MacLeod, R. J., et al. (2009). FGF9-induced proliferative response to eosinophilic inflammation in oesophagitis. *Gut* 58(2), 166–173, <http://dx.doi.org/10.1136/gut.2008.157628>.
- Mulder, D. J., Pooni, A., Mak, N., Hurlbut, D. J., Basta, S., & Justinich, C. J. (2011). Antigen presentation and MHC class II expression by human esophageal epithelial cells: role in eosinophilic esophagitis. *Am J Pathol* 178(2), 744–753, <http://dx.doi.org/10.1016/j.ajpath.2010.10.027>.
- Netzer, P., Gschossmann, J. M., Straumann, A., Sendensky, A., Weimann, R., & Schoepfer, A. M. (2007). Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. *Eur J Gastroenterol Hepatol* 19(10), 865–869, <http://dx.doi.org/10.1097/MEG.0b013e32825a6ab4>.
- Niranjani, R., Rayapudi, M., Mishra, A., Dutt, P., & Dynda, S. (2013). Pathogenesis of allergen-induced eosinophilic esophagitis is independent of interleukin (IL)-13. *Immunol Cell Biol* 91(6), 408–415, <http://dx.doi.org/10.1038/icb.2013.21>.
- Noti, M., Wojno, E. D., Kim, B. S., Siracusa, M. C., Giacomini, P. R., Nair, M. G., et al. (2013). Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nat Med* 19(8), 1005–1013, <http://dx.doi.org/10.1038/nm.3281>.
- Odemuyiwa, S. O., Ghahary, A., Li, Y., Puttagunta, L., Lee, J. E., Musat-Marcu, S., et al. (2004). Cutting edge: human eosinophils regulate T cell subset selection through indoleamine 2,3-dioxygenase. *J Immunol* 173(10), 5909–5913.
- Odze, R. D. (2009). Pathology of eosinophilic esophagitis: what the clinician needs to know. *Am J Gastroenterol* 104(2), 485–490, <http://dx.doi.org/10.1038/ajg.2008.40>.
- Odze, R. D. (2012). Histologic features of gastroesophageal reflux disease and eosinophilic esophagitis. *Gastroenterol Hepatol* 8(7), 472–473.
- Otani, I. M., Anilkumar, A. A., Newbury, R. O., Bhagat, M., Beppu, L. Y., Dohil, R., et al. (2013). Anti-IL-5 therapy reduces mast cell and IL-9 cell numbers in pediatric patients with eosinophilic esophagitis. *J Allergy Clin Immunol* 131(6), 1576–1582, <http://dx.doi.org/10.1016/j.jaci.2013.02.042>.
- Persad, R., Huynh, H. Q., Hao, L., Ha, J. R., Sergi, C., Srivastava, R., et al. (2012). Angiogenic remodeling in pediatric EoE is associated with increased levels of VEGF-A, angiogenin, IL-8, and activation of the TNF- $\alpha$ -NF- $\kappa$ B pathway. *J Pediatr Gastroenterol Nutr* 55(3), 251–260, <http://dx.doi.org/10.1097/MPG.0b013e32824b6391>.
- Peterson, K. A., Byrne, K. R., Vinson, L. A., Ying, J., Boynton, K. K., Fang, J. C., et al. (2013). Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol* 108(5), 759–766, <http://dx.doi.org/10.1038/ajg.2012.468>.
- Peterson, C. G., Skoog, V., & Venge, P. (1986). Human eosinophil cationic proteins (ECP and EPX) and their suppressive effects on lymphocyte proliferation. *Immunobiology* 171(1–2), 1–13, [http://dx.doi.org/10.1016/S0171-2985\(86\)80013-4](http://dx.doi.org/10.1016/S0171-2985(86)80013-4).
- Price, M. M., Oskeritzian, C. A., Falanga, Y. T., Hari Kumar, K. B., Allgood, J. C., & Alvarez, S. E. (2013). A specific sphingosine kinase 1 inhibitor attenuates airway hyperresponsiveness and inflammation in a mast cell-dependent murine model of allergic asthma. *J Allergy Clin Immunol* 131(2), 501–511, <http://dx.doi.org/10.1016/j.jaci.2012.07.014> (e501).
- Rajavelu, P., Rayapudi, M., Moffitt, M., & Mishra, A. (2012). Significance of para-esophageal lymph nodes in food or aeroallergen-induced iNKT cell-mediated experimental eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 302(7), G645–G654, <http://dx.doi.org/10.1152/ajpgi.00223.2011>.
- Ramirez, R. M., & Jacobs, R. L. (2013). Eosinophilic esophagitis treated with immunotherapy to dust mites. *J Allergy Clin Immunol* 132(2), 503–504, <http://dx.doi.org/10.1016/j.jaci.2013.04.053>.
