Overview of eosinophilic oesophagitis

ABSTRACT
Eosinophilic oesophagitis is a disease that has been recognized in the past 30 years. It causes dysphagia and other symptoms of oesophageal dysfunction. Eosinophilic oesophagitis presents either with a chronic feeling of difficulty swallowing, with food moving slowly through the oesophagus, or as an acute food bolus obstruction requiring emergency attention. Patients may also experience chest pain at this time. It is an inflammatory disorder, thought to be driven by food or environmental antigens, where the most distinctive cell type is eosinophils. Eosinophilic oesophagitis is mediated through a local IgG4 mechanism and does not manifest as a systemic disease. It is diagnosed only on endoscopy and biopsy – there are characteristic endoscopic appearances with oedema, rings, furrows and strictures but the golden rule in its diagnosis is to perform multiple biopsies from multiple sites in the oesophagus in all patients with dysphagia or other oesophageal dysfunction. Finding a peak concentration of >15 eosinophils per high power field in this situation is diagnostic of eosinophilic oesophagitis. Eosinophilic oesophagitis is not usually related to gastro-oesophageal reflux disease, but the two conditions may co-exist. Current therapies include topical steroids (oro-dispersible formulation of budesonide), proton pump inhibitors and dietary exclusions. Therapeutic oesophageal dilatation is reserved for refractory symptoms or tight strictures.

Eosinophilic oesophagitis is a disease that has been recognized in the past 30 years, that causes dysphagia and other symptoms of oesophageal dysfunction. As it is relatively new (Lucendo et al, 2017a) and because of a lack of licenced specific medication the understanding and management of this disease has been limited.

The definition of disease
Eosinophilic oesophagitis is a chronic, local immune-mediated oesophageal disease, characterized clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation. Other systemic and local causes of oesophageal eosinophilia should be excluded. Clinical manifestations or pathological data should not be interpreted in isolation (Lucendo et al, 2017a).

Epidemiology
Eosinophilic oesophagitis is significantly more common in men than women (3:1) and the literature reports a rising frequency of significant proportion over the past 20 years. How much this increase is related to the disease incidence increasing and how much is the increased level of diagnosis of prevalent disease is very hard to evaluate, but the condition had never been recognized before 1993 and, even then, was regarded as a rare event. Now there are cohorts of many thousands of patients in the national registers of Spain, Switzerland, the Netherlands and the USA (where insurance records show a massive increase in disease prevalence) (Hruz et al, 2011; Arias and Lucendo, 2013; van Rhijn et al, 2013; Dellon et al, 2014a).

Aetiology and pathogenesis
The underlying cause of eosinophilic oesophagitis is generally accepted to be an antigen-driven effect occurring only in the oesophagus, with food the most likely source of antigens (Liacouras et al, 2011). Alternative antigens from the environment such as pollen and pollution are potential sources but evidence for this is rarely found in individual patients and is rarely helpful in therapy or symptom prevention. The eosinophilic inflammation is quite organ specific because the antigens in eosinophilic oesophagitis do not cause eosinophilic inflammation elsewhere in the gastrointestinal tract and only affect the oesophagus. Although other food allergies may occur and symptoms of food intolerance may occur elsewhere in the gut, it is surprising that patients who suffer dysphagia and oesophageal dysfunction from eosinophilic inflammation rarely have pathological levels of eosinophils elsewhere in the gut.

Eosinophilic oesophagitis is not manifested through the typical allergic pathways of IgE, but is a local IgG4-mediated mucosal inflammation in the oesophagus. The condition is not caused by acid reflux – indeed, acid reflux may be less common in patients with eosinophilic oesophagitis than it is in the general population (Lucendo et al, 2017a). However, the two can occur together, because of the high frequency of gastro-oesophageal reflux disease, which can sometimes create confusion in diagnosis.

Presentation
The most specific and indicative symptom of eosinophilic oesophagitis is a feeling of food sticking in the chest after swallowing (Attwood et al, 1993; Straumann et al, 1994). Sometimes it is just a feeling of the food moving slowly, in other patients it clearly feels as if food sticks for a while and in some the sticking of a food bolus continues for a long time.

