

EOSINOPHILIC OESOPHAGITIS IN CHILDREN: MANAGEMENT OPTIONS FOR INDUCING AND MAINTAINING DISEASE CONTROL

MA Furman | MBChB(UCT), DCH, FRCPCH

Clinical Lead, Centre for Paediatric Gastroenterology, Royal Free London NHS Foundation Trust

Email | mark.furman@nhs.net

ABSTRACT

Over the past decade the incidence of eosinophilic oesophagitis (EoE) has risen significantly and has become a common condition seen in paediatric gastroenterology centres around the world. The association with atopic disease is well known, and treatment options remain concentrated on acid suppression, dietary eliminations and topical corticosteroids. One of the greatest challenges is planning long-term disease management. Currently there is little published data on maintenance treatment for EoE in children. Many children remain on long-term elimination diets or topical steroids and undergo multiple repeat endoscopies. Large multicentre studies are required to gain a better understanding of this challenging condition, to standardise maintenance treatment and to find better methods for reliable disease surveillance.

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INTRODUCTION

EoE is an emerging chronic immune-mediated condition, defined by the histological finding of greater than 15 eosinophils per high power field in oesophageal biopsies (see Figure 1). In this condition, the eosinophilia is not a feature in other areas of the gastrointestinal tract¹ and is associated with symptoms relating to oesophageal dysfunction. The inflammation can be patchy and, while it is typically considered to be a clinico-pathologic disease, at follow-up surveillance endoscopies the symptoms frequently do not correlate with the microscopic findings.^{2,3} Therefore follow-up and surveillance of this condition currently rely heavily on repeated endoscopic examination of the oesophagus, with biopsies. Treatments focus on a combination of proton pump inhibitors (PPI), dietary exclusions and corticosteroids. The incidence is rising alongside the increase in other atopic disease as well as inflammatory bowel diseases (IBD), such as Crohn's Disease. In the United States the prevalence in children is estimated to be around 40–50/100 000.^{4,5}

DIAGNOSIS

Symptoms may vary depending on age of presentation. Infants and toddlers are more likely to present with gastro-oesophageal reflux (GOR)-type symptoms and feeding issues, whereas older children and adolescents are more likely to experience symptoms related to oesophageal dysfunction, such as dysphagia, heartburn, regurgitation or, in more extreme cases, food bolus impaction from oesophageal muscle spasm or strictures.⁶ The majority

of patients with EoE have an associated atopic condition, such as asthma, eczema, food allergy or allergic rhinitis (the last being associated with some seasonal variation in the EoE in some patients).^{7,8}

ENDOSCOPY

Oesophago-gastroduodenal endoscopy (OGD) is the current essential gold standard investigation for diagnosing EoE. Endoscopic features are important, but much more important is obtaining the biopsies for histological analysis. Multiple biopsies are recommended from the lower, middle and upper areas. Endoscopic findings range from endoscopically normal mucosa to severely strictured oesophagus with minimal luminal patency. Other typical findings include the more subtle, milder so-called 'crepe-paper features' (small eosinophilic abscesses), more marked erythema, similar to gastro-oesophageal reflux disease (GORD), longitudinal linear streaking (see Figure 2), concentric rings ('trachealisation') and friable, ulcerated and damaged mucosa with bleeding.⁶ Oesophageal strictures or spasms with food bolus impaction is one of the most severe findings, requiring urgent therapeutic intervention.⁹ In the worst affected cases, mucosal laceration (sometimes with associated haematemesis) may occur. The ESPGHAN EoE Working Group has established a database called Paediatric European EoE Registry (pEEr) to achieve a better understanding of the disease incidence, management and outcomes across European centres. The patient entries include well-defined endoscopic classification. Standardisation of endoscopic