- Read, A. J., & Pandolfino, J. E. (2012). Biomechanics of esophageal function in eosinophilic esophagitis. *J Neurogastroenterol Motil* 18(4), 357–364, <http://dx.doi.org/10.5056/jnm.2012.18.4357>.
- Reitamo, S., Wollenberg, A., Schopf, E., Perrot, J. L., Marks, R., Ruzicka, T., et al. (2000). Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. The European Tacrolimus Ointment Study Group. *Arch Dermatol* 136(8), 999–1006.
- Rocha, R., Vitor, A. B., Trindade, E., Lima, R., Tavares, M., Lopes, J., et al. (2011). Omalizumab in the treatment of eosinophilic esophagitis and food allergy. *Eur J Pediatr* 170(11), 1471–1474, <http://dx.doi.org/10.1007/s00431-011-1540-4>.
- Roman, S., Hirano, I., Kwiatek, M. A., Gonsalves, N., Chen, J., Kahrilas, P. J., et al. (2011). Manometric features of eosinophilic esophagitis in esophageal pressure topography. *Neurogastroenterol Motil* 23(3), 208–214, <http://dx.doi.org/10.1111/j.1365-2982.2010.01633.x> (e111).
- Rothenberg, M. E. (2009). Biology and treatment of eosinophilic esophagitis. *Gastroenterology* 137(4), 1238–1249, <http://dx.doi.org/10.1053/j.gastro.2009.07.007>.
- Royce, S. G., Cheng, V., Samuel, C. S., & Tang, M. L. (2012). The regulation of fibrosis in airway remodeling in asthma. *Mol Cell Endocrinol* 351(2), 167–175, <http://dx.doi.org/10.1016/j.mce.2012.01.007>.
- Royce, S. G., Miao, Y. R., Lee, M., Samuel, C. S., Tregear, G. W., & Tang, M. L. (2009). Relaxin reverses airway remodeling and airway dysfunction in allergic airways disease. *Endocrinology* 150(6), 2692–2699, <http://dx.doi.org/10.1210/en.2008-1457>.
- Rubinstein, E., Cho, J. Y., Rosenthal, P., Chao, J., Miller, M., Pham, A., et al. (2011). Siglec-F inhibition reduces esophageal eosinophilia and angiogenesis in a mouse model of eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 53(4), 409–416, <http://dx.doi.org/10.1097/MPG.0b013e32818218f8>.
- Schoepfer, A. M., Gonsalves, N., Bussmann, C., Conus, S., Simon, H. U., Straumann, A., et al. (2010). Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. *Am J Gastroenterol* 105(5), 1062–1070, <http://dx.doi.org/10.1038/ajg.2009.657>.
- Schoepfer, A. M., Safroneeva, E., Bussmann, C., Kuchen, T., Portmann, S., Simon, H. U., et al. (2013). Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 145(6), 1230–1236, <http://dx.doi.org/10.1053/j.gastro.2013.08.015> (e1231–1232).
- Schroeder, S., Robinson, Z. D., Masterson, J. C., Hosford, L., Moore, W., Pan, Z., et al. (2013). Esophageal human beta-defensin expression in eosinophilic esophagitis. *Pediatr Res* 73(5), 647–654, <http://dx.doi.org/10.1038/pr.2013.23>.
- Sherrill, J. D., Gao, P. S., Stucke, E. M., Blanchard, C., Collins, M. H., Putnam, P. E., et al. (2010). Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. *J Allergy Clin Immunol* 126(1), 160–165, <http://dx.doi.org/10.1016/j.jaci.2010.04.037> (e163).
- Sherrill, J. D., & Rothenberg, M. E. (2011). Genetic dissection of eosinophilic esophagitis provides insight into disease pathogenesis and treatment strategies. *J Allergy Clin Immunol* 128(1), 23–32, <http://dx.doi.org/10.1016/j.jaci.2011.03.046> (quiz 33–24).
- Spergel, J. M. (2010). New genetic links in eosinophilic esophagitis. *Genome Med* 2(9), 60, <http://dx.doi.org/10.1186/gm181>.
- Spergel, J. M., Beausoleil, J. L., Mascarenhas, M., & Liacouras, C. A. (2002). The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 109(2), 363–368.
- Spergel, J. M., Brown-Whitehorn, T. F., Beausoleil, J. L., Franciosi, J., Shuker, M., Verma, R., et al. (2009). 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr* 48(1), 30–36, <http://dx.doi.org/10.1097/MPG.0b013e3281788282>.
- Spergel, J. M., Brown-Whitehorn, T. F., Cianferoni, A., Shuker, M., Wang, M. L., Verma, R., et al. (2012). Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 130(2), 461–467, <http://dx.doi.org/10.1016/j.jaci.2012.05.021> (e465).