Patients may have intermittent symptoms but in many dysphagia is present all the time, albeit in varying degrees. By tolerating the symptom and adapting the diet to include...
softer foods or liquids, sufferers become accustomed to the condition and often cannot remember precisely when the problem started. What often brings the symptoms to attention is when the patient eats in public – at a restaurant or a party – and has to leave the table to try and remove food which is stuck to relieve the distress.

Occasionally the first time the symptom is brought to medical attention is when a food bolus gets stuck for hours and the patient presents to the emergency department. This can be a problem because in many countries patients with food bolus obstruction are referred to ear nose and throat surgeons, who do not perform flexible endoscopy and do not biopsy the oesophagus. The single commonest cause of food bolus obstruction is eosinophilic oesophagitis (Liacouras et al, 2011) and such patients should always be referred to the gastroenterology department. Endoscopy can be planned for the earliest opportunity, preferably within 12 hours.

In children the presentation is also insidious and not clear in its origin. Very young children (<5 years) do not express difficulty in swallowing, especially if they are still eating soft foods. In these, parents note that the child has regurgitation, vomiting or failure to thrive (Kelly et al, 1995). When the disease onset is early in life then the child has no reference for what is normal and just accepts that solids might be difficult to get down. The child may avoid certain foods and be labelled as a picky eater. Older girls may be labelled as having anorexia nervosa – not a common situation but one where great relief is felt when a definitive cause of the symptoms of eating difficulty is found.

The effects of eosinophilic oesophagitis on quality of life

Because of its insidious onset the effects of eosinophilic oesophagitis on quality of life are not always easy to quantify and patients minimize their symptoms by food avoidance techniques. There is no point in asking if a patient has difficulty with solids if that person has stopped trying to eat solids for the past 10 years. Reaching a diagnosis has a major impact on patients who have suffered a condition they did not understand and where previous medical encounters failed to make the diagnosis. In young children distinguishing eosinophilic oesophagitis from other causes of vomiting or regurgitation is very helpful in providing a therapy that allows growth to develop correctly. In older children, especially adolescents, having a diagnosis helps when it removes the label of ‘eating disorder’.

In adults the symptoms often persist, intermittently, and patients learn to avoid foods which are physically tough and likely to get stuck. These are usually not the foods that are the source of antigen drive, and so such avoidance only manages the symptoms without dealing with the underlying inflammation, and the disorder persists.

Patients who suffer symptoms of oesophageal dysfunction will often present their symptom to the GP as ‘indigestion’, as that is a term used to describe discomfort in the oesophagus. However, the discomfort of eosinophilic oesophagitis is quite different and not usually that painful, but a feeling of food sticking and a nagging discomfort, with difficulty continuing to eat (until the bolus has moved on). It is not relieved by antacids or alginates. If the GP does not take a careful and specific history he/she may simply accept the label of indigestion, or even worse attribute the term dyspepsia (just Greek for indigestion) and the patient is then stuck with an incorrect diagnosis and little hope of specific treatment.

A challenge for GPs and hospital consultants is to distinguish eosinophilic oesophagitis from other upper gastrointestinal conditions – gastro-oesophageal reflux disease, dysmotility or oesophageal cancer. Table 1 gives a useful list of the features distinguishing eosinophilic oesophagitis from gastro-oesophageal reflux disease. Although most doctors know about achalasia, it is quite rare (incidence 1/100 000 population per annum) whereas the incidence of eosinophilic oesophagitis may be over 10 times this figure. A trial of proton pump inhibitors is often used as a diagnostic manoeuvre in gastro-oesophageal reflux disease but for a variety of reasons can be unreliable. One reason is that even without acid being involved in the pathogenesis of eosinophilic oesophagitis, a minority of patients seem to respond to proton pump inhibitor therapy relating to a local epithelial immune effect of proton pump inhibitor in the oesophagus (see treatment options below).