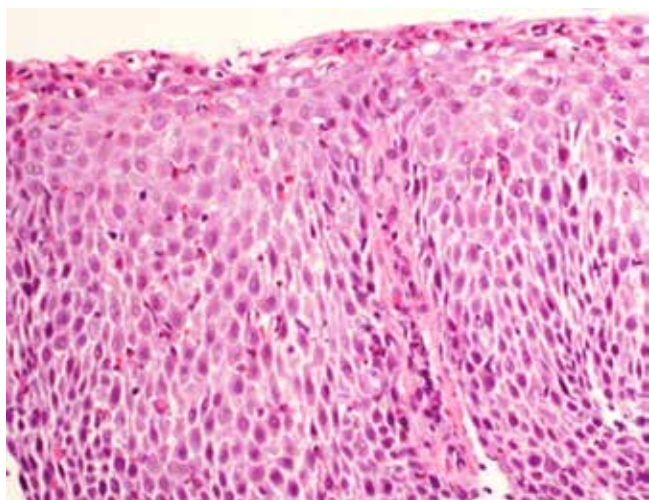


Figure 1: Dense eosinophilic infiltrate in oesophageal biopsy

reporting is helpful in comparisons of cases on a much wider scale. In those patients with severe symptoms of dysphagia, it is advisable to perform a low-dose fluoroscopic swallow to assess for the presence of a stricture.¹⁰

TREATMENT STRATEGY

Initial treatment with high-dose proton pump inhibitors (PPI) for 8–12 weeks will identify the 20–30% of patients whose disease responds to PPI therapy alone.^{3,11} Omeprazole at up to double the usual age-dependent dosing has been shown to be effective, at a dose of 1 mg/kg twice daily.²² Repeat endoscopy after this initial treatment identifies those patients as having PPI-responsive oesophageal eosinophilia (PPI-REE). There is some debate whether patients with PPI-REE represent a separate disease entity, or whether they are actually on the spectrum of EoE, with a disease phenotype which and therefore may actually be PPI-responsive EoE (PPI-REoE) rather than PPI-REE.¹² In those whose disease does not enter histological remission, an alternative strategy is indicated. The option then is a choice between food-elimination diets (FED), steroids or a combination of the two.

FED are indicated in those who do not respond adequately to initial PPI monotherapy. Targeted eliminations, guided by specific IgE testing, do not appear to be as effective as combination elimination or exclusive elemental nutrition (EEN) with an elemental dietary formula. Empiric 4 FED, which exclude cow's milk, soya, egg and wheat, and 6 FED, which in addition also exclude peanut and shellfish, are effective in the dietary management of EoE. Kagalwalla et al found that on food reintroduction after 6 FED, cow's milk was the commonest precipitating food.¹³ Where FED has been ineffective and, particularly, where symptoms remain significant, further treatment escalation is indicated. A choice between exclusive enteral feeds with an amino-acid formula or swallowed topical steroids needs to be made. Multiple FED can be very difficult to maintain, often resulting in poor dietary compliance and social challenges,



Figure 2: Deep linear furrowing in mid-oesophagus in paediatric patient with EoE

particularly in school-age children. Options and choices may depend on patient and parent choice. Unfortunately, after the reintroduction of food after a period of EEN, the relapse rate is very high, and EEN is not a practical maintenance strategy.¹⁴

Topical corticosteroids are effective in inducing remission in EoE. Studies have demonstrated the efficacy of both swallowed fluticasone¹⁵ and oral viscous budesonide (OVB).¹⁶ The OVB dose is dependent on height, 1 mg/day being given to those children <152 cm tall, and 2 mg/day to those >152 cm tall.²³ Both of these have excellent first-pass metabolism, minimising systemic steroid effects. It is critical to deliver these within a thickening agent to improve application and contact with the oesophageal mucosa for as long as possible. Solutions that have been used as suspending agents include Sucralose and even honey.¹⁷ The author has experience with Ora-Blend® as an effective suspending agent within his centre. In one study with Fluticasone, 65% patients had complete remission.¹⁵ In a paediatric study OVB was demonstrated to be effective with two different delivery vehicles after ten weeks of therapy.¹⁶ Currently, no corticosteroid viscous solution is commercially available, so patients and carers have to mix the doses each day. Budesonide is dispensed as nebulisers – for nebulisers – and mixed with the suspending agent immediately prior to ingestion. Where possible, ingesting in the left or right lateral position slows down passage through the oesophagus, with the aim of increasing the contact time with the mucosa. No eating or drinking should occur for at least 30 minutes after each dose.

Systemic steroids, such as prednisolone, have also been reported to be effective, and may be indicated in cases where there is a lack of response to other treatments, or poor adherence to dietary exclusions.⁶ A recent publication by Harel et al reported findings of adrenal suppression, even in topical steroid use.¹⁸ No patient in the series had any clinical Addisonian features. The author highlighted a

particular issue with those patients using topical steroids for concomitant treatment of another atopic disease, including inhaled and dermatological applications. Although the steroids used for topical EoE treatments have extensive first-pass metabolism, caution is advised when starting treatment. Furthermore, weaning rather than sudden cessation of treatment is something that may need to be considered, even though this is not currently part of any published guidance on EoE.

