

REVIEW

Recent advances in the pathophysiology and management of eosinophilic oesophagitis

J. Epstein¹ and J. O. Warner²

¹Department of Paediatric Gastroenterology, Chelsea and Westminster Hospital, London, UK and ²Paediatric Section, Faculty of Medicine, Imperial College, Wright Fleming Institute, London, UK

Clinical & Experimental Allergy

Correspondence:

Jenny Epstein, Department of
Paediatric Gastroenterology, Chelsea
and Westminster Hospital, 369
Fulham Road, London SW10 9NH, UK.
E-mail: j.epstein@imperial.ac.uk
Cite this as: J. Epstein and J. O.
Warner, *Clinical & Experimental
Allergy*, 2014 (44) 802–812.

Summary

Eosinophilic oesophagitis is an increasingly recognized allergic gastrointestinal disease, which is becoming more common. Although the average age at diagnosis is 30–50 years, it often affects very young children and carries significant long-term morbidity. While our understanding of its pathophysiology is accumulating, the precise pathways by which the disease arises remain unclear. There are inconsistencies in its diagnosis and definition, and a drive towards international standardization is underway. Current methods for diagnosis and monitoring are relatively invasive, and controversies surround their interpretation. Management strategies are imperfect and involve burdensome long-term dietary exclusions, or drug treatments with uncertain efficacy or serious side-effects. It is the focus of a rapidly increasing body of research, the latest insights from which are systematically presented in this review.

Review methodology: literature search strategy

We present an exhaustive review of the recent literature using the following search strategy. Medline was interrogated for 'eosinophilic oesophagitis' published between December 2008 and December 2013. All resulting abstracts were assessed and those most relevant and important were selected for inclusion. Key earlier papers are also included in our review, which were selected for their particular contribution to the topic.

Eosinophils in the gut

In health, a large proportion of eosinophils home to and reside in the gut and other mucosal surfaces. Here, they appear to serve a sentinel function. Under normal conditions, eosinophils are found from stomach through to colon, where they have a relatively activated phenotype [1]. Notably, they are not found in healthy oesophagus [2]; their presence wherein denotes eosinophilic oesophagitis (EoO). Epithelial damage attracts and activates eosinophils [3] which in health induce remodelling and repair. The presence of eosinophils at normal tissue surfaces is crucial to epithelial homeostasis and luminal defence. They provide not only a fast innate response but also bridge to adaptive immune mechanisms.

Given the properties of eosinophils (to be detailed further below), it is logical that excessive eosinophil activity leads to direct tissue damage as well as immune and inflammatory hyper-reactivity. This is seen both in eosinophil-mediated diseases of the gut and in widespread allergic processes, particularly of the skin and respiratory tract. Eosinophil-derived cationic proteins are found in bronchoalveolar lavage fluid of asthmatic patients and in the skin lesions of patients with atopic dermatitis, where they cause direct tissue damage, increase vascular permeability and recruit other immune cells involved in the allergic response such as mast cells. The Th2 cytokines interleukin (IL)-5 and IL-13 are key inducers of growth, differentiation, recruitment, activation and survival of eosinophils. These cytokines up-regulate eotaxin-3 expression, a major eosinophil chemoattractant [4]. They are implicated in various atopic diseases, and as such, they present candidate therapeutic targets which are under current study.

Eosinophilic oesophagitis: clinical features

Clinical evaluation of EoO should include careful history taking, with recognition that EoO presents differently at different ages. In young childhood, this may be

predominantly with food refusal, feeding difficulties with screaming and back-arching during feeds, vomiting and poor growth [5]. Older children and adults tend to present with more specific dysphagia, epigastric pain, heartburn, anorexia and early satiety. Eczema is a common accompanying morbidity. Indeed, gut-associated problems should be sought in infants presenting with eczema. Children and adults may find strategies to counteract their oesophageal limitations, such as texture avoidance and water drinking, and an awareness of this is important especially when a strong clinical suspicion exists. Symptoms of EoO may closely mimic those of gastro-oesophageal reflux disease (GORD); the similarities and differences are outlined in Table 1. Physical examination should include detailed growth assessment with careful plotting of sequential weight, height and head circumference on appropriate charts. We have recently seen a number of infants with eczema and eosinophilic gastrointestinal disease (EGID) with faltering head growth and sometimes neurodevelopmental consequences.

Oesophago-gastro-duodenoscopy (OGD) remains at the cornerstone of diagnosis. Macroscopic findings

typical (but not pathognomonic) of EoO include transverse oesophageal rings ('trachealization'), white exudates, longitudinal furrows, general narrowing and mucosal fragility (Fig. 1). A recent large meta-analysis suggests that at least one macroscopic abnormality is identified in 93% of patients, and although such findings have a relatively high specificity, their low sensitivity and variable predictive values make them an unreliable tool for diagnosis [6]. The diagnostic process will be discussed in more detail below.

Eosinophilic oesophagitis: epidemiology

An abnormal increase in eosinophils may be observed in single or multiple areas of the gastrointestinal tract. The clinical manifestations of EGID are widespread and varied, including weight loss, failure to thrive, dysphagia, abdominal pain, nausea, vomiting, diarrhoea and constipation. There is a broad cross-over with many other gastrointestinal conditions, and thus, a high index of clinical suspicion must be maintained. Gastrointestinal eosinophilia can represent primary (idiopathic or

Table 1. Clinical features of eosinophilic oesophagitis vs. gastro-oesophageal reflux disease

	Eosinophilic oesophagitis	Gastro-oesophageal reflux disease
Clinical features		
Abdominal pain	Yes	Yes
Vomiting	Yes	Yes
Feeding difficulties	Yes	Sometimes
Food impaction	Yes	Rarely
Male: female	Male predominant	No sex difference
Atopy	Frequently associated	Occasionally
Food sensitization	Frequently associated	May be associated
Lower oesophageal pH monitoring	Usually normal	Abnormal
Endoscopic appearances		
Oesophagitis	Sometimes	Yes
Oesophageal rings	Yes	No
Exudates	Yes	No
Furrows	Yes	No
Narrowing	Sometimes	No
Histological findings		
Eosinophil no.	> 15/HPF	0–9/HPF
Surface layering	Yes	No
Extracellular granules	Yes	No
Oesophageal site	Proximal/distal	Distal
Microabscesses	Yes	No
Basal hyperplasia	Yes	Sometimes
Fibrosis	Yes	Rarely

HPF, high power field.