Furthermore, a proton pump inhibitor trial is not a gold standard diagnostic test for gastro-oesophageal reflux disease and it is not desirable that treatment trials are used in diagnostic algorithms.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Eosinophilic oesophagitis</th>
<th>Gastro-oesophageal reflux disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant symptom</td>
<td>Dysphagia</td>
<td>Heartburn, regurgitation</td>
</tr>
<tr>
<td>Food impaction</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gender</td>
<td>Male predominance</td>
<td>Male = female</td>
</tr>
<tr>
<td>Age</td>
<td>Children, young adults</td>
<td>Middle-age</td>
</tr>
<tr>
<td>Endoscopic findings</td>
<td>Oedema, rings, exudates,</td>
<td>Erosions, ulcers, Barrett’s adeno</td>
</tr>
<tr>
<td></td>
<td>strictures, crépe paper,</td>
<td>carcinoma, strictures. Normal</td>
</tr>
<tr>
<td></td>
<td>oesophagus (tissue fragility),        findings on</td>
<td></td>
</tr>
<tr>
<td></td>
<td>narrow calibre</td>
<td>endoscopy occur in the minority</td>
</tr>
<tr>
<td></td>
<td>oesophagus. Normal findings on</td>
<td>(Hirano et al, 2013). Schatzki ring</td>
</tr>
<tr>
<td></td>
<td>endoscopy occur in the minor</td>
<td>is occasionally present</td>
</tr>
<tr>
<td>Ambulatory pH testing</td>
<td>Usually negative, sometimes</td>
<td>Positive</td>
</tr>
<tr>
<td>History</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>≥15 eosinophils/high power field</td>
<td>&lt;5 eosinophils/high power field</td>
</tr>
<tr>
<td>Aetiology</td>
<td>Immune-mediated or antigen-</td>
<td>Acid reflux</td>
</tr>
<tr>
<td></td>
<td>mediated response</td>
<td></td>
</tr>
<tr>
<td>Atopic conditions</td>
<td>Associated with allergic</td>
<td>No association with atopic</td>
</tr>
<tr>
<td></td>
<td>asthma, skin eczema, and</td>
<td>conditions</td>
</tr>
<tr>
<td></td>
<td>rhinitis</td>
<td></td>
</tr>
</tbody>
</table>
Rather than biopsying every patient with reflux symptoms, only biopsy those with dysphagic symptoms or clear endoscopic patterns of eosinophilic oesophagitis.

**Diagnosis of eosinophilic oesophagitis**

Significant diagnostic delay still exists, particularly in young people. At any age the symptom of dysphagia requires endoscopy and biopsy (Liacouras et al, 2011). The only way eosinophilic oesophagitis can be diagnosed is via a biopsy, which can only be done via an endoscopy. Perform six biopsies from multiple sites (Nielsen et al, 2014), either taken from areas of clear endoscopic abnormality, or two at the upper end, two in the middle and two at the lower end of the oesophagus. Diagnosis is nearly 100% when taking the six biopsies, but only 50% when taking a single biopsy. The finding of >15 eosinophils per high power field is diagnostic of eosinophilic oesophagitis.

Less invasive alternatives are being investigated such as the Cytosponge (a sponge in a small capsule) on a string that is released in the stomach and pulled back to the mouth by the string (Katzka et al, 2015). Another investigational device is the String test of eosinophilic oesophagitis (Furuta et al, 2013), but there are no clear diagnostic criteria for the levels of abnormality, and currently it is most likely to have value on monitoring response to therapy and avoiding repeat gastroscopies.

**Endoscopic appearances**

The presence of endoscopic abnormalities in patients with eosinophilic oesophagitis has been increasingly recognized and should help to prompt the need for biopsy (Hirano et al, 2013). The signs are not pathognomonic and the pattern of abnormality varies from patient to patient. These patterns can include:

- Linear furrows extending through much of the lumen and sometimes in a quadrantic distribution
- Rings that appear relatively fixed and not just associated with the patient straining
- White exudates that could be confused with a candida appearance
- Generalized oedema
- Focal strictures
- A generalized narrow bore oesophagus.

In a small number of patients, the oesophagus demonstrates the tissue fragility sign – where mucosal tears occur with a simple biopsy. These are not serious as they are not deep and they heal quickly, but they can cause some initial concern to endoscopists. In practice fragility is rare – more common is that the oesophagus is relatively stiff and to achieve a good biopsy the scope needs to be turned perpendicular to the oesophagus and the biopsy forceps advanced directly onto the wall. This gives a more reliable tissue sample than a tangential sample from a scope pointing down the lumen.

