

Eosinophilic oesophagitis: investigations and management

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ABSTRACT

Eosinophilic oesophagitis (EO) is an immune/antigen mediated, chronic, relapsing disease characterised by dysphagia, food bolus impaction and a dense oesophageal eosinophilic infiltrate. Characteristic endoscopic features include corrugated rings, linear furrows and white exudates, but none are diagnostic. Despite its increasing prevalence, EO remains underdiagnosed. There is a strong association with other atopic conditions. Symptoms, histology and endoscopic findings can overlap with gastro-oesophageal reflux disease. Currently endoscopy and oesophageal biopsies are the investigation of choice. Oesophageal physiology studies, endoscopic ultrasound, impedance planimetry and serology may have a role in the diagnosis and monitoring of response to therapy. Acid reducing medication is advocated as first line or adjuvant therapy. Dietary therapy is comprised of elimination diets or can be guided by allergen assessment. In adults, topical corticosteroids are the mainstay of therapy. Endoscopic dilatation is safe and effective for the treatment of non-responsive strictures. Other therapeutic options (immunomodulators, biological agents, leukotriene receptor antagonists) are under investigation.

INTRODUCTION

Eosinophilic oesophagitis (EO) is a chronic relapsing, immune/antigen mediated disease of the oesophagus with rapidly increasing incidence and prevalence.^{1–3} EO should be suspected in all young adults presenting with a history of unexplained solid food dysphagia and in children with refractory reflux symptoms and malnutrition. The diagnosis is based on a compilation of clinical signs and symptoms combined with a dense oesophageal eosinophilic infiltrate in the absence of other causes of oesophageal eosinophilia. Although atopy is not universal, EO is frequently associated with allergic conditions such as asthma, skin and food allergies.^{4 5}

Despite the increasing incidence and prevalence of EO, it remains under-diagnosed. Diagnosis can be delayed for years as patients often remain well and are often mislabelled as having a functional disorder or reflux disease with no alarm symptoms.⁶ The 2011 international consensus recommendations for the diagnosis and management of EO are described in table 1.⁷

Investigations and therapy for EO are in continuous development. In this review an approach to the investigation and treatment of EO is proposed based on a comprehensive review of the literature as well as expertise from an experienced London teaching hospital—St Thomas' Hospital. The clinical presentation and pathogenesis of EO are

described in the companion article by Bystrom and O'Shea⁸ in this issue of the journal.

INVESTIGATIONS

All patients presenting with unexplained solid food dysphagia and acute food bolus impaction should be investigated to rule out EO. Early diagnosis and treatment improves quality of life and may prevent (or reverse) oesophageal remodelling associated with chronic disease.

Endoscopy with oesophageal biopsies and histology are the current gold standard investigations to diagnose EO. Specialised investigations such as pH monitoring and oesophageal manometry help differentiate EO from primary motility disorders and gastro-oesophageal reflux disease (GORD). The role of future diagnostic tests such as endoscopic ultrasound (EUS) and impedance planimetry are also discussed briefly. The clinical algorithm for the investigation and treatment of patients with suspected EO at St Thomas' Hospital is presented in figure 1.

Endoscopy

The diagnosis of EO is dependent on *both* clear histological evidence of eosinophilic infiltration in the oesophageal mucosa⁹ as well as corroborating symptoms (see companion article by Bystrom and O'Shea⁸). Some of the endoscopic features associated with EO are presented in figure 2A–D and further described by Bystrom and O'Shea⁸. The presence of these features at endoscopy, although not specific, should raise suspicion and trigger collection of biopsies. A recent endoscopic scoring system is described in the companion paper.

Current international consensus guidelines recommend that *at least* two biopsies should be taken from each of the proximal and mid/distal oesophageal segments (minimum of four biopsies in total) whenever EO suspicion arises regardless of endoscopic findings.^{7 10} Diagnosis should be based on peak eosinophil counts obtained from the most densely populated high powered field (hpf) with a threshold number of 15 eosinophils/hpf. The companion paper by Bystrom and O'Shea⁸ reviews the histological features of EO in detail.

pH monitoring

The most important condition from which EO needs to be distinguished is GORD. The relationship between EO and GORD is complex^{11–14}; GORD can cause oesophageal injury that results in mild distal eosinophilic infiltration,¹⁵ GORD and EO can coexist as separate disease entities, and EO symptoms can be identical to GORD.