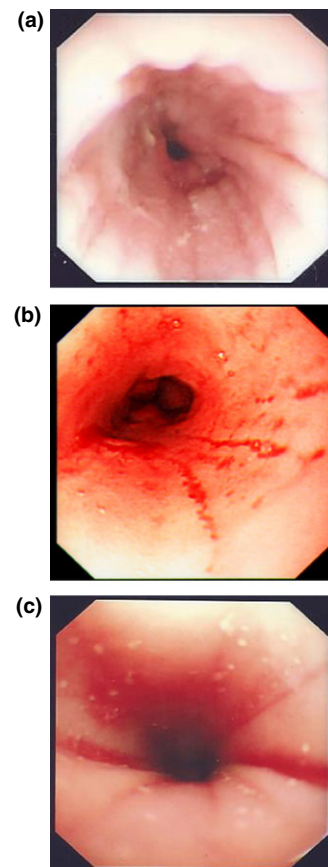


Fig. 1. Macroscopic appearances at endoscopy. (a) Oesophageal furrowing. (b) Oesophageal narrowing and mucosal fragility. (c) White exudates.

allergic) EGID, or it may be secondary to a number of different conditions (Table 2).

The incidence of EGID has increased dramatically over the last decade, as has clinical interest in these conditions. EoO is the commonest and best defined EGID. A search on PubMed for eosinophilic oesophagitis today yields 1116 results published in the last decade. In the decade before this, the same search yielded 81 results. Much of this increase is due to enhanced recognition, although eosinophilic disease is probably also genuinely increasing in prevalence alongside the global increase in allergic disease seen throughout the industrialized world [7]. Incidence estimates vary widely within the literature, largely due to diagnostic inconsistencies. A recent Swiss population-based prospective study showed an average incidence of 2.45 cases per 100 000 with a mean age at diagnosis of 41 years (range: 9–77) [8]. The incidence was shown to increase over 20 years, most recently up to 7.4 per 100 000. Prevalence of EoO at the close of this study was 42.8 per 100 000. The incidence of EoO in children varies from 0.7 to 10 cases per 100 000 per person year, and prevalence 0.2–43 per 100 000 [9].

Eosinophils: background and function in health

Eosinophils are granulocytes of the innate immune system with cytotoxic effector functions against parasites and helminths. Their role in allergy is long established, in which their cytotoxic functions are directed against host tissues. They circulate in relatively low numbers in peripheral blood, comprising < 4% of total peripheral white blood cells. Eosinophils localize to mucosal surfaces and lymphoid tissues, and when activated, they quickly mobilize to the site of infestation or allergen exposure.

Characteristic to eosinophil structure are their cytoplasmic granules. These contain cytotoxic basic proteins, cytokines, chemokines, growth factors and matrix metalloproteinases (MMP) and undergo regulated release when the cell is stimulated, by a process known as piecemeal degranulation (PMD) [10]. The PMD vesicles are mobilized from the cytoplasmic granules and trafficked to the cell membrane where they dock and are released [11, 12]. Thus, eosinophils are able to exert their effects rapidly by the secretion of pre-formed stored mediators and have no requirement for *de novo* protein synthesis, an important property in the innate host response.

The cationic cytotoxic proteins are major components of eosinophil granules and include major basic protein (MBP) [13], eosinophil peroxidase (EPO) [14], eosinophilic cationic protein (ECP) [15] and eosinophil-derived neurotoxin sometimes known as eosinophil protein X (EDN/EPX) [16]. These proteins have direct antihelminthic and cytotoxic effects, as well as a wider range of indirect effects through their cell signalling functions, properties which are more recently coming to light. Eosinophil granules also contain a very broad variety of cytokines, chemokines and growth factors, further expanding their complex cell signalling role, and these include both pro- and anti-inflammatory mediators as well as cytokines involved in Th1, Th2 and regulatory immune responses [17]. Eosinophils are also involved in cross-talk with the enteric nervous system, secreting neuroactive compounds and themselves degranulating in response to nerve-derived mediators. Eosinophils degranulate in response to IgA [18], defending against luminal invaders. They also directly secrete antibacterial compounds including ECP and EDN and extrude extracellular traps that sequester and kill pathogens [19].

Table 2. Eosinophilic gastrointestinal diseases and differential diagnoses

	Type of eosinophilic gastrointestinal disease				
	Eosinophilic oesophagitis	Eosinophilic gastritis	Eosinophilic gastroenteritis	Eosinophilic enteritis	Eosinophilic colitis
Differential diagnosis: eosinophilic	More widespread gastrointestinal eosinophilia				
	Hypereosinophilic syndrome				
	Churg–Strauss syndrome				
Differential diagnosis: non-eosinophilic	Infection (viral, bacterial, parasitic)				
	GORD				
	Drug or food hypersensitivity				
	Connective tissue disease (scleroderma, systemic lupus erythematosus)				
	Crohn's disease				
	Coeliac disease				
	Malignancy				
	Ulcerative colitis				

GORD, gastro-oesophageal reflux disease.

Eosinophilic oesophagitis: immune pathology and allergy

The precise aetiology of EoO is unknown; however, it is understood to be an allergic (Th2-mediated) disease. Local IgE production may occur and through mast cell degranulation (producing eotaxin and cysteinyl leukotrienes) induce eosinophil recruitment. Additionally, IgE can combine with receptors on antigen-presenting cells creating a phenomenon known as antigen focussing which induces further Th2 activation and via IL-5 further eosinophilic inflammation. There is mounting evidence that it has a hereditary component [20]. Candidate genes identified to date include *CCL26* encoding eotaxin 3 [21], and thymic stromal lymphopoietin (TSLP) at 5q22 [22, 23], an important 'master switch' driving allergic (Th2) sensitization, and a cytokine implicated in the pathogenesis of EoO. Inhibition of TSLP in animal models of EoO limits both the development of disease and the severity of established disease, making it a potential future therapeutic clinical target [24]. Specific EoO genotyping is not yet in clinical use.

The observation of seasonal variation in incidence of EoO would suggest that aeroallergens play a role [25, 26]; however, such data come from adult studies, and in children, food allergens are probably more relevant. Seasonality may also of course arise through eating seasonally available foods. A seasonal variation in incidence is not universally found, even between the groups working within the same country [27]. The other possibility is that the combined exposure to an allergenic food and inhalant allergen enhances adverse reactions. This is certainly true in peanut allergy with anaphylaxis more likely to occur in the pollen season in pollen-allergic individuals. In addition, there are cross-reactivities between some foods and inhalants, for example house dust mite and molluscs, tree pollen and tree fruits. Finally, grain mites can contaminate cereals and cause reactions in house dust mite-allergic subjects.

Atopic diseases such as asthma, eczema and allergic rhinitis commonly coexist in patients with EoO [20]. A variable proportion of patients with EoO also have IgE-mediated food allergy [25, 28]. It is possible that two separate EoO phenotypes exist, one with and one without multiple concurrent allergies. Our experience with two cohorts of patients presenting via a paediatric gastroenterology and a paediatric allergy centre certainly supports this concept. Such anecdotal observations hold relevance to the advancing understanding of the pathogenesis of EoO and are the subject of our current study.