**Pathology**

Since eosinophilic oesophagitis is relatively new, and often not in the experience of the local pathologist, the laboratory report from the biopsy may just come back as ‘inflamed probably reflux’ (Kanakala et al, 2010). To avoid this, it is wise to ask specifically for the pathologist to count the maximum eosinophil density per high power field, in each region if possible, and to highlight that the reason for this is because of the history of dysphagia and possibly also because the endoscopic signs indicate the likelihood that eosinophilic oesophagitis is the diagnosis. If this is not established practice in the hospital, then it is worth visiting the pathology team and discussing the value of this approach in patients who have appropriate history. Rather than biopsying every patient with reflux symptoms, only biopsy those with dysphagic symptoms or clear endoscopic patterns of eosinophilic oesophagitis. This will be cost effective and receive the support of the pathology department.

**Complications**

**Stricture**

Left untreated eosinophilic oesophagitis is progressively more likely to end up with stricturing disease. About 10% of patients seem to suffer strictures (Schoepfer et al, 2013; Dellon et al, 2014b) and these require special attention – see therapy below.

**Acute food bolus obstruction**

This is a highly distressing disturbance to a patient and requires immediate attendance at an emergency department. No particular therapy is effective other than arranging an endoscopy to remove the food bolus. This may involve extraction of the bolus piecemeal, possibly using an overtube for airway protection, or pushing the bolus into the stomach. The latter strategy should only be undertaken gently and where there is a lumen available to allow passage of the bolus and the endoscope. There is a risk of perforation with this manoeuvre but this has been rarely reported.

**Spontaneous perforation**

Eosinophilic oesophagitis is now the commonest disease underlying spontaneous perforation of the oesophagus (Liacouras et al, 2011). Such a perforation is of a different pattern to those historically described as having Boorhaave’s syndrome because in eosinophilic oesophagitis it is mainly just air and fluid passing through a frayed muscular wall, not food or solid material leaving the lumen of the oesophagus. The size of the perforation is usually small and the character of the perforation multiple localized points of mural disruption. Once this has been diagnosed by contrast radiology then the usual therapy is stent, antibiotics and intravenous feeding until the signs of mediastinal inflammation have settled down. Surgical resection or repair of such perforations has very rarely been reported.
Therapy

Diet

Diet has been a mainstay of therapy since an elemental diet was found to be effective in a group of children presenting with eosinophilic oesophagitis (Kelly et al, 1995). However, this is only viable in the short term and once stopped the inflammation returns. Importantly this study identified the probability that antigens in the diet had precipitated the inflammation.

A more practical dietary approach would be to exclude the foods that are the source of the driving antigen. However, using allergy tests, particularly skin tests, to try and identify the causative agents is extremely unreliable. The oesophagus does not respond to the antigens presented in the same way as the skin. As a result allergy tests are not helpful to direct diets in the vast majority.

The commonest dietary approach then is to exclude the commonest likely foodstuffs and see if this works. By excluding the six (or seven) most likely culprits this multifood elimination approach has become the commonest form of dietary therapy (Kagalwalla et al, 2006; Gonsalves et al, 2012; Lucendo et al, 2013). The ‘six food elimination diet’ excludes dairy products, eggs, wheat, soy, peanut/tree nuts and fish/shellfish (Gonsalves et al, 2012), but other researchers (Lucendo et al, 2013) recommend avoidance of legumes in addition. After 12 weeks if the symptoms have improved a gastroscopy is performed to document whether inflammation has resolved. This occurs in up to 70% of patients but the continued exclusion of all components is regarded as too burdensome and so the foods are gradually introduced and the patients rescreened (if asymptomatic) at 12 weeks.

This regimen can find a personalised effective diet in >60% of patients but requires persistence and leads to significant cost, over a year, and often six or more endoscopies. It also requires intensive dietician follow up and advice to ensure there are no dietary deficiencies. Patients left on such exclusion diets find them difficult to follow for social and practical reasons. The quality of life effects of being on a highly restrictive exclusion diet are particularly severe in children and adolescents (Harris et al, 2013). Gonsalves et al (2012), working in a centre with great enthusiasm for diets, achieved <15% compliance with such diets in adults at 12 months after establishing efficacy.