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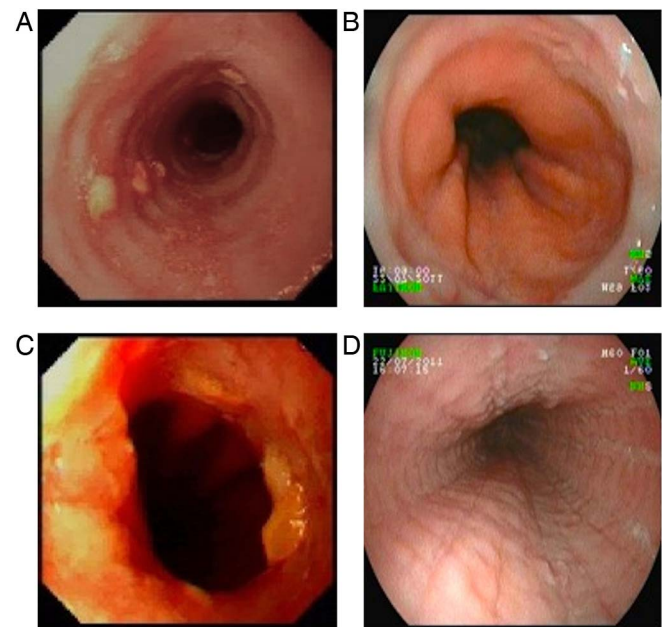
Review

Table 1 Updated 2011 diagnostic criteria for eosinophilic oesophagitis

Clinical symptoms	Dysphagia, food impaction, refractory reflux symptoms
Histology	Multiple biopsies from proximal and mid/distal oesophagus, peak number of eosinophils ≥ 15 in at least one high power field from at least one biopsy
Exclusion criteria	Rule out GORD and PPI responsive eosinophilia (PPI-R) Exclusion of other causes of oesophageal eosinophilia
Response to therapy	Remission of symptoms and histology following exclusion diet or steroid therapy

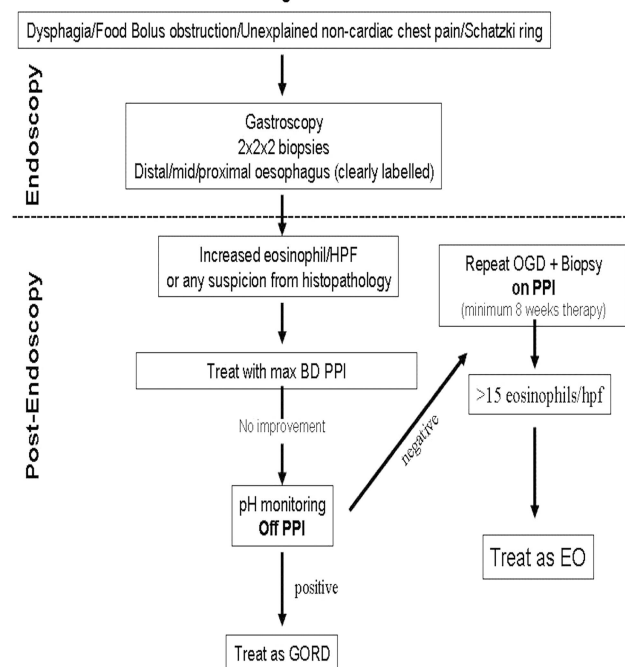
GORD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor.

pH monitoring can play an important role in dissecting the overlap between EO and GORD, especially in patients who are refractory to acid reducing therapy.⁷ Abnormalities of ambulatory pH studies are found in up to 20% of patients with EO,^{16 17} but their significance in this setting is not clear. In the context of a mild oesophageal eosinophilia, where pH monitoring shows evidence of pathological oesophageal acid exposure, greater attention can be directed towards optimising anti-reflux rather than EO therapy. On the other hand, recent studies have identified a subgroup of EO patients who improve clinically and histologically with proton pump inhibitor (PPI) therapy despite a negative pH study.¹² It is not clear whether this group is indeed a separate entity (PPI responsive EO) or if standard (24 h catheter based) diagnostic pH testing may have missed a subset of patients with true GORD. Standard 24 h catheter based pH studies may be confounded by: (1) modified patient behaviour due to discomfort and social embarrassment; and (2) study brevity as a wide day-to-day variation in reflux events and symptoms may reduce the diagnostic accuracy of shorter studies.

**Figure 2** Endoscopic features associated with eosinophilic oesophagitis. (A) Mucosal oedema with eosinophilic aggregates. (B) Schatzki ring. (C) Lower oesophageal stricture. (D) Linear furrows and corrugated rings (feline oesophagus).

These shortcomings can be overcome with prolonged (at least 48 h) wireless pH monitoring.^{18 19} Therefore, in the context of a patient with convincing GORD symptoms yet with a mild eosinophilia, if standard pH studies are negative, it may be prudent to consider prolonged wireless pH monitoring to decide if further attention towards anti-reflux therapy is required in the first instance.

EO Investigation

**Figure 1** Proposed investigation pathway for patients suspected of having eosinophilic oesophagitis (EO). BD, twice daily; GORD, gastro-oesophageal reflux disease; HPF, high power field; OGD, oesophago-gastro-duodenoscopy; PPI, proton pump inhibitor.

