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Improving clinical diagnosis and management of eosinophilic oesophagitis in adult patients

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Eosinophilic Oesophagitis (EoE) is a chronic antigen-mediated immune disease of the oesophagus, newly recognised in the past 30 years.[1,2] It is the most prevalent cause of chronic oesophagitis after gastro-oesophageal reflux disease. EoE commonly presents with dysphagia to solids and food bolus impaction. It is common in men between 30 to 50 years of age, with an increasing prevalence in recent years.[3-5]

EoE is a disease that can significantly affect quality of life in the working age population. With current available clinical therapies, patients can usually be effectively managed, particularly following recently developed topical steroids; an oro-dispersible formulation of budesonide.[5] However, significant delays in diagnosis and suboptimal management of this group of patients remain common.[5-6] This may partly be due to the lack of simple practical guidelines and limited understanding of the disease among frontier health professionals.[6-11] Clinical and basic research of EoE have achieved significant progresses in recent years;[12-14] several clinical guidelines have been developed to improve clinical diagnosis and care of patients with EoE.[5,15] However, recent clinical audit data across NHS district general hospitals and tertiary hospitals suggest that further improvements in clinical diagnosis and management are still required.[7-11] Two simple algorithms for endoscopic diagnosis (Algorithm 1*) and clinical management of EoE (Algorithm 2**) have been recently published; they have referenced the latest research progress and clinical guidelines.[5,15] These algorithms may assist health professionals in clinical practice and improve the daily care of EoE patients.

Algorithm for endoscopic diagnosis of EoE

According to current clinical guidelines, EoE should be diagnosed when there are symptoms of oesophageal dysfunction, at least 15 eosinophils per high-power field (hpf) on oesophageal biopsy, and after a comprehensive assessment of non-EoE disorders that could cause or potentially contribute to oesophageal eosinophilia.[15] For an early and accurate EoE diagnosis, it is important to understand the clinical features and presentations of patients with EoE. A variety of symptoms have been linked to EoE (Table 1), including oesophageal dysphagia, food impaction, chest pain, heartburn, odynophagia, abdominal pain, regurgitation, vomiting and malnutrition.[6,15-17] Several studies describing the presenting symptoms of EoE clearly show a different pattern between adults and young children. In adults, dysphagia (70–80%) and food impaction (33–54%) constitute the most common symptoms.[5,15-17] The severity of symptoms and their impacts on quality of life may be underestimated as a result of long-standing and subtle accommodation, such as eating slowly and avoiding certain foods.[1] Therefore, careful history taking is important. It would be easy to suspect EoE and arrange to take oesophageal biopsies in a young man with an atopic comorbidity such as asthma, a long-standing history of dysphagia or food impaction; however, a patient presenting with heartburn, epigastric pain or nausea/vomiting may present as a challenge in determining whether oesophageal biopsies are required.[5]

Table 1. Common symptoms of EoE

• Dysphagia
• Food impaction
• Chest pain
• Reflux symptoms
• Regurgitation
• Odynophagia
• Abdominal pain
• Vomiting
• Anorexia and early satiety
• Non-specific throat symptoms, such as globus

It is also important to note that patients with EoE often suffer from atopic comorbidities such as asthma, atopic dermatitis, or immediate-type food allergies, as well as family history of EoE or dysphagia.[15] The presence of these conditions should increase the clinical index of suspicion and promote the need for oesophageal biopsies during upper gastrointestinal (GI) endoscopy. This may be particularly helpful when a patient presents with non-specific oesophageal symptoms and/or the oesophageal mucosa appears normal (Figure 1).

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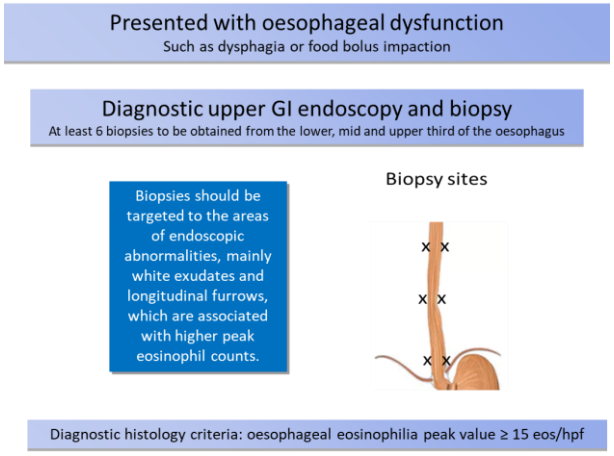