Drugs

Topical steroids

Until very recently there was no licensed therapy for eosinophilic oesophagitis, so the instructions on therapy were not standardized and poorly available. Very few randomized clinical trials had been done and the pattern of historical treatments was based mainly on uncontrolled studies. From experience the most effective therapies were topical steroids but the available therapies were borrowed from asthma therapy, notably fluticasone sprays (Gupta et al, 2015), or formulations self-prepared in hospital pharmacies using budesonide powder dissolved in a slurry of sugar syrup (Straumann et al, 2010). Neither of these provided a standardized way of getting topical steroid to the surface of the oesophagus and the doses were not scientifically based.

An approved topical steroid has become available for patients with eosinophilic oesophagitis (Miehlke et al, 2016; Lucendo et al, 2017b). This treatment (Jorveza) is an oro-dispersible tablet held in the mouth on the tongue, taken at a time when there is no plan to eat or drink anything that might wash it away from the surface of the oesophagus. The optimal timing of a dose is last thing at night, after the patient has brushed his/her teeth and is not taking any further mouthwash or fluids. A person who is asleep makes less saliva and swallows less often, making the budesonide available to the oesophageal epithelium for much longer than taking it during the day with subsequent drinks and meals.

Clinical trials of this formulation have been completed for induction of remission of inflammation and symptoms, and it is dramatically effective after 12 weeks with 85% of patients receiving remission of symptoms and complete clearance of underlying eosinophilic inflammation (defined as <5 eosinophils per high power field) (Lucendo et al, 2017b).

The oro-dispersible tablet is very acceptable to patients and side effects are limited. In clinical trials 10% of patients developed clinically apparent thrush (oral pharyngeal candida) and this is easy to treat with a course of nystatin suspension, while continuing the topical steroid. Clinical trials showed a 63% clinico-pathological complete response in 6 weeks, which reached 85% when treatment was extended to 12 weeks. It may make sense that all patients be given a 12-week course initially, as this reduces the number of gastroscopies needed to find clinical resolution, reducing the cost for the hospital and improving convenience for patients. Further studies are needed and it will be important to develop guidance about using long-term maintenance topical steroid therapy for this chronic disease. Such studies are underway but will take some years to report. Long-term side effects are very unlikely as the first pass metabolism of any absorbed budesonide is complete, and levels of adrenal suppression or other systemic effects are very low.

Systemic steroids should not be used – they have no therapeutic advantage over topical steroids and have severe side effects when used long term.

Proton pump inhibitors

This class of drugs has two potential methods of action. By reducing the acidity of stomach fluids, if reflux happens the symptoms may be reduced. However, there is no evidence that acid reflux is involved in the pathogenesis of eosinophilic oesophagitis and the improvement seen in some patients is not related to the presence or absence of acid in the lumen of the oesophagus. Work in Stuart Spechler’s laboratory by Cheng et al (2013) has identified that, in a minority of patients, proton pump inhibitors...
can reduce the inflammatory drivers in the oesophageal epithelium by a direct effect on the eotaxin-3–eosinophil pathway. The precise mechanism of action is not well understood and may vary between patients (Lucendo et al, 2016).

Clinical observational studies of proton pump inhibitors have shown symptom and histological improvement in 23–60% of patients but full symptom and histological remission is reported on average in <40% of patients. No adequate randomized controlled studies have been done involving proton pump inhibitor therapy in eosinophilic oesophagitis. Of the two published, one had a majority of patients with gastro-oesophageal reflux disease (Peterson et al, 2010), and the other an inadequate topical steroid dose, with only 33% response to fluticasone 440 μg (Moawad et al, 2013). Often patients who present with eosinophilic oesophagitis have been prescribed proton pump inhibitors for many years and they are aware that its effect is incomplete, so using a proton pump inhibitor is not helpful for these patients. In a newly diagnosed patient, naive to proton pump inhibitors, it might be worth starting a course of full dose proton pump inhibitor (such as omeprazole 40 mg twice daily) and performing a standardized symptom check, endoscopy and biopsy at 12 weeks, in order to guide long-term maintenance with a proton pump inhibitor or switch to topical steroid. It is now agreed by international consensus that proton pump inhibitors should not be used in the diagnostic process of eosinophilic oesophagitis and that patients responding to proton pump inhibitors have an otherwise similar phenotype of eosinophilic oesophagitis to those who do not respond to proton pump inhibitors (Dellon et al, 2018).