Eosinophilic oesophagitis is independently associated with coeliac disease and usually does not respond to gluten exclusion when the two conditions coexist [29]. This raises the possibility of an autoimmune basis for both, although the HLA genotypes DQ2/DQ8 which predispose to coeliac disease do not occur at greater

frequency in patients with EoO [30]. Intriguingly, a higher prevalence of EoO in patients with Ehlers–Danlos syndrome and other connective tissue disorders has been observed [31]. In this cohort, gene expression profiles differ, and it may be that eosinophils behave differently if the extracellular matrix is altered. This may hold the explanation for mechanisms of tissue damage and remodelling, important to disease progression in EoO. Other recent evidence from paediatric EoO biopsies supports this concept, demonstrating up-regulation of genes coding for extracellular matrix proteases and reduced expression of intercellular junction proteins [32].

Eosinophilic oesophagitis: diagnosis and definition

To fulfil the diagnosis of EoO, a minimum of 15 eosinophils per high power field (HPF) must be seen in at least one oesophageal biopsy [33]. However, the diagnosis rests on both histological and clinical features and uncertainties exist in both. Ideally, multiple biopsy specimens should be examined from different oesophageal sites. Using 15 eosinophils per HPF as a threshold, taking 2, 3 or 6 biopsies yields a diagnostic sensitivity of 84%, 97% or 100%, respectively [34]. A pathologist experienced in the diagnosis of EoO will additionally seek other signs of eosinophil activation and degranulation, mucosal inflammation, hyperplasia and fibrosis (Fig. 2a, b, e). The inflammatory infiltrate in EoO typically also contains mast cells and CD4+ T cells (Fig. 2c, d). The eosinophil count should be from an area of peak density, and the size of the high power field may vary from one laboratory to another. Some definitions require greater than 15 eosinophils per HPF; some greater than 20, or 25 eosinophils per HPF. Thus, subjective elements exist in the diagnosis of EoO, and discrepancies may arise in its identification between one professional unit and another. This gives rise to non-conformity within the literature, and thus, data on all aspects of EoO, from epidemiology to the evaluation of therapies, are complex to interpret. As recognition of the disease increases, attempts are being made to standardize its definition, diagnosis and management internationally [33], and evidence suggests that consensus guidelines are increasingly being adopted and are directing meaningful further study [35]. This has already been achieved for assessing inflammation profiles in bronchial biopsies with standardization of sampling, fixing, sectioning, immunohistochemical and cell counting. These standards could be easily applied to gut biopsies.

While the diagnosis of EoO requires the exclusion of GORD, the situation is further complicated by the responsiveness in some cases of oesophageal eosinophilia to proton pump inhibitor (PPI) treatment [36]. Eosinophils are also sometimes seen in GORD,

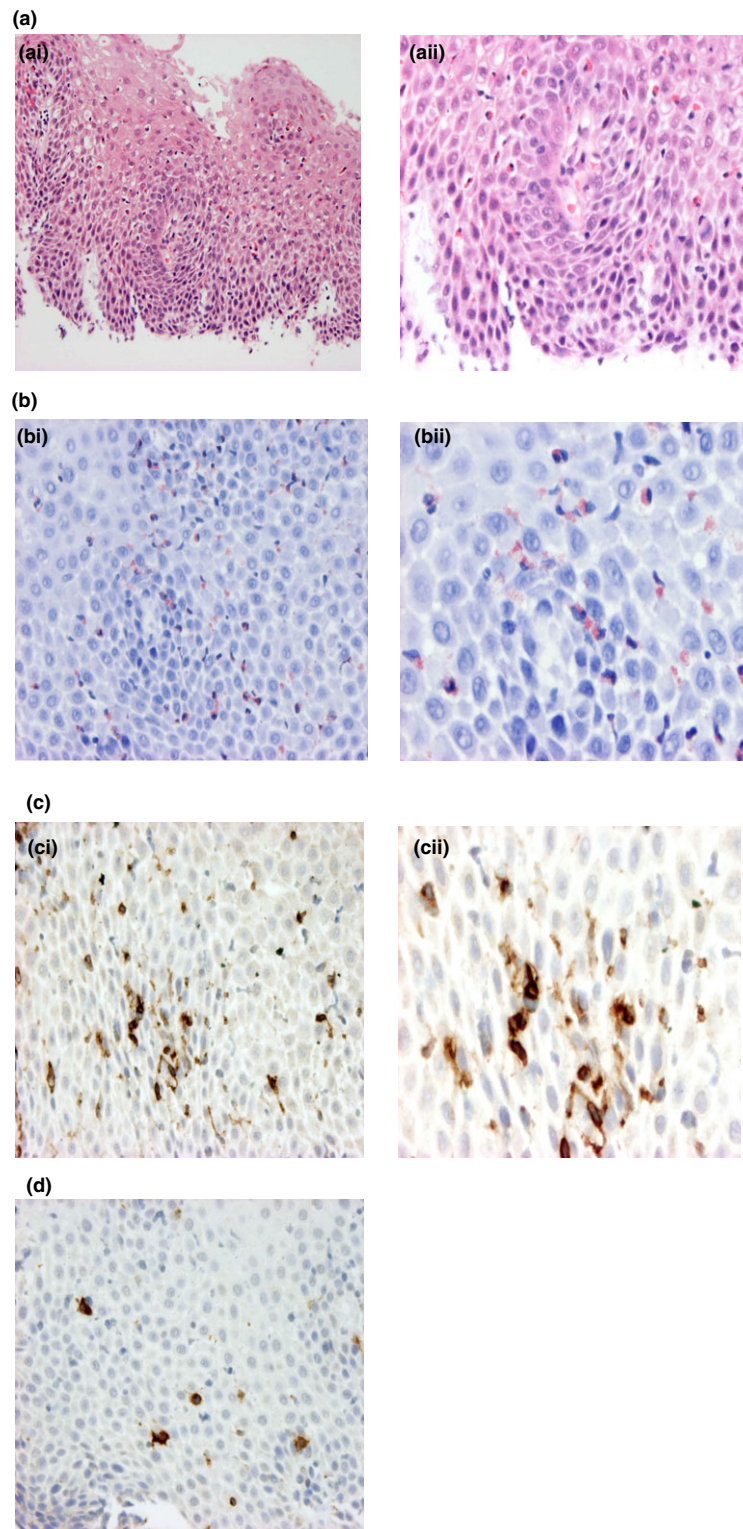


Fig. 2. Oesophageal mucosal appearances at histology. (a) Haematoxylin and eosin stain showing eosinophil infiltration and basal cell hyperplasia (ai: magnification $\times 10$, aii: magnification $\times 20$). (b) Carbol chromotrope 2R stain showing whole and degranulated eosinophils (bi: magnification $\times 20$, bii: magnification $\times 40$). (c) CD4 stain showing CD4+ T cell infiltration (ci: magnification $\times 20$, cii: magnification $\times 40$). (d) CD117 stain showing mast cell infiltration (Magnification $\times 20$). (Images courtesy of Dr Nicholas D Francis).