Figure 1. Endoscopic diagnosis of eosinophilic oesophagitis

During the endoscopic procedure, the endoscopist should closely observe the oesophageal lumen and its mucosa for the endoscopic features common in patients with EoE. As shown in Table 2, common endoscopic features of EoE patients include fixed oesophageal rings, narrowing or strictures, linear furrows, white plaques or exudates, oedema (including decreased vasculature, pallor), and mucosal fragility (also termed crêpe-paper mucosa).[18,19] In a small proportion of subjects, the oesophageal mucosa may appear normal.[5] While the above endoscopic findings are common, they are not pathognomonic to EoE and are unlikely to all appear together within one case.[19]

Oesophageal stricture in EoE is different from the focal distal oesophageal strictures found in patients with gastroesophageal reflux disease. Strictures in patients with EoE may affect the whole or a segment of the oesophagus with reduced calibre of the oesophageal lumen, whereas the mucosa itself may appear normal. While it is common for such strictures or a narrowing of the oesophagus to escape detection during endoscopy, they become evident in contrast oesophagrams.[20,21] Two recent studies reported that 71% of adults and 55% of children with eosinophilic oesophagitis did not have oesophageal narrowing recognized at the time of endoscopy but the narrowing was identified during oesophagography. Therefore, combing both upper GI endoscopy and oesophagram study may improve the diagnosis of patients with EoE, particular for assessment of oesophageal narrowing/strictures.[22,23]

Table 2. Common endoscopic features of patients with EoE

• Fixed oesophageal rings
• Narrowing or strictures
• Linear furrows
• White plaques or exudates
• Oedema (including decreased vasculature, pallor)
• Mucosal fragility, also termed crêpe-paper mucosa
• Normal mucosa (up to 10% patients presented without macroscopic mucosal abnormality under endoscopy)

In all cases where EoE is a clinical possibility (even when normal mucosa is visualized), oesophageal biopsy specimens should be obtained.[5] However, there has been substantial variation in biopsy protocols, both in literature and reported practice pattern surveys. This is problematic because the eosinophilic infiltration in EoE can be patchy; if the oesophagus is insufficiently sampled, the diagnosis can be missed. For example, levels of oesophageal eosinophilia can vary widely, not only in terms of location in the oesophagus but also within biopsies themselves.[5,24] It has been clearly shown that increasing the number of biopsies increases the diagnostic sensitivity; one single biopsy had a sensitivity of 55% and five biopsies a sensitivity of 100% in the diagnose of EoE.[25-27] Recent guidelines recommend that at least six biopsies (from at least the proximal, mid and distal oesophagus) need to be taken to maximise diagnostic accuracy.[6] These biopsies should focus on areas with endoscopic mucosal abnormalities, such as white exudates and longitudinal furrows, which are associated with higher peak eosinophil counts.[5] In a suspected EoE patient, biopsies should be taken despite a normal endoscopic appearance of the oesophagus, which has been reported in up to 10% of patients.[5]

After oesophageal biopsies are obtained, they can be fixed in formalin or paraformaldehyde, rather than Bouin's fixative, since formalin is more effective at preserving the integrity of eosinophils.[28] Hematoxylin-eosin staining is sufficient for histological assessment of EoE in routine clinical practice.[5] An increased number of eosinophils in the oesophageal epithelium, which is a mucosa typically devoid of eosinophils, is the histologic hallmark of eosinophilic oesophagitis. A cut-off value of at least 15 eosinophils per hpf is thought to approach a sensitivity of 100% and specificity of 96% for establishing the histologic diagnosis of eosinophilic oesophagitis.[29] Many factors could affect the accuracy of the histologic assessment, including the microscope used, location in the biopsy specimen assessed, and the protocol for assessing the eosinophils by the reporting pathologist. Standard practice is to ask for a report of the peak eosinophil count hpf.[30] Besides peak eosinophil count, additional histological features may include eosinophil microabscesses, basal zone hyperplasia, dilated intercellular spaces, eosinophil surface layering, papillary elongation, and lamina propria fibrosis.[31]

Proton pump inhibitor (PPI) use is very common among patients attending for upper gastrointestinal endoscopy. As one of the commonly used therapeutic agents for EoE, PPI will affect mucosal eosinophil cell counts. A diagnosis of EoE may not be definitively ruled out in patients who are on PPI therapy and have lower levels of eosinophilic counts on oesophageal biopsies. For these patients, clinicians may have to decide if further evaluation without PPI therapy should be considered.[15]