Oesophageal manometry

Presently the role of manometry in the investigation of EO is unclear. Up to 40% of EO patients exhibit abnormal patterns of motility with conventional (4–8 sensor) oesophageal manometry.^{20–22} Although this implies a high prevalence of oesophageal dysmotility in EO, the significance of this is not clear. Motility disorders reported include spasm, high pressure contractions, tertiary contractions, lower oesophageal sphincter (LOS) pressure abnormalities, and a variety of other non-specific peristaltic disorders of questionable significance. Manometrically, EO can mimic almost any oesophageal dysfunction, but major motility disorders (achalasia, diffuse oesophageal spasm) are rare.^{21 23 24}

High resolution manometry (HRM) is a technological advance on conventional systems. It uses a catheter with up to 36 sensors with complex computer processing algorithms to present pressure data with clarity and visually intuitive spatial resolution. In addition, novel parameters can provide measurements of the very forces that drive bolus transport.²⁵ Recently, HRM has also been shown to facilitate the detection of symptomatic dysfunction during and after eating and drinking, an advance from standard small volume water swallows.^{26 27} When compared with GORD or healthy controls, HRM studies in EO identified abnormal bolus pressurisation patterns associated with resistance to flow at or above the LOS. In a study of 14 patients with EO who underwent HRM, Fox *et al*²⁸ showed that patients were more likely to have normal oesophageal motility but abnormal intra-bolus pressurisation in the distal oesophagus during solid bolus swallows, and that symptoms were more

likely to coincide with these events. Furthermore, both symptoms and pressurisation abnormalities improved with topical steroid therapy or dilation. Such findings are possibly the result of a decrease in the compliance within the oesophagus and LOS (see EndoFLIP below) which may be a consequence of chronic inflammation, fibrosis, and oesophageal remodelling.^{29–31}

Although recent studies suggest that the utility of HRM may be helpful in identifying subtle changes associated with resistance to flow, its role in clinical practice is not yet established. Manometry may be useful in the study of patients with refractory symptoms, as well as in the assessment of response to therapy, as symptomatic resolution is often also associated with manometric improvement.

An example of a patient with increased intra-bolus pressurisation in the lower oesophagus as a consequence of resistance to flow of the bolus passage into the stomach is presented in figure 3B.

Future diagnostic approaches

Diagnostic challenges in EO have led towards several advances in technology (eg, EUS and impedance planimetry, described below). In addition, non-invasive biomarkers in development (eg, transforming growth factor β (TGF- β), eotaxin, interleukin 5 (IL-5), and major basic protein (MBP)) might also soon be used to monitor response to therapy; described in detail in the article by Bystrom and O'Shea⁸.

Endoscopic ultrasound

EUS can identify mucosal and muscular abnormalities in the oesophageal wall of EO patients.^{32–33} In comparative studies EUS identified increased thickness of the mucosal, submucosal, and muscularis propria layers both in the distal and the proximal oesophagus compared to GORD and healthy controls.^{16–31–32–34} EUS is also able to detect therapy induced mucosal and muscular changes in EO.³³

EUS may have a potential role to play in the assessment of morphological features of oesophageal remodelling before and after therapy. Larger studies are required to determine the efficacy of EUS in clinical practice.

Impedance planimetry (EndoFLIP)

Studies that assess the mechanical effect of tissue remodelling in EO are limited.⁷ To date, radiography, endoscopy, and histology have been used to determine the degree of oesophageal fibrosis; however, these tools are unable to address the degree to which oesophageal stiffness is affected. EndoFLIP (Crospon Medical Devices, Galway, Ireland) uses 'impedance planimetry' to simultaneously measure pressure and volume within the oesophagus and LOS. Impedance planimetry is a technique for measuring pressure and cross-sectional area inside a pliable bag placed in the distal end of a catheter. By introducing such a device into the oesophagus, measurements of oesophageal wall distensibility and compliance can be acquired. In a study which compared 33 EO patients with 15 controls, Kwiatek *et al*³¹ found that oesophageal wall distensibility and compliance were significantly lower in patients with EO.

Although its place in clinical practice is yet to be determined, measuring oesophageal distensibility may prove to be an important tool, especially in the assessment of response to therapy in patients with EO.

MANAGEMENT

The primary aim of treatment should be symptom reduction and, in the paediatric population, maintenance of growth and development.⁷

There are three important reasons to diagnose and initiate effective therapy early in EO:

1. Dysphagia significantly impairs the quality of life of patients and development in children.
2. Prolonged food impaction requires emergency endoscopy which can risk the development of mucosal tears and other complications.
3. Persistence of untreated eosinophilic inflammation may evoke oesophageal remodelling and fibrosis predisposing to further functional impairment, worsening dysphagia, and increasing the risk of food bolus obstruction.

A relatively novel concept of mucosal healing as a benchmark of treatment has recently been considered.³⁵ EO is presumed to be a progressive disease with persistent eosinophilia contributing to fibrosis and remodelling which in turn leads to worsening dysphagia and food impaction. An alternative theory is that patients can be differentiated by their phenotypic response to the same insult—that is, eosinophilia can induce superficial inflammation in some and fibrosis in others. Long term longitudinal studies to confirm the natural history of EO are lacking and there remains disagreement, even among experts, regarding the long term outcome of untreated disease. Regardless, appropriate anti-eosinophilic therapy can improve, or resolve, symptoms and mucosal damage (including fibrosis).^{29–36} Early diagnosis and treatment will always achieve the best long term outcome.