Candida infection has been reported as a result of prolonged topical oesophageal steroid use. If this is noticed on follow-up endoscopy, brushings should be taken and sent for analysis.

DISEASE MONITORING

Follow-up endoscopies after treatment interventions are part of most current recommendations, and as paediatric endoscopy is usually performed under general anaesthesia, this will result in multiple anaesthetics. Although symptoms may improve on treatment, the histological activity of the disease may still be significant, rendering symptom assessments relatively unreliable in many patients. The patients who feel well despite ongoing significant histological inflammation present a particular challenge in both convincing them of the need to continue on the treatments and also with disease surveillance. There is currently no commercially available test, other than endoscopy, that is reliable for disease activity assessment.

MAINTENANCE

Whether the patient has PPI-REE, responds to a FED or requires a course of steroids, entering a state of remission or disease control is usually achievable. The greatest challenge for many will be that of disease-free maintenance. For those who are PPI responsive, and for those who are on a single FED, remaining disease-free is more easily achievable than for those who have required steroids, 6 FED or EEN. There is excellent evidence of effective steroid dosing for the initial treatment phase, but not much is published on the maintenance choices and doses.¹⁵

Where FEDs have been continued, a food challenge should be planned at some time. This may be influenced by the season for those who develop allergic rhinitis, and aiming for a winter challenge may be preferable in those cases. After each challenge, a clinical review should be conducted, and an endoscopic reassessment should be considered. Doing so should take into account the number of endoscopies already completed in that patient and the likelihood of needing further procedures. In those patients whose symptoms relapse, eliminating the food again would be a reasonable plan, without the need for endoscopic evidence of relapse.

The maintenance dose with topical steroids is less clear.

Some discussion about half of the induction dose has been published.¹³ Andreae et al reported good long-term results with two puffs a day of swallowed fluticasone from a metered dose inhaler (MDI), with a mean follow-up of 20.4 months. Improvement in endoscopic and histological features, including fibrosis, was observed on annual endoscopies, along with symptom improvement. No effect on growth was noted.²⁴

The risks of possible adrenal suppression imply that adrenal function tests should be considered in those on longer-term treatment with steroids.¹⁸ Other complications of chronic steroid use include potential growth effects and also the risk of developing oesophageal candidiasis.

Not much experience has been published on the use of immunomodulators in EoE, but a publication by Netzer et al found that the use of azathioprine and 6-mercaptopurine in EoE in three patients was successful in maintaining remission for several years.¹⁹ One of the benefits of thiopurine use in EoE maintenance is the hope that this would have a steroid-sparing effect, but larger studies are needed over a longer period before this can be recommended in disease guidelines.

Modalities other than endoscopies are also being developed, with the intention of avoiding repeated endoscopies. Methods to assess for oesophageal eosinophilia could facilitate better clinico-pathological correlation, without the need for endoscopically obtained biopsies.

As some patients may have a strong influence of aeroallergens in their disease pathogenesis, treatment holidays during the winter months may be something to consider. In those who have severe aeroallergen reactions, immunotherapy may be considered as an option. There have been reports of SLIT improving EoE,²⁰ and aeroallergens have been implicated in seasonal exacerbations of EoE. SCIT has also been suggested as a possible treatment in managing EoE in combination with allergic rhinitis;²¹ however, the author has experience of a patient with significant worsening, requiring systemic steroids, after use of both SLIT and SCIT for aeroallergen sensitisation.

LOOKING AHEAD

Interleukin-5 antagonists have been studied in both adult and paediatric age groups and have been demonstrated to reduce eosinophil concentration within the oesophageal mucosa. The greatest effect was in those with higher eosinophil counts, but, disappointingly, there was an absence of significant clinical response to this.^{25,26} Further research is required in the hope that a targeted approach to EoE will be identified. But at the moment the approach remains broad, with a combination of acid suppression, dietary intervention and corticosteroids being the main option currently. Immunomodulators

appear to have a potential role, but understanding the natural disease progression and the different phenotypes is important in assessing the risk of starting long-term immunosuppression in these patients. Understanding the aetiology and developing effective, safe and tolerable maintenance treatment which retains remission and

prevents complications remains the big challenge in EoE.

DECLARATION OF CONFLICT OF INTEREST

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