In addition, several local and systemic diseases with different clinical and histological features can be associated with oesophageal eosinophilia and should be ruled out before a diagnosis of EoE is finally made. Diseases to be discounted include, for example, eosinophilic gastroenteritis, achalasia, parasitic infection, hypereosinophilic syndrome, celiac disease, Crohn's disease, infectious esophagitis, drug hypersensitivity, vasculitis, pemphigus, connective tissue disorders, graft versus host disease.[5,15]

Algorithm for clinical management of EoE

The mainstays of EoE therapy are drugs (such as topical corticosteroids and PPIs), dietary exclusions, and endoscopic dilations. Unfortunately, none of these therapies are able to eradicate the disease; therefore, similar to the management of any chronic condition, EoE requires induction and maintenance treatment. Patients with EoE should have a structured long-term follow-up plan.[5,6] Both drug therapy and dietary exclusions can be used for induction therapy. The decision on initial therapy for a newly diagnosed patient, however, should be individualised and patient driven, based on the patient's

condition, preferences, the goals of care and the subject's lifestyle and needs; the availability of a specialist dietician on EoE in the local hospital in case of dietary therapy may also be an important factor.[6,32-33]

Regarding PPI therapy, substantial evidence suggests that PPIs can be used to treat EoE in adolescents and adults[5] while response was measured by histologic improvement; clinical responses were less frequently studied and it has been difficult to draw conclusions about symptom benefit. The meta-analysis by Lucendo et al reported a pooled histologic response rate of 50% (95% CI, 40–59) for PPI use in adults, although there was substantial heterogeneity.[34] Furthermore, studies have confirmed that the anti-inflammatory action of PPI on patients with EoE is likely independent of its anti-acid properties, via inhibition of Eotaxin 3 eosinophil pathway.[35] However, the precise mechanism of action is not well understood and may vary between patients.[34] Due to its low cost, good safety profile, convenience, and the effectiveness of PPI therapy on EoE,[5] many believe that PPI should be considered as an initial or early induction treatment.[5] However, PPI has not been licenced for EoE treatment and it may not be suitable as an initial therapy for some cases. Newly diagnosed EoE patients could perhaps be divided into three subgroups based on whether patients were exposed to PPI therapy and their response to the medication: PPI responsive, PPI nonresponsive, and PPI naïve.[15] Gastroesophageal reflux disease and EoE may coexist; so some patients may need to be treated for both acid reflux and EoE inflammation. In this case, PPI would be the best initial option, especially if PPI has not been adequately used and previously demonstrated some potential effectiveness, or the patient is naïve to PPI therapy (Figure 2).

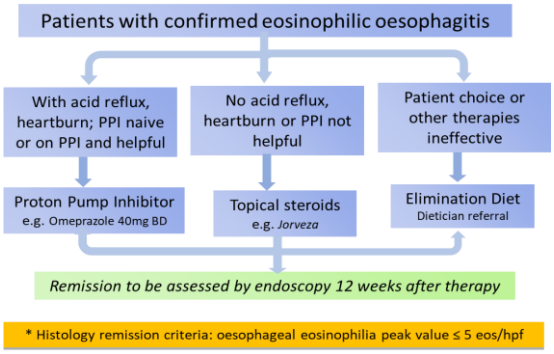

Figure 2. Clinical management of eosinophilic oesophagitis

Topical corticosteroids are the most widely used treatment for EoE and have proven efficacy in inducing clinical, endoscopic and histological remission in active EoE. Until recently, off-label use of topical corticosteroids was a mainstay of therapy but a licenced topical corticosteroid (Jorveza) is now available for patients with EoE.[36] Clinical trials have demonstrated that Jorveza, an oro-dispensable budesonide tablet, can dramatically improve oesophageal mucosa inflammation and the clinical symptoms of patients with EoE. After 12 weeks, 85% of patients enter remission and underlying eosinophilic inflammation (defined as <5 eosinophils per hpf) is completely cleared.[36] This treatment offers good tolerability, with a major improvement in quality of life, as well as reducing the need for endoscopies. In addition, topical corticosteroids have a good side effect profile and complications are rare.[6,32-33] Key advantages of steroid therapy include the effectiveness of topical corticosteroids in achieving histologic, endoscopic, and symptomatic remission, while preventing complications such as fibrosis and food impactions.[6,32-33] It is therefore worth considering whether patients should also be offered topical steroid as an initial therapy if they have no gastroesophageal reflux disease-related symptoms or are PPI non-responsive (Figure 2).