Therapeutic options can be divided into disease modifying anti-eosinophil therapy (ie, dietary and pharmacological) and endoscopic therapy.

Dietary therapy

Dietary therapy is especially effective in children with EO and can result in near complete resolution of clinical and histologic abnormalities (including in fibrosis).^{37–38} Three forms of dietary therapies have been shown to be effective: (1) elemental diet; (2) dietary restriction guided by allergy testing; and (3) dietary restriction based on the elimination and reintroduction of all likely food allergens.

The 2011 consensus guidelines recommend that dietary therapy should be considered in all children as well as motivated adults diagnosed with EO.⁷ Compliance can be difficult in adults, and encouragement and motivation are key to success. Dietary therapy must always be undertaken with guidance from an experienced dietician to ensure that an adequate intake of calories, essential vitamins, and micronutrients are maintained. Ultimately foods identified as EO triggers will be restricted indefinitely while other foods are reintroduced.

Elemental diet

All solid foods are replaced with an elemental formula comprised of synthetic amino acids, carbohydrates, and medium chain triglycerides, thereby avoiding all potential culprit food allergens. In an observational study of 25 children on a 6 week elemental diet, 22 (88%) achieved significant reduction in the peak oesophageal count (≤ 10 eosinophils/hpf) as well as symptomatic improvement.³⁹ In another study, Markowitz *et al* showed that after 4 weeks on an elemental diet, 51 patients with EO showed a significant improvement in vomiting, abdominal pain, and dysphagia with a reduction in the median eosinophil/hpf count from

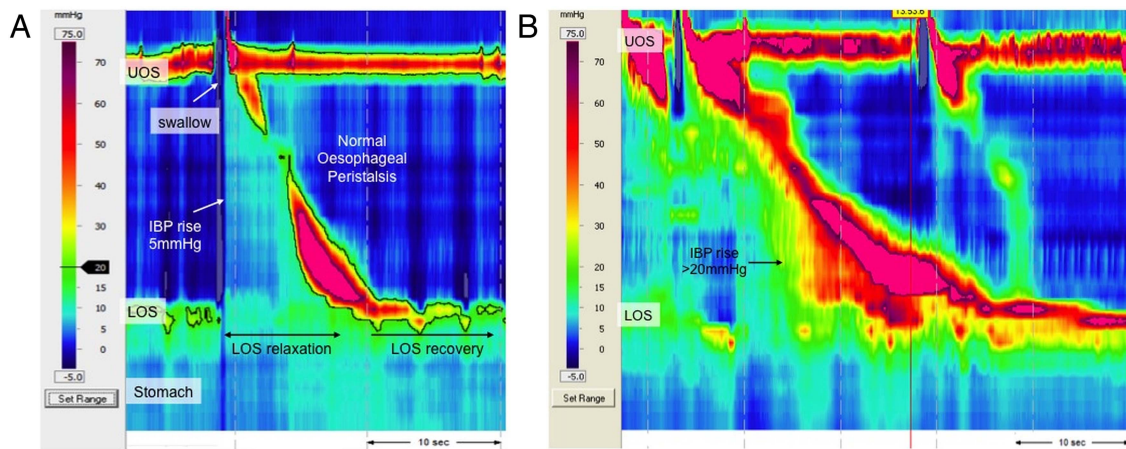


Figure 3 High resolution manometry trace of a swallow (ManoScan 360, Sierra Scientific Instruments, Mountain View, California, USA). (A) This normal trace (of co-author RS) depicts oesophageal pressure activity from the pharynx to the stomach. Pressure sensors on the catheter are spaced at <2 cm intervals. Recordings are analysed and presented as a spatiotemporal plot; time is depicted on the x axis, distance from the nares on the y axis, and amplitude on the z axis, with pressure presented as changes in colour (left hand legend). Intra-bolus pressure (IBP) is a measure of the compartmentalised pressure between the lower oesophageal sphincter (LOS) and the peristaltic contraction. The IBP was 5 mm Hg. (B) A patient with eosinophilic oesophagitis presented with symptoms of dysphagia described as a sensation of food sticking in his oesophagus, occasionally forcing him to vomit. High resolution manometry (HRM) revealed increased oesophageal pressurisation in the distal oesophagus (raised IBP >20 mm Hg). No stricture was seen on white light endoscopy. UOS, upper oesophageal sphincter.

34 to 1 ($p<0.01$). The average time to clinical improvement was 8.5 days.⁴⁰ Compliance is a challenge, especially in adults, as the non-palatable formula requires long term nasogastric feeding. Furthermore, with the reintroduction of food, relapse is common unless the culprit antigen is identified and eliminated permanently.