- Steiss, J. O., Schmidt, A., Nahrlich, L., Zimmer, K. P., & Rudloff, S. (2012). Immunoglobulin E monitoring and reduction of omalizumab therapy in children and adolescents. *Allergy Asthma Proc* 33(1), 77–81, <http://dx.doi.org/10.2500/aap.2012.33.3500>.
- Stevoff, C., Rao, S., Parsons, W., Kahrilas, P. J., & Hirano, I. (2001). EUS and histopathologic correlates in eosinophilic esophagitis. *Gastrointest Endosc* 54(3), 373–377.
- Straumann, A., Bussmann, C., Conus, S., Beglinger, C., & Simon, H. U. (2008). Anti-TNF- $\alpha$  (infliximab) therapy for severe adult eosinophilic esophagitis. *J Allergy Clin Immunol* 122(2), 425–427, <http://dx.doi.org/10.1016/j.jaci.2008.06.012>.
- Straumann, A., Conus, S., Degen, L., Felder, S., Kummer, M., Engel, H., et al. (2010). Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 139(5), 1526–1537, <http://dx.doi.org/10.1053/j.gastro.2010.07.048> (e1521).
- Straumann, A., Conus, S., Grzonka, P., Kita, H., Kephart, G., Bussmann, C., et al. (2010). Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 59(1), 21–30, <http://dx.doi.org/10.1136/gut.2009.178558>.
- Straumann, A., Hoelsi, S., Bussmann, C., Stuck, M., Perkins, M., Collins, L. P., et al. (2013). Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. *Allergy* 68(3), 375–385, <http://dx.doi.org/10.1111/all.12096>.
- Tantibhadhyangkul, U., Tatevian, N., Gilger, M. A., Major, A. M., & Davis, C. M. (2009). Increased esophageal regulatory T cells and eosinophil characteristics in children

- with eosinophilic esophagitis and gastroesophageal reflux disease. *Ann Clin Lab Sci* 39(2), 99–107.
- Tobey, N. A., Carson, J. L., Alkiek, R. A., & Orlando, R. C. (1996). Dilated intercellular spaces: a morphological feature of acid reflux-damaged human esophageal epithelium. *Gastroenterology* 111(5), 1200–1205.
- Uh, S. T., Kim, T. H., Shim, E. Y., Jang, A. S., Park, S. W., Park, J. S., et al. (2013). Angiotensin-converting enzyme (ACE) gene polymorphisms are associated with idiopathic pulmonary fibrosis. *Lung* 191(4), 345–351, <http://dx.doi.org/10.1007/s00408-013-9469-1>.
- Vicario, M., Blanchard, C., Stringer, K. F., Collins, M. H., Mingler, M. K., Ahrens, A., et al. (2010). Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. *Gut* 59(1), 12–20, <http://dx.doi.org/10.1136/gut.2009.178020>.
- Vignozzi, L., Filippi, S., Morelli, A., Comeglio, P., Cellai, I., Sarchielli, E., et al. (2012). Testosterone/estradiol ratio regulates NO-induced bladder relaxation and responsiveness to PDE5 inhibitors. *J Sex Med* 9(12), 3028–3040, <http://dx.doi.org/10.1111/j.1743-6109.2012.02946.x>.
- Walsh, G. M. (2013). Profile of reslizumab in eosinophilic disease and its potential in the treatment of poorly controlled eosinophilic asthma. *Biologics* 7, 7–11, <http://dx.doi.org/10.2147/BTT.S30133>.
- Weatherhead, S. C., Wahie, S., Reynolds, N. J., & Meggitt, S. J. (2007). An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. *Br J Dermatol* 156(2), 346–351, <http://dx.doi.org/10.1111/j.1365-2133.2006.07686.x>.
- Yamazaki, K., Murray, J. A., Arora, A. S., Alexander, J. A., Smyrk, T. C., Butterfield, J. H., et al. (2006). Allergen-specific in vitro cytokine production in adult patients with eosinophilic esophagitis. *Dig Dis Sci* 51(11), 1934–1941, <http://dx.doi.org/10.1007/s10620-005-9048-2>.
- Zhang, Y., & Zhou, B. (2012). Functions of thymic stromal lymphopoietin in immunity and disease. *Immunol Res* 52(3), 211–223, <http://dx.doi.org/10.1007/s12026-012-8264-z>.
- Zhang, Y., Zhou, X., & Zhou, B. (2012). DC-derived TSLP promotes Th2 polarization in LPS-primed allergic airway inflammation. *Eur J Immunol* 42(7), 1735–1743, <http://dx.doi.org/10.1002/eji.201142123>.