although the infiltrate is less dense, perhaps between 6 and 9 eosinophils per HPF. A continuum therefore appears to exist between GORD and EoO, with presumably an overlap group lying in the middle who have GORD and allergic features. Taking these features into account, a practical approach to the evaluation of a patient with symptoms or signs suggestive of EoO is proposed in Fig. 3. This algorithm includes that group of patients with GORD and allergy, who have oesophageal eosinophilia which is non-diagnostic for EoO (5–15 eosinophils per HPF). It also introduces a trial of PPI as a prerequisite for the diagnosis of EoO. However, PPI responsiveness may be transient [37], and the caveat exists that despite ongoing PPI therapy, EoO may relapse in some individuals. Therefore, endoscopic re-evaluation must be prompted by clinical course in all cases.

In addition to eosinophil numbers, certain markers of eosinophil activation (as mentioned above and depicted in Fig. 2) also appear useful in differentiating EoO from GORD. These include eosinophilic microabscesses, surface layering of eosinophils, extracellular eosinophil

granules, basal cell hyperplasia and lamina propria fibrosis [38–41]. More targeted cellular stains can also aid in the diagnosis of EoO and its differentiation from GORD, including mast cell tryptase [42] as well as staining for biomarkers such as eotaxin-3 and MBP [43]. Other modalities of investigation may have a role in the diagnosis of EoO and its differentiation from GORD. These include lower oesophageal pH monitoring, multiple intraluminal impedance testing [44, 45] and endoscopic ultrasonographic measurement of oesophageal mucosal and muscular wall thickness [44, 46]. More recently, high-resolution manometry has been used to characterize disordered oesophageal motility in EoO [47]. Many patients had pan-oesophageal pressurization (unlike GORD and other controls), and this motor abnormality was associated with food bolus impaction, suggesting that impaction in EoO may relate as much to dysmotility as stricture formation. Clinical and endoscopic scoring systems have been proposed to create a logistic regression model with reasonable power to differentiate between EoO and GORD [48]; however, such systems remain to be validated.

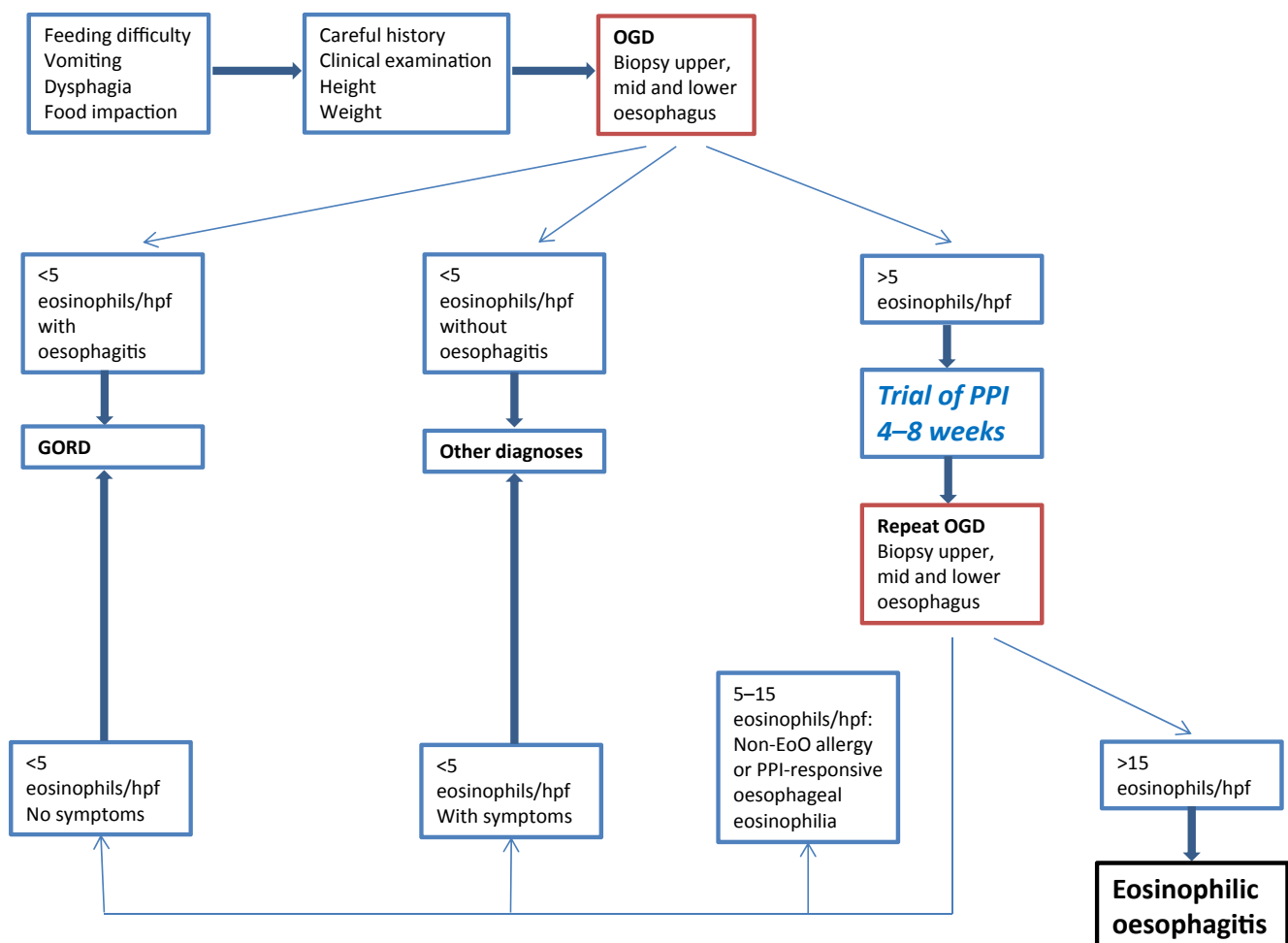


Fig. 3. Diagnostic algorithm for eosinophilic oesophagitis in childhood.