Dietary elimination directed by allergy testing

Food elimination directed by skin prick or atopy patch testing has shown promising results.^{41–42} Targeted dietary restrictions are symptomatically effective in up to 70–80% of patients due to improved patient adherence; however, in a study of 319 patients with EO, a histological response rate of only 53% was achieved.⁴³ Furthermore, diagnostic accuracy can be a problem as false positive and false negative results with allergy testing are not uncommon. Studies examining both the positive and negative predictive value of targeted dietary restrictions in EO are required. Until further evidence arises, dietary therapy guided by allergy testing remains experimental and is not recommended as a standard treatment option.

Six food elimination diet

Six food elimination diet (SFED) has been shown to be effective in the management of EO. The elimination of cow's milk, soy, wheat, egg, peanuts/tree nuts, and seafood can provide both symptomatic and histological regression in EO. This is then followed by a stepwise reintroduction of food groups until the culprit allergen is identified and eliminated indefinitely. In a retrospective observational study, Kagalwalla *et al*³⁹ showed that out of 35 children with EO who completed a 6 week SFED, 26 (74%) achieved a reduction in the peak eosinophil count (≤ 10 eosinophils/hpf) and this was associated with a good symptomatic response. In a recent study whereby 50 adults with EO completed a 6 week SFED, 32 patients showed a histological response. In 70% of patients the peak eosinophil count reduced to ≤ 10 eosinophils/hpf (from 44 to 13 eosinophils/hpf in the distal oesophagus and from 34 to 8 eosinophils/hpf in the

proximal oesophagus before and after SFED, respectively). A symptomatic response was observed in 94% compared to before therapy ($p<0.0001$). Furthermore, in 20 patients who achieved a histological response and completed reintroduction of foods, oesophageal eosinophil counts returned to pre-treatment levels ($p<0.0001$).⁴⁴ The most common food culprits were wheat (60% of patients) and cow's milk (50% of patients).

Although compliance can be a challenge, the SFED is better tolerated than an elemental diet as a near normal diet can be enjoyed; however, perseverance and a close relationship with an experienced dietician are paramount.

Pharmacological therapy

As dietary therapy has not been well studied in adults and compliance can be a challenge, drug therapy remains the mainstay of treatment in adult patients with EO.

Topical corticosteroids

Given their improved safety profile and reduced systemic absorption, topical corticosteroids have become the mainstay of EO therapy. These aim to deliver particulate steroids to the squamous epithelium where they provide an anti-inflammatory effect. Both fluticasone propionate and budesonide have been shown to be effective in inducing and maintaining long term remission (up to 50 weeks).^{45–46} Topical corticosteroids have also been shown to reduce or even reverse fibrosis.^{29–47}

The lack of an appropriate topical preparation has led to adaptation from various existing therapies used for asthma. Fluticasone propionate pressurised metered dose inhaler or Accuhaler can be swallowed (without inhaling). Randomised clinical trials of topical fluticasone propionate for 6 weeks have shown both histologic and symptomatic improvements in 50–80% of patients with EO.^{45–46–48} In a recent double blind, randomised, placebo controlled trial of 42 adult patients with a new diagnosis of EO,⁴⁶ a >50% histological response was observed in 13/19 (68%) patients and dysphagia was reduced in 12/19 (63%) patients who completed 6 weeks of 880 μ g twice

daily fluticasone therapy. In the placebo group, although there was no histological response ($p<0.001$), 7/15 (47%) also exhibited an improvement in dysphagia ($p=0.49$ compared with fluticasone).

Oral budesonide administered in the form of a liquid or oral viscous slurry is effective in induction and maintenance of remission in EO.⁴⁹ In a randomised, double blind, placebo controlled trial, Straumann *et al*²⁹ evaluated the effect of high dose swallowed budesonide (1 mg twice daily for 15 days) on adolescent and adult patients with active EO. Budesonide significantly decreased the mean number of oesophageal eosinophils from 68.2 to 5.5 eosinophils/hpf ($p=0.0001$) in the budesonide group and from 62.3 to 56.5 eosinophils/hpf ($p=0.48$) in the placebo group. Dysphagia also improved in the budesonide group ($p<0.001$). Endoscopically, therapy produced a reversal of white exudates and red furrows as well as a significant reduction in the fibrosis score ($p=0.026$).

To maximise contact time of aerosolised steroid particulates with the oesophageal mucosa, when using the metered dose inhaler, patients should be asked to seal the device with the lips and spray into the back of the throat before swallowing (not inhaling). With the powdered Accuhaler, patients should be asked to suck the powder directly from the device before swallowing. In either case, patients should swallow repeatedly without rinsing their mouth, and they should not eat or drink for at least 30 min afterwards.⁵⁰ Ten per cent of patients with swallowed topical corticosteroids develop oropharyngeal or oesophageal candidiasis at some point, but this is normally easily treated with standard antimycotic agents. There have been no long term safety data for the use of swallowed topical corticosteroids; however, these medications have been well established as maintenance therapy for obstructive lung diseases.