The relative value of each type of therapy has been observed in a study by Philpott et al (2016) who found that 23% of patients who completed 8 weeks of proton pump inhibitor were responsive; when combined with diet the response rate rose to 69% initially, but dropped to 55% at 9 months. Budesonide alone produced a 92% response. Although this was not a placebo-controlled trial it gives a good representation of the range of outcomes with current approaches, and shows the advantage of a simple topical steroid therapy over a proton pump inhibitor alone, without needing the complexity or expense of dietary strategies.

Other drugs
Biologic agents such as omalizumab, and other drugs with similar mechanisms, have not proven effective in clinical trials to date (Straumann et al, 2010b).

Dilatation
Patients resistant to topical steroid or dietary therapy should be considered for dilatation. Since the underlying pathogenesis of eosinophilic oesophagitis involves remodelling of the oesophageal wall with fibrosis the single most effective treatment for strictures or resistant disease is dilatation (Schoepfer et al, 2010). The method of dilatation is not well studied but following the British Society of Gastroenterology guidelines for oesophageal therapeutic dilatation is a straightforward process that is well within the capability of most gastroenterology departments (Sami et al, 2018). When a stricture is present it is good to aim for a lumen of 17 mm eventually, although this may take a number of sessions to achieve. If no stricture is visible it is still worth stretching the lumen as a bore of 11 mm may not appear narrow when viewed down the endoscope but is enough to cause severe symptoms with swallowed solids.

Refining the process of dilatation by using the new EndoFlip device, which gives a compliance measure of the wall of the oesophagus, is a hope for the future. This is currently limited by the algorithm used in that instrument as it only gives a compliance reading for the narrowest point. In eosinophilic oesophagitis it is often necessary to dilate the whole length of the oesophagus and this is worth doing as a routine protocol when performing dilatation therapy. Patients may suffer significant pain for up to 48 hours after such a dilatation (more so than after dilation of peptic stricture) and should be forewarned about this. The risks of dilatation are no greater than for other disorders, with perforations occurring in 0.1%.

The future of eosinophilic oesophagitis therapy
There is still a need to clarify the maintenance therapy for eosinophilic oesophagitis and to identify the number of endoscopic follow ups needed to advise patients on their response to and need to continue therapy. Relying on short-term symptom responses is inaccurate because the improvement in symptoms may not be matched by improved levels of inflammatory histological markers (Safoneeva et al, 2016). Conversely some therapies may improve the inflammatory components of epithelial damage but have little effect on the underlying fibrosis. There is hope that taking long-term topical steroids may help reverse the remodelling that occurred before starting therapy (Aceves et al, 2010; Rajan et al, 2016) and currently this is the only medication likely to achieve this. Using standardized questionnaires (such as the EEsai questionnaire, Schoepfer et al, 2014), identifying the most economic model of repeat endoscopy and improving measures of measuring the compliance of the oesophageal wall as it remodels will all help to educate physicians on the optimum therapeutic approach and follow-up programme for chronic sufferers of eosinophilic oesophagitis.

Dietary therapy may develop more patient acceptable and economic models of care. It is possible that using diet supplemented by diet holidays covered by the use of topical steroids could balance the benefits of both approaches.

For now, the best balance of quality of life and nutrition is to use topical steroids, both for induction of remission (licenced) and for maintenance (as yet unlicenced), with the option of dietary therapy for those with specific motivation and support to manage this process.
Conclusions
Eosinophilic oesophagitis is becoming a common disorder, which causes dysphagia and significant restrictions to quality of life. It is a distinct clinico-pathological entity, that deserves early diagnosis and specific therapy. New developments in therapy and an increasing incidence make it an important disease area for doctors to be aware of.

Conflict of interest: Professor SE Attwood has participated in advisory boards and research projects with Dr Falk Pharma, Reckitt Benkiser and AstraZeneca. The opinions expressed in this article are those of the author and not of any of these companies.


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