Newer tools are under exploration, including the oesophageal string test [49] and measurements of oesophageal mechanics using an endoscopic functional luminal imaging probe (EndoFLIP) [50]. This latter modality uses impedance planimetry to determine the cross-sectional area of the oesophagus and also assesses its responses to pressure, that is, the distensibility and compliance of the oesophageal wall. These were both found to be reduced in adults with EoO compared to controls, independently of mucosal eosinophil counts or PPI therapy, highlighting the consistency of mechanical dysfunction in EoO, and perhaps in future to provide a standard to quantify this.

In the oesophageal string test, patients swallowed an Enterotest capsule attached to a string and the proximal part of the string was taped to the patient's cheek, holding the string in position within the oesophagus for 24 h [49]. Enterotest capsules were previously used for sampling within the gastrointestinal tract, although in this new application it is simply used as a counterweight for the string. The device was then withdrawn at endoscopy, the fluid eluted from the oesophageal portion of the string and analysed for eosinophil-derived proteins, including MBP-1, EPO, ECP and EDN/EPX. Levels of these eosinophil-derived biomarkers correlated with mucosal eosinophil counts and distinguished between children with active EoO, asymptomatic EoO, GORD and control subjects. On this principle, it may be possible to develop and validate a minimally invasive method of measuring oesophageal inflammation and response to treatments.

Thus, the gold standard investigation, OGD, as well as providing an imperfect reflection of disease activity for the reasons detailed above, is also relatively invasive, especially in children, in whom it is often performed under general anaesthetic. The search continues for peripheral or less invasive biomarkers for the diagnosis and monitoring of EoO. To date, no such disease marker has been identified, either in the peripheral blood or in the stool, although oesophageal fluid may prove a source of such markers and work is ongoing to find minimally invasive sampling methods and validation of mediator levels. Recently, fractionated exhaled nitric oxide has been measured in EoO patients. Although levels differed slightly before and after treatment with topical steroids, they did not correlate with clinical or histological response [51]. Changes in exhaled nitric oxide may reflect inflammation in the airway rather than the oesophagus.

Circulating (total and specific) IgE levels are increased in some patients with EoO, but the association is by no means consistent, and levels do not provide a reliable corollary with disease activity or response to treatment [52]. It is logical to hypothesize that allergic sensitization and specific IgE response is generated

locally within the oesophageal mucosa and not seen in skin or blood, and indeed, there is evidence to support this [53]. Nonetheless, the clinical practice to fully investigate patients with EoO for both aero- and food allergen sensitization is sound, partly because identifying and avoiding triggers may improve oesophageal function and partly to address holistically any current or potential future allergic comorbidities. The combined use of specific IgE and skin prick testing is appropriate to this aim. There has been a suggestion that atopy patch testing may also have a place in achieving a specific allergy diagnosis. This is based on the assumption that delayed T cell-mediated hypersensitivity may be involved. However, there is no standardization of this investigation and results are unconvincing.

Eosinophilic oesophagitis: treatments

Dietary therapy remains the most effective and non-toxic treatment for EoO, and this is especially true in children [54–56]. It may be that children are more likely to adhere to dietary exclusions than adults, and the motivation to avoid steroids is stronger in children; however, dietary therapy is probably equally efficacious in adults [57, 58]. A fully elemental (amino acid) diet is the most efficacious, followed by an elimination diet based on those foods which are statistically the most likely culprits in EoO, for example a six food elimination diet (cows' milk, soy, egg, wheat, nuts and fish) [59–61]. Cow's milk is the most commonly implicated food, and in some patients, dairy exclusion alone may be adequate [62]. Individually tailored elimination diets based on targeted foods may be useful in selected patients [63], and such an approach, although more resource-consuming, tends to result in a less restrictive diet than standard six food elimination. It appears that sensitization to culprit foods is unlikely to diminish over time (at least in the short-term), and reintroduction of successfully eliminated foods reactivates disease. However, longer-term data are currently unavailable on this, and it is not clear whether dietary therapy must be seen as a truly long-term or lifelong solution. Some patients may improve in terms of tolerating previously implicated foods, although asthma, rhinitis and inhalant allergies may replace the foods, a pattern compatible with the 'allergic march' – progressive manifestations of allergic disease within an individual.

Proton pump inhibitor therapy has a role in the management of EoO, both as an initial diagnostic tool to help differentiate EoO from GORD and also to alleviate symptoms. As a therapy, it may be useful in patients who have PPI-responsive oesophageal eosinophilia [36] and in those who have a degree of GOR concurrent with, or consequential to, EoO [64]. Independent from their acid-suppressing action, PPI drugs inhibit Th2-driven

eotaxin-3 production in human oesophageal cell culture [65]. Eotaxin-3 is an important eosinophil chemoattractant and this may be the mechanism by which oesophageal eosinophilia responds to PPI therapy. There may be a role for histamine (H2) receptor antagonists because there are H2 receptors on many pro-inflammatory cells. If IgE and mast cells are involved, then histamine may be playing a part in the pathology.

Corticosteroids are effective at inducing remission in EoO [66], but the disease usually relapses when treatment is withdrawn [67]. Because of their side-effect burden particularly with respect to growth and bone mineralization, this is not a first-choice treatment option, especially in children. However, in adults, steroids form more of a cornerstone of treatment, and their efficacy has been demonstrated both in the induction of remission [68] and as a longer-term maintenance treatment [69], by both clinical and histological indicators. When steroids are used in EoO, topical delivery is preferred to systemic, in order to minimize side-effects. This can be given in the form of swallowed fluticasone inhalations or swallowed budesonide, either nebulized or in a viscous suspension. New evidence suggests that a swallowed viscous suspension is more efficacious, both symptomatically and histologically, probably because it produces greater local oesophageal budesonide exposure [70]. Swallowed fluticasone appears to be less effective clinically, and it may have a high rate of oesophageal candidiasis, in some series 26% [71]. Novel pharmacological delivery systems may be developed in future which could yield further improvements in treatment efficacy.

There is no proven efficacy for sodium cromoglycate or leukotriene receptor antagonists in EoO; however, patients with other allergic comorbidities may derive benefit from these therapies.

Anti-IL-5 (mepolizumab) therapy, although it reduces oesophageal eosinophil numbers, has so far produced somewhat disappointing clinical results [72, 73]. Interestingly, as well as reducing eosinophils, a recent sub-analysis of the tissues revealed also reduced mast cell numbers with anti-IL-5, similar to the findings in asthma [74]. Further trials are ongoing. A large double-blind randomized controlled trial of anti-IL-5 (in this case reslizumab) in 226 children and adolescents similarly showed reduced oesophageal eosinophil counts, as well as improvements in disease activity assessment scores, although the clinical improvement did not differ significantly to that observed in the placebo group [75]. There is a single report of the use of anti-IgE (omalizumab) in two patients with severe multiple food intolerances and eosinophilic oesophagitis, in whom symptom improvement was reported but this was not supported by endoscopic or histological change [76]. Perhaps local application of anti-IL-5 or anti-IgE should

be trialled. If local IgE production is occurring, even in the absence of mast cell involvement, IgE-mediated antigen focussing in antigen-presenting cells will promote Th2 activity and thus eosinophil activation.