The current updated international consensus guidelines recommend using fluticasone (metered dose inhaler, puffed and swallowed) or budesonide (as a viscous suspension) as the mainstay of therapy (table 2). However, questions remain regarding the appropriate duration and consequence of long term of therapy.

Systemic corticosteroids

Systemic corticosteroids are rarely used as first line or maintenance therapy. EO almost always recurs once corticosteroids are discontinued^{51 52} and the long term toxic side effects (osteopenia, poor growth, and adrenal suppression) are well known to all physicians.

Early studies showed that systemic corticosteroids induce both clinical and histologic improvement in EO patients.^{51 53} Symptoms are reported to improve within 7–10 days. In this setting, the recommended dose of prednisolone is 1–2 mg/kg/day (maximum 60 mg/day).

Because of concerns regarding toxicity of long term use, systemic corticosteroids should be reserved for the treatment of

patients in the acute setting with severe debilitating dysphagia, patients requiring hospitalisation, or those experiencing large volume weight loss or dehydration.

Proton pump inhibitors

Overlap between GORD and EO is becoming increasingly recognised. Persistent reflux disease may contribute to (a mild) oesophageal eosinophilia or EO may lead to secondary GORD.^{7 12} Furthermore, a subset of patients with EO whose symptoms and histopathological features are responsive to PPI therapy (PPI responsive oesophageal eosinophilia) has recently been described.^{12 54}

On the other hand, PPIs may also be useful as adjuvant therapy to topical corticosteroids as they may alleviate symptoms related to undiagnosed GORD.⁵⁵ Moreover, recent studies allude to the additional anti-inflammatory (immune/antigen driven response) and barrier healing (prevent further immune activation) properties of PPIs on the oesophagus.⁵²

Guidelines recommend that GORD should initially be excluded with a course of twice daily PPI therapy for 8–12 weeks.⁷ Refractory GORD symptoms not responding to PPI therapy should raise the suspicion of EO, especially in individuals with atopic disease. In PPI responsive EO, the long term effect on fibrosis development and oesophageal remodelling without disease modifying therapy is not known. Therefore, in patients whose oesophageal symptoms do not respond or who become refractory to PPI-only therapy, anti-eosinophil treatment should not be delayed, although co-therapy with PPI may benefit those with EO/GORD overlap.

In cases of uncertainty, ambulatory pH monitoring may provide support for suspected underlying severe GORD, which may exist as a separate entity and/or exacerbate EO symptoms. In cases where 24 h catheter based pH measurements are uncertain, borderline or not tolerated, prolonged wireless pH monitoring (Bravo) might help identify patients with GORD. If positive, more emphasis may be required to optimise GORD therapy further (eg, increase the PPI dose or frequency, change to an alternative PPI, or consider other acid reducing therapies).

PPI therapy should always be tried first in patients with symptoms suggestive of EO, even in the presence of biopsy confirmed eosinophilia; although it is rarely very much higher than 15–20 hpf. Where anti-eosinophil therapy is initiated, adjuvant PPI therapy may help treat those with coexisting GORD.

Montelukast

Montelukast, a leukotriene receptor antagonist (LTRA) which actively and selectively blocks the leukotriene D4 receptor in eosinophils, can be an option to improve symptoms in patients not responding to standard therapy. In a pilot study of eight patients treated with montelukast for a median period of 14 months, although there was little change in the eosinophil density, half of the patients described subjective improvements in dysphagia.⁵⁶ On the other hand, in a recent prospective study, Lucendo *et al*⁵⁷ showed that after 6 months of therapy with fluticasone propionate, eosinophil density was significantly reduced ($p=0.003$); however, when this was followed with a 3 month course of montelukast, eosinophil counts returned to baseline. Furthermore, while symptom scores significantly decreased with topical steroids ($p=0.003$), they too worsened with initiation of montelukast therapy.

Montelukast is currently not recommended as a first line therapy in the management of EO, but could be considered in

Table 2 2011 consensus guidelines recommendations for steroid treatment in eosinophilic oesophagitis

	Fluticasone propionate (metered dose inhaler-swallowed)	Budesonide (viscous suspension)
Children (<10 years)	88–440 µg 2–4 times daily	1 mg daily
Older children and adults	440–880 µg twice daily	2 mg daily

Review

patients not responding to either dietary or corticosteroid therapy.

Immunomodulators

As with other inflammatory gastrointestinal diseases, it is theorised that immunomodulators such as azathioprine (AZA) and 6-mercaptopurine (6-MP) could be effective as steroid sparing agents in EO. Furthermore, AZA has been successful in treating patients with eosinophilic gastroenteritis.⁵⁸ Unfortunately, to date only one study assessed the effect of immunomodulator therapy on EO with such purine analogues. In a case series of three steroid refractory adult patients with EO, Netzer *et al*⁵⁹ showed that following AZA therapy, clinical and histological remission was maintained for a prolonged period (range 3–8 years). In two patients who relapsed, remission was successfully recovered with a short course of topical corticosteroids followed by AZA maintenance therapy.