Diet therapy also continues to be an important first-line option for motivated patients and clinicians, with removal of the six most common food allergens associated with a 70% histologic response in both paediatric and adult studies.[37-38] Less restrictive diets have been devised to reduce the need for repeated endoscopies. This is the only therapy that could potentially cure EoE by avoiding the identified food or food component. However, this therapy requires intensive dietician review and follow up. Furthermore, it is considered to be very expensive, could take 12 months and requires six or more endoscopy assessments and biopsies for a six-food elimination diet regime.[37-39] Finally, dieticians with interests in gastroenterology and EoE may not be immediately available for some local hospitals (such as NHS district general hospitals) (Figure 2).

Endoscopic dilation should be recommended to all EoE patients who have dysphagia/food impaction that is related to fibrostenotic abnormalities (either narrow-calibre oesophagus or strictures) and unresponsive to medical or dietary therapy (Figure 3).[5,40] Endoscopic dilation is highly effective, with clinical improvement documented in 75% of patients in a meta-analysis. Mucosal lacerations after dilation should not be considered complications, but rather the intended outcome of the endoscopic procedure.[41]

The therapeutic responses for patients treated with either drug and dietary therapy will be assessed clinically and with endoscopy biopsy following a 12-week treatment. Patients may have a mismatch between symptoms and histopathologic features, which creates the need for multiple assessments of disease activity (Figure 3). As a result, the goals of induction therapy will include the improvement of symptoms, control of inflammation, and restoration of function.[5,15,41-43] Complete histology remission is defined as peak eosinophil count <5 per hpf on oesophageal mucosa biopsies,[44] and the absence of any additional histological features of EoE, such as eosinophil micro abscesses, basal zone hyperplasia, dilated intercellular spaces, eosinophil surface layering, papillary elongation, and lamina propria fibrosis.[5,44-45] However, clinicopathologic dissociation in EoE may be possible and has been reported after pharmacological therapy with a PPI or topical corticosteroids.[5] Symptoms may improve without histological remission and, conversely, dysphagia and/or food impaction may persist despite the absence of inflammation in patients who have fibro-stricture features. These situations must be assessed on a case-by-case basis. Based on clinical, endoscopy and histological findings, it may be necessary to continue the initial therapy for a period of time, adjust dose or swap to another therapy. It is also important to involve the patient in the decision-making process.[5] For those patients who exhibited a complete lack of response to initial therapy, it might be necessary to re-assess the EoE diagnosis and consider alternative treatment including, if EoE remains the possible diagnosis, elemental diet or novel therapies (Figure 3).[15]

Maintenance therapy and follow up after an effective initial therapy remains poorly studied. While all patients in remission can be offered maintenance treatment, this option has been strongly recommended in patients with severe disease phenotypes or complications, including malnutrition or failure to thrive, oesophageal fibrostenosis, strictures requiring dilation, recurrent food bolus impaction, history of perforation,

and symptoms that recur quickly after treatment discontinuation.[46-47] Regular follow-up, including endoscopies with biopsy, may be indicated because a proportion may lose response over time.[15] A recent study on maintenance therapy with topical steroid showed that a 48-week treatment with oro-dispensible Budesonide tablet was safe and highly effective vs placebo in maintaining EoE patients in clinicohistological remission.[36]

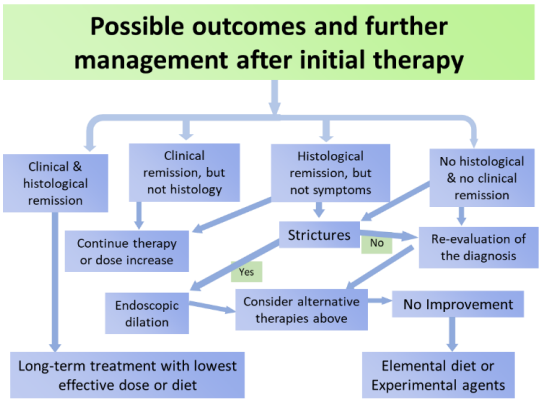

Figure 3. Possible outcomes and further management after initial medical therapy

Novel therapeutic approaches to induce remission in EoE patients target allergic cytokine mediators, including interleukin-4, 5, and 13, and have produced promising results. The role of biologic therapies in the management of EoE is yet undefined but the increasing recognition of steroid-refractory patients, as well as potential effects on oesophageal remodelling, are unmet needs.[48]

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* For access to Algorithm 1 at:
http://www.worldjmed.com/user/image/algorithm-for-endoscopic-diagnosis-of-eoe.pdf

** For access to Algorithm 2 at:
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