Finally, chemoattractant receptor-homologous molecule on Th2 cells (CRTH2) is a prostaglandin (PG) D(2) receptor, expressed by eosinophils and various Th2 cells, mediating chemotaxis and activation. OC000459, a selective CRTH2 antagonist, has recently been trialled in EoO, producing a modest reduction in mucosal eosinophil numbers against placebo in a small randomized controlled trial [77]. Lack of correlation between eosinophil numbers and clinical picture is a recurring theme in EoO research, and a dissociation between symptoms and histology is frequently reported [78]. While trials of other biological therapies (anti-IL-5 and anti-IgE, described above) demonstrate reduced eosinophils without clinical benefit, in the case of anti-CRTH2 the investigators did also show a modest decrease in disease activity as per physician's global assessment.

Eosinophilic oesophagitis: long-term course and complications

The natural history of EoO is not straightforward to define, partly because of the lack of uniformity in the original definition and diagnosis of the condition. Oesophageal eosinophilia in childhood is associated with significantly reduced health-related quality of life, over at least the 15 years following diagnosis [79]. In recognition of this, an EoO-specific paediatric quality of life inventory is currently undergoing validation [80]. Many recognized sequelae exist, including food impaction, oesophageal stricture, narrow calibre oesophagus, oesophageal tears and (rarely) perforations. It remains unclear which proportion of EoO patients progress to such complications, and estimates in the literature are very wide ranging [33]. Certainly in any patient with these presentations, EoO should be considered. Furthermore, the fragility of the oesophagus in EoO is apparent, and it may be reasonable to assume an increased perforation risk of these patients at endoscopy [81, 82], both diagnostic and therapeutic. Although early published guidelines recommended extreme caution in therapeutic oesophageal dilatation in EoO, more recent and extensive data based on systematic review of 1000 dilatations in 500 patients with EoO gave a perforation rate of only 0.3%, more in keeping with the standard risk in non-EoO patients [83]. Oesophageal dilatation is now therefore an accepted and effective treatment for strictures or narrow calibre oesophagus in EoO.

Evidence is accumulating particularly within the adult EoO population that the natural course may

mirror that of Crohn's disease, starting with an uncomplicated inflammatory phenotype and progressing to more complex stricturing behaviour as fibrosis sets in. A retrospective analysis of 200 patients with EoO of all ages showed that a longer delay to initial diagnosis was associated with more fibrotic disease and oesophageal strictures [84]. This suggests that eosinophilic oesophageal inflammation left unchecked predisposes to the development of complications, and supports the importance of early recognition and perhaps more aggressive treatment. The efficacy of steroid treatment in reversing oesophageal fibrosis is described, and recent evidence suggests that dietary therapy is equally able to achieve this [85–87]. However, some studies are less optimistic, such as a recent prospective assessment of subepithelial collagen deposition and pro-fibrotic gene expression, before and after 1 year of topical steroid treatment [88]. The investigators showed only a slight (non-significant) reduction in subepithelial fibrosis, although pro-fibrotic gene expression was down-regulated, significantly in the case of CCL18. This would parallel the situation in

asthma, in which subepithelial collagen deposition is possibly irreversible and unaffected by steroids.

Summary

The role of eosinophils in human health and disease is increasingly being elucidated. Eosinophilic oesophagitis is an important eosinophilic disease which carries a high morbidity, and discrepancies in its diagnosis, definition and management remain. Key outstanding questions to be answered include: clearer delineation of its natural history; identification of reliable, and ideally less invasive, biomarkers for diagnosis and monitoring; more sensitive assays for specific IgE both in serum and in oesophageal secretions; and refinement of treatment options, perhaps individually targeted, based on genotype or allergic phenotype.

Conflict of interests

The authors declare no conflict of interest.

References

- 1 Straumann A, Kristl J, Conus S *et al.* Cytokine expression in healthy and inflamed mucosa: probing the role of eosinophils in the digestive tract. *Inflamm Bowel Dis* 2005; 11:720–6.
- 2 Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol* 2006; 24:147–74.
- 3 Stenfeldt AL, Wenneras C. Danger signals derived from stressed and necrotic epithelial cells activate human eosinophils. *Immunology* 2004; 112:605–14.
- 4 Sherrill JD, Rothenberg ME. Genetic dissection of eosinophilic esophagitis provides insight into disease pathogenesis and treatment strategies. *J Allergy Clin Immunol* 2011; 128:23–32.
- 5 Mukkada VA, Haas A, Maune NC *et al.* Feeding dysfunction in children with eosinophilic gastrointestinal diseases. *Pediatrics* 2010; 126:e672–7.
- 6 Kim HP, Vance RB, Shaheen NJ, Dellon ES. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2012; 10:988–96.
- 7 van Rhijn BD, Verheij J, Smout AJ, Bredenoord AJ. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol Motil* 2013; 25:47–52.
- 8 Hruz P, Straumann A, Bussmann C *et al.* Escalating incidence of eosinophilic esophagitis: a 20 year prospective, population-based study in Olten County Switzerland. *J Allergy Clin Immunol* 2011; 128:1349–50.
- 9 Soon IS, Butzner JD, Kaplan GG, Debruyn JC. Incidence and prevalence of eosinophilic esophagitis in children: systematic review and meta-analysis. *J Pediatr Gastroenterol Nutr* 2013; 57:72–80.
- 10 Melo RC, Spencer LA, Dvorak AM, Weller PF. Mechanisms of eosinophil secretion: large vesiculotubular carriers mediate transport and release of granule-derived cytokines and other proteins. *J Leukoc Biol* 2008; 83:229–36.
- 11 Logan MR, Lacy P, Odemuyiwa SO *et al.* A critical role for vesicle-associated membrane protein-7 in exocytosis from human eosinophils and neutrophils. *Allergy* 2006; 61:777–84.
- 12 Moqbel R, Coughlin JJ. Differential secretion of cytokines. *Sci STKE* 2006; 338:pe26.
- 13 Gleich GJ, Loegering DA, Maldonado JE. Identification of a major basic protein in guinea pig eosinophil granules. *J Exp Med* 1973; 137:1459–71.
- 14 Olsen RL, Little C. Purification and some properties of myeloperoxidase and eosinophil peroxidase from human blood. *Biochem J* 1983; 209:781–7.
- 15 Olsson I, Venge P. Cationic proteins of human granulocytes. II. Separation of the cationic proteins of the granules of leukemic myeloid cells. *Blood* 1974; 44:235–46.
- 16 Durack DT, Ackerman SJ, Loegering DA, Gleich GJ. Purification of human eosinophil-derived neurotoxin. *Proc Natl Acad Sci USA* 1981; 78:5165–9.
- 17 Hogan SP, Rosenberg HF, Moqbel R *et al.* Eosinophils: biological properties and role in health and disease. *Clin Exp Allergy* 2008; 38:709–50.
- 18 Monteiro RC, Hostoffer RW, Cooper MD, Bonner JR, Gartland GL, Kubagawa H. Definition of immunoglobulin A receptors on eosinophils and their enhanced expression in allergic individuals. *J Clin Invest* 1993; 92:1681–5.
- 19 Yousefi S, Gold JA, Andina N *et al.* Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense. *Nat Med* 2008; 14:949–53.
- 20 Noel RJ, Putnam PE, Rothenberg ME. *N Engl J Med* 2004; 351:940–1.
- 21 Blanchard C, Wang N, Stringer KF *et al.* Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006; 116:536–47.
- 22 Rothenberg ME, Spergel JM, Sherrill JD *et al.* Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat Genet* 2010; 42:289–91.
- 23 Sherrill JD, Gao PS, Stucke EM *et al.* Variants of thymic stromal lymphopoietin and its receptor associate with