Until large studies show that the efficacy of immunomodulator therapy outweighs the side effect profile and need for continuous monitoring, the routine use of AZA and 6-MP is not yet recommended.

Biological agents

Inflammatory cytokines (eg, IL-5, IL-13, and TGF- β) play an important role in the pathogenesis of EO. Although there is presently no clear evidence to suggest that biologics are effective in the management of EO, research in this area is in progress. Table 2 in the companion paper by Bystrom and O'Shea⁸ describes some of the clinical trials on the use of biologics in EO.

Endoscopic dilatation

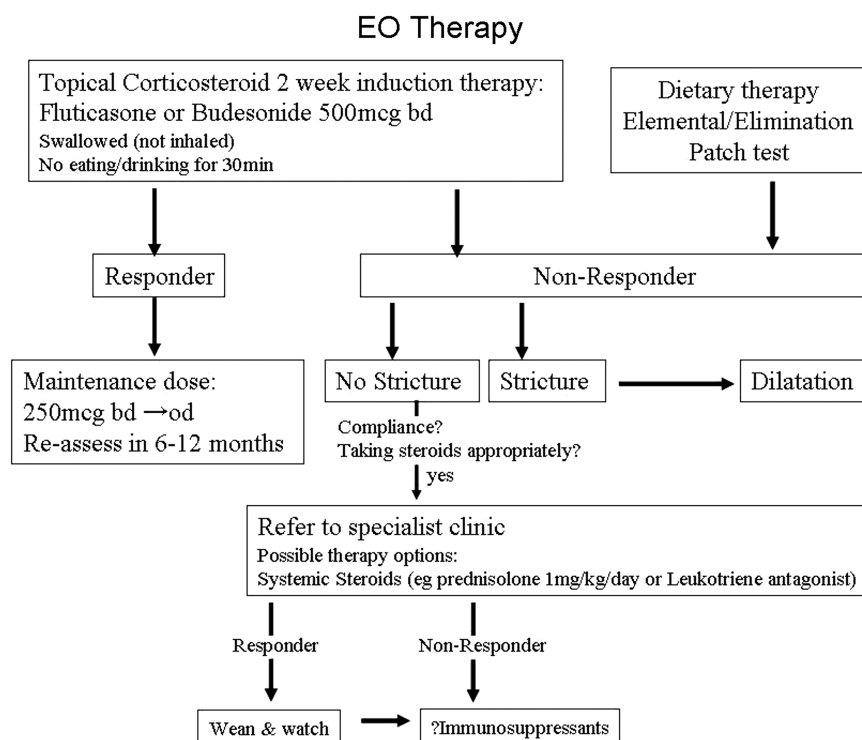
In a proportion of patients with EO, tissue remodelling and fibrosis is thought to lead to the development of fixed oesophageal stricturing unresponsive to other forms of therapy. Although endoscopic dilatation (bougienage or through-the-

scope pneumatic dilatation) is a valuable therapeutic option, there is no standardised guidance regarding when and how to perform the procedure in this group of patients. In the non-EO setting, the risk of major complications (perforation and bleeding) of benign stricture dilatation has been reported as 0.5%.⁶⁰ Initial reports suggested that, in EO, dilatation may predispose to deep oesophageal tears and perforation due to oesophageal mucosal fragility and tissue remodelling.^{61 62} However, recent studies have shown that this risk is no greater than that of the non-EO population.³⁶ Two large systematic reviews involving 1000 dilatations in 500 patients with EO have shown that this procedure is safe with a perforation risk as low as 0.1–0.3%.^{63 64} In a retrospective review of 207 patients with EO, Straumann *et al* showed that dilatation resulted in an improvement of dysphagia with no perforations or major bleeding; however, 74% experienced significant yet self-limiting retrosternal pain.

The role of oesophageal dilatation as primary therapy in EO is open to question as it does not address the source pathology. Schoepfer *et al*⁶⁵ showed that dysphagia recurred within 23 $\pm$ 22 months in patients treated with dilatation only therapy with no change in the degree of eosinophilia. Bohm *et al*⁶⁴ showed that in 42 patients with EO who were treated with dilatation, 81%, 46%, and 41% remained symptom free at 3 months, 1 year, and 2 years post-procedure, while the degree of oesophageal eosinophilia remained unchanged.

Oesophageal dilatation is useful in the treatment of EO patients with oesophageal narrowing and obstructive symptoms not responsive to conventional anti-eosinophil therapy or who require urgent stricture relief. The risk of perforation is similar to that of dilatation in benign disease; however, patients should be warned of the risk of (sometimes severe) post-procedure, self-limiting retrosternal pain. Dilatation has no influence on the underlying disease process and co-therapy with anti-eosinophilic regimens should always be sought to reduce the rate of recurrence.

Figure 4 Proposed therapeutic algorithm for patients suspected of having eosinophilic oesophagitis (EO).
bd, twice daily; od, once daily.



Endoscopic surveillance

Endoscopic surveillance in EO is not well defined. Guidelines from the American College of Gastroenterology⁶⁶ recommend endoscopy with oesophageal biopsies to assess response to dietary therapy when food antigens are being withdrawn or reintroduced, although no definite time interval is recommended. Putnam *et al*⁶⁷ suggest that in children endoscopy should be repeated 12 weeks after diet initiation or change in medication, thus allowing sufficient time for a histological response to therapy. Therefore, it may be reasonable to repeat endoscopy with biopsies after 8–12 weeks of PPI, topical corticosteroid or dietary therapy to confirm an adequate response, especially if symptoms persist, although the cost effectiveness of this approach is yet to be proven. Future studies should provide further guidance in this regard.

An algorithm showing the various therapeutic options currently available for the management of EO is presented in figure 4.

CONCLUSION

EO is under-diagnosed and mislabelled, largely due to the low rate of clinical suspicion, delayed request for endoscopy, inadequate number and distribution of oesophageal biopsies, and its histopathological similarity to GORD. Although any symptom can present at any age, the assortment of symptoms associated with EO commonly vary with age; younger patients present with feeding difficulty, abdominal pain, vomiting, and weight loss while adults present with dysphagia, chest pain, and reflux-like symptoms. Complications due to delayed treatment include stricture formation, recurrent food bolus obstruction, food fear, and malnutrition. Acid reflux may contribute to eosinophilic pathogenesis or coexist as a separate entity. Dysmotility is likely to be a consequence of reduced compliance of the oesophagus and LOS.

The primary aim of therapy is to improve symptoms, although inducing mucosal healing is fast becoming a priority with the intent of reducing oesophageal remodelling and stricture formation. Anti-eosinophil treatment can be divided into dietary exclusion and pharmacological therapy. Exclusion diets can either be guided by identifying culprit allergens or can be based on the elimination of all possible allergens followed by their stepwise reintroduction. With regard to pharmacological therapy, a PPI trial may help identify the subset of patients who are responsive to acid reducing therapy. pH monitoring may be considered in those whose symptoms are strongly suggestive of GORD. Topical corticosteroids, namely swallowed fluticasone or budesonide, are the mainstay of therapy. Early initiation usually induces histological resolution and a gratifying symptomatic response with an improved quality of life. Early therapy may reduce, or even reverse, oesophageal remodelling and fibrosis. The lack of readily available therapeutic formulations for topical oral corticosteroids remains a challenge. The appropriate length of therapy is not yet formalised although current expert opinion recommends review at 1 year. Endoscopic dilatation can be considered in patients with symptomatic strictures in whom there is poor response to medical treatment or in the acute setting.

Future trials are required to identify alternative, safe, steroid-sparing therapies to prevent long term sequelae and improve quality of life. Purine analogue immunosuppressants and novel biologic agents may one day provide a therapeutic alternative for patients with refractory EO.

Main messages

- ▶ All endoscopy units should initiate a standard biopsy protocol for all patients presenting with unexplained dysphagia and food bolus impaction.
- ▶ Oesophageal physiology studies are useful adjuncts to distinguish EO from gastro-oesophageal reflux disease and primary motility disorders.
- ▶ Dietary therapy and topical corticosteroids are the mainstay of the therapy once diagnosis is confirmed. Endoscopic dilatation of strictures related to EO is safe and effective.

Research questions

- ▶ Ascertain the role of proton pump inhibitors in the management of EO.
- ▶ Identify effective steroid sparing agents in the management of EO.

Key references

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Self assessment questions

Please answer true (T) or false (F) for the below,

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

Review

2. Eosinophilic oesophagitis

- A. Is more common in patients over the age of 50
- B. Is frequently associated with atopy
- C. Presents in children with severe reflux symptoms and growth failure
- D. Is an immune/antigen mediated disease
- E. Has characteristic endoscopic features in the majority of patients

3. Dietary therapy

- A. Is the mainstay of therapy for EO in adults
- B. Elemental diet is an effective therapy in EO
- C. SFED has been shown to induce both histological and symptomatic response
- D. Relapse is not common on reintroduction of normal diet after successful dietary therapy
- E. Elimination diet based on allergy testing is not beneficial in patients with EO

4. Pharmacotherapy for EO

- A. High dose proton pump inhibitor therapy should be tried in all patients with suspected EO
- B. Topical corticosteroids are the most effective therapy for induction and maintenance of remission in EO
- C. Systemic steroids should be used to treat all patients diagnosed with EO
- D. Budesonide should be inhaled to be effective in EO
- E. Immunosuppressants are a treatment of choice in patients diagnosed with EO

5. Endoscopy in EO

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

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Competing interests None.

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Answers

1. A-F, B-T, C-T, D-F, E-F
2. A-F, B-T, C-T, D-T, E-F
3. A-F, B-T, C-T, D-F, E-F
4. A-T, B-T, C-F, D-F, E-T
5. A-T, B-T, C-T, D-F, E-F



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