- eosinophilic esophagitis. *J Allergy Clin Immunol* 2010; 126:160–5.
- 24 Noti M, Wojno ED, Kim BS *et al.* Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. *Nat Med* 2013; 19:1005–13.
 - 25 Almansa C, Krishna M, Buchner AM *et al.* Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. *Am J Gastroenterol* 2009; 104:828–33.
 - 26 Moawad FJ, Veerappan GR, Lake JM *et al.* Correlation between eosinophilic oesophagitis and aeroallergens. *Aliment Pharmacol Ther* 2010; 31:509–15.
 - 27 Sorser SA, Barawi M, Hagglund K, Almojaned M, Lyons H. Eosinophilic esophagitis in children and adolescents: epidemiology, clinical presentation and seasonal variation. *J Gastroenterol* 2013; 48:81–5.
 - 28 Prasad GA, Alexander JA, Schleck CD *et al.* Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol* 2009; 7:1055–61.
 - 29 Abraham JR, Persad R, Turner JM, Huynh HQ. Gluten-free diet does not appear to induce endoscopic remission of eosinophilic esophagitis in children with coexistent celiac disease. *Can J Gastroenterol* 2012; 26:521–4.
 - 30 Lucendo AJ, Arias Á, Pérez-Martínez I *et al.* Adult patients with eosinophilic esophagitis do not show an increased frequency of the HLA-DQ2/DQ8 genotypes predisposing to celiac disease. *Dig Dis Sci* 2011; 56:1107–11.
 - 31 Abonia JP, Wen T, Stucke EM *et al.* High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders. *J Allergy Clin Immunol* 2013; 132:378–86.
 - 32 Abdunnour-Nakhoul SM, Al-Tawil Y, Gyftopoulos AA *et al.* Alterations in junctional proteins, inflammatory mediators and extracellular matrix molecules in eosinophilic esophagitis. *Clin Immunol* 2013; 148:265–78.
 - 33 Dellon ES, Gonsalves N, Hirano I *et al.* ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* 2013; 108:679–92.
 - 34 Shah A, Kagalwalla AF, Gonsalves N, Melin-Aldana H, Li BU, Hirano I. Histopathologic variability in children with eosinophilic esophagitis. *Am J Gastroenterol* 2009; 104:716–21.
 - 35 Sperry SL, Shaheen NJ, Dellon ES. Toward uniformity in the diagnosis of eosinophilic esophagitis (EoE): the effect of guidelines on variability of diagnostic criteria for EoE. *Am J Gastroenterol* 2011; 106:824–32.
 - 36 Dranove JE, Horn DS, Davis MA, Kerek KM, Gupta SK. Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia. *J Pediatr* 2009; 154:96–100.
 - 37 Dohil R, Newbury RO, Aceves S. Transient PPI responsive esophageal eosinophilia may be a clinical subphenotype of pediatric eosinophilic esophagitis. *Dig Dis Sci* 2012; 57:1413–19.
 - 38 Aceves SS, Newbury RO, Dohil R, Schwimmer J, Bastian JF. Distinguishing eosinophilic esophagitis in pediatric patients: clinical, endoscopic, and histologic features of an emerging disorder. *J Clin Gastroenterol* 2007; 41:252–6.
 - 39 Kephart GM, Alexander JA, Arora AS *et al.* Marked deposition of eosinophil-derived neurotoxin in adult patients with eosinophilic esophagitis. *Am J Gastroenterol* 2010; 105:298–307.
 - 40 Mueller S, Neureiter D, Aigner T, Stolte M. Comparison of histological parameters for the diagnosis of eosinophilic oesophagitis versus gastroesophageal reflux disease on oesophageal biopsy material. *Histopathology* 2008; 53:676–84.
 - 41 Protheroe C, Woodruff SA, de Petris G *et al.* A novel histologic scoring system to evaluate mucosal biopsies from patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2009; 7:749–55.
 - 42 Dellon ES, Chen X, Miller CR *et al.* Tryptase staining of mast cells may differentiate eosinophilic esophagitis from gastroesophageal reflux disease. *Am J Gastroenterol* 2011; 106:264–71.
 - 43 Dellon ES, Chen X, Miller CR, Woosley JT, Shaheen NJ. Diagnostic utility of major basic protein, eotaxin-3, and leukotriene enzyme staining in eosinophilic esophagitis. *Am J Gastroenterol* 2012; 107:1503–11.
 - 44 Dalby K, Nielsen RG, Kruse-Andersen S, Fenger C, Durup J, Husby S. Gastroesophageal reflux disease and eosinophilic esophagitis in infants and children. A study of esophageal pH, multiple intraluminal impedance and endoscopic ultrasound. *Scand J Gastroenterol* 2010; 45:1029–35.
 - 45 Rosen R, Furuta G, Fritz J, Donovan K, Nurko S. Role of acid and nonacid reflux in children with eosinophilic esophagitis compared with patients with gastroesophageal reflux and control patients. *J Pediatr Gastroenterol Nutr* 2008; 46:520–3.
 - 46 Korsapati H, Babaei A, Bhargava V, Dohil R, Quin A, Mittal RK. Dysfunction of the longitudinal muscles of the oesophagus in eosinophilic oesophagitis. *Gut* 2009; 58:1056–62.
 - 47 Martín Martín L, Santander C, Lopez Martín MC *et al.* Esophageal motor abnormalities in eosinophilic esophagitis identified by high-resolution manometry. *J Gastroenterol Hepatol* 2011; 26:1447–50.
 - 48 Mulder DJ, Hurlbut DJ, Noble AJ, Justinich CJ. Clinical features distinguish eosinophilic and reflux-induced esophagitis. *J Pediatr Gastroenterol Nutr* 2013; 56:263–70.
 - 49 Furuta GT, Kagalwalla AF, Lee JJ *et al.* The oesophageal string test: a novel minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. *Gut* 2013; 62:1395–405.
 - 50 Kwiatek M, Hirano I, Kahrilas PJ, Rothe J, Luger D, Pandolfino JE. Mechanical properties of the esophagus in eosinophilic esophagitis. *Gastroenterology* 2011; 140:82–90.
 - 51 Leung J, Nguyen-Traxler A, Lee EM *et al.* Assessment of fractionated exhaled nitric oxide as a biomarker for the treatment of eosinophilic esophagitis. *Allergy Asthma Proc* 2012; 33:519–24.
 - 52 Erwin EA, James HR, Gutekunst HM, Russo JM, Kelleher KJ, Platts-Mills TA. Serum IgE measurement and detection of food allergy in pediatric patients with eosinophilic esophagitis. *Ann Allergy Asthma Immunol* 2010; 104:496–502.
 - 53 Vicario M, Blanchard C, Stringer KF *et al.* Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. *Gut* 2010; 59:12–20.
 - 54 Spergel JM. Eosinophilic esophagitis in adults and children: evidence for a food allergy component in many patients. *Curr Opin Allergy Clin Immunol* 2007; 7:274–8.
 - 55 Spergel JM, Brown-Whitehorn TF, Beausoleil JL *et al.* 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr* 2009; 48:30–6.

- 56 Chehade M, Aceves SS. Food allergy and eosinophilic esophagitis. *Curr Opin Allergy Clin Immunol* 2010; 10:231–7.
- 57 Peterson KA, Byrne KR, Vinson LA *et al.* Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol* 2013; 108:759–66.
- 58 Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 2012; 142:1451–9.
- 59 Henderson CJ, Abonia JP, King EC *et al.* Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2012; 129:1570–8.
- 60 Kagalwalla AF, Shah A, Li BU *et al.* Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr* 2011; 53: 145–9.
- 61 Lucendo AJ, Arias A, González-Cervera J *et al.* 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* 2013; 131: 797–804.
- 62 Kagalwalla AF, Amsden K, Shah A *et al.* Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2012; 55:711–16.
- 63 Spergel JM, Brown-Whitehorn TF, Cianferoni A *et al.* Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012; 130:461–7.
- 64 Krarup AL, Villadsen GE, Mejlgaard E, Olesen SS, Drewes AM, Funch-Jensen P. Acid hypersensitivity in patients with eosinophilic oesophagitis. *Scand J Gastroenterol* 2010; 45:273–81.
- 65 Zhang X, Cheng E, Huo X *et al.* Omep-razole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. *PLoS ONE* 2012; 7: e50037.
- 66 Konikoff MR, Noel RJ, Blanchard C *et al.* A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006; 131:1381–91.
- 67 Helou EF, Simonson J, Arora AS. 3-yr-follow-up of topical corticosteroid treatment for eosinophilic esophagitis in adults. *Am J Gastroenterol* 2008; 103:2194–9.
- 68 Straumann A, Conus S, Degen L *et al.* Budesonide is effective in adult and adolescent patients with active eosinophilic esophagitis. *Gastroenterology* 2010; 139:1526–37.
- 69 Straumann A, Conus S, Degen L *et al.* Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2011; 9:400–9.
- 70 Dellon ES, Sheikh A, Speck O *et al.* Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology* 2012; 143:321–4.
- 71 Alexander JA, Jung KW, Arora AS *et al.* Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012; 10:742–9.
- 72 Straumann A, Conus S, Grzonka P *et al.* Antiinterleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010; 59:21–30.
- 73 Assa'ad AH, Gupta SK, Collins MH *et al.* An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology* 2011; 141:1593–604.
- 74 Otani IM, Anilkumar AA, Newbury RO *et al.* Anti-IL-5 therapy reduces mast cell and IL-9 cell numbers in pediatric patients with eosinophilic esophagitis. *J Allergy Clin Immunol* 2013; 131: 1576–82.
- 75 Spergel JM, Rothenberg ME, Collins MH *et al.* Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2012; 129:456–63.
- 76 Rocha R, Vitor AB, Trindade E *et al.* Omalizumab in the treatment of eosinophilic esophagitis and food allergy. *Eur J Pediatr* 2011; 170:1471–4.
- 77 Straumann A, Hoesli S, Bussmann C *et al.* Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. *Allergy* 2013; 68:375–85.
- 78 Penttinen S, Putnam PE, Collins MH, Rothenberg ME. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2009; 48:152–60.
- 79 DeBrosse CW, Franciosi JP, King EC *et al.* Long-term outcomes in pediatric-onset esophageal eosinophilia. *J Allergy Clin Immunol* 2011; 128:132–8.
- 80 Franciosi JP, Hommel KA, Greenberg AB *et al.* Development of the pediatric quality of life inventory eosinophilic esophagitis module items: qualitative methods. *Gastroenterology* 2012; 12:135.
- 81 Nantes O, Jimenez FJ, Zozaya JM, Vila JJ. Increased risk of esophageal perforation in eosinophilic esophagitis. *Endoscopy* 2009; 41(Suppl. 2):E177–8.
- 82 Shim LS, Grehn M. Education and imaging. Gastrointestinal: oesophageal perforation during endoscopy for food impaction in eosinophilic oesophagitis. *J Gastroenterol Hepatol* 2010; 25:428.
- 83 Dellon ES. Diagnosis and management of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012; 10:1066–78.
- 84 Schoepfer A, Safroneeva E, Bussmann C *et al.* Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 2013; 145:1230–6.
- 85 Lieberman JA, Morotti RA, Konstantinou GN, Yershov O, Chehade M. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. *Allergy* 2012; 67:1299–307.
- 86 Kagalwalla AF, Akhtar N, Woodruff SA *et al.* Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodeling and reverses with treatment. *J Allergy Clin Immunol* 2012; 129:1387–96.
- 87 Abu-Sultaneh SM, Durst P, Maynard V, Elitsur Y. Fluticasone and food allergen elimination reverse sub-epithelial fibrosis in children with eosinophilic esophagitis. *Dig Dis Sci* 2011; 56:97–102.
- 88 Lucendo AJ, Arias A, De Rezende LC *et al.* 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* 2011; 128:1037–46.