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# THE MEDICAL MANAGEMENT OF EOSINOPHILIC ESOPHAGITIS

## INTRODUCTION

Eosinophilic esophagitis (EoE) was first recognised as a unique condition in the early 1990s. It was described by Alex Straumann[1] who identified 10 children with resistant 'gastro-esophageal reflux disease (GERD) symptoms' with typical endoscopic features and esophageal eosinophilia who achieved resolution of symptoms and esophageal eosinophilia with an elemental formula. While once a rare condition, EoE is being increasingly diagnosed worldwide, with an incidence rate estimated to be 5 to 10 per 100,000[2]. While widely recognised as being a Th-2 inflammatory disorder, predominantly triggered by food allergens, there is a growing body of literature supporting the role of aeroallergens in the condition[3,4]. Management of the condition involves close collaboration amongst gastroenterology and allergy specialists. At least half of affected patients will have other allergic disorders including allergic rhinitis, asthma, eczema and some will also have IgE-mediated food allergies. Workup and management of aeroallergen sensitivities is important as swallowed aeroallergens may be a contributing factor to eosinophilic esophagitis, with many patients noting a seasonal exacerbation in their symptoms[5].

## DIAGNOSIS OF EOSINOPHILIC ESOPHAGITIS

EoE is diagnosed when there are ≥ 15 eosinophils/high power field (hpf) in esophageal biopsies in a patient with symptoms of esophageal dysfunction, when other causes of esophageal eosinophilia have been ruled out. Other histologic features should also be present such as thickening of the basal cell layer, eosinophilic layering and possible eosinophilic micro-abscesses. Symptoms can be variable, depending on age of presentation and include nausea, vomiting, heartburn, abdominal pain, dysphagia and food impaction[6,7]. Vomiting and feeding aversion may be more common in very young children, with the more classic dysphagia and food impaction more common in older children, adolescents and adults[8]. Endoscopic features should be described using the EoE Endoscopic Reference Score (EREFS) which characterizes edema, esophageal rings, exudates, linear furrows and strictures[9].

Until relatively recently, it was recommended that diagnostic evaluation be performed following a trial of proton pump inhibitor (PPI) therapy, to remove potential GERD as a cause for the esophageal eosinophilia[7]. It is now recognised that a significant proportion of patients will have PPI-responsive EoE[10]. Therefore, the most recent diagnostic guidelines from the AGREE conference no

longer include the requirement for patients to have a trial of PPI therapy prior to endoscopic evaluation, as this strategy will not distinguish between GERD and PPI-responsive EoE[6].

## THERAPEUTIC OPTIONS

Treatments of EoE are aimed at improving symptoms, improving inflammation and preventing complications, mainly stricture development[11].

There are 2 broad therapeutic approaches: 1) dietary-based (elimination diets) or 2) medications (proton-pump inhibitors and swallowed topical steroids). Dilations may be required to manage esophageal strictures. The American Gastroenterology Association Institute and the Joint Task Force on Allergy Immunology Practice Parameters (AGA-JTF) has proposed a guideline for management of EoE and looks at both dietary and medical strategies[3,12].

### Dietary Management – Elimination diets

Elimination diets are frequently used to treat EoE. The most effective elimination diet is an elemental diet, with remission rates of up to 90% described[13]. Despite the high efficacy, this is rarely used, except in the youngest children, due to the unpalatability of the amino acid-based formula and the usual need for a nasogastric tube. Therapy with an elemental formula is often prolonged with the need for multiple endoscopic procedures trying to identify the trigger food(s). A more popular approach is the use of empiric elimination diets based on the most common food allergens.

The six-food elimination diet is the most effective of the empiric elimination diets, with remission rates being about 70% in adults and children[14-16]. The most common food allergens in children are milk, followed by wheat, egg, soy, and peanuts[15], whereas in adults, the most common food allergens are wheat, followed by milk, egg, soy and peanut[14].

The six-food elimination diet is quite restrictive. Some physicians will elect to start with a milk-elimination diet, as milk is the most commonly identified food allergen. An improvement in symptoms, endoscopic and histologic features (with eosinophil count < 15/hpf) was noted in just over 50% of children in one study[17].

An interesting approach has been proposed by Molina-Infante et al with a step-up approach to dietary elimination. In their '2-4-6 prospective study', participants including adults (n=105) and children (n=25) first eliminated 2 foods (milk and gluten-containing grains). Forty-three percent (56 patients) achieved clinical and histologic remission with this strategy. Patients not in remission moved to a 4-food elimination diet (also removing eggs and legumes, including soy, lentils, chickpeas, beans, peas and peanuts). Those who failed the 4-food group elimination diet stepped up to a six-food group elimination diet, which also included the removal of all seafood and fish, with remission rates of 60% and 79% described in the 4-food and 6-food groups, respectively. Milk was identified as one of the triggering antigens in 52% of participants, and gluten in 16%. Twenty-eight percent were sensitive to both gluten and milk. Milk was the sole food allergen in 33% of children and 18 % of adults[18].

With all elimination diets, it is preferable to re-evaluate endoscopically as new foods are introduced, as there is a poor correlation between symptoms and histologic disease activity[19]. Eliminating a specific food group should be undertaken for a minimum of 6 weeks[20] with some experts suggesting a longer duration. The need for repeated endoscopies is a significant drawback to dietary elimination strategies, with the consequence of missed work for parents and adult patients, missed school days, need for general anaesthesia (in children) and general increased risk associated with repeated procedures. In my practice, I aim to scope after 8 weeks. In addition, early childhood is a critical period for oromotor development. Interruption to this process can result in significant feeding issues and food aversions[21]. In older children and teens, dietary elimination can have a significant impact on quality of life[22].

Involvement of a registered dietician is very important for any child or adult following an elimination diet. The registered dietician can educate the patient on the elimination diet, while ensuring the diet does not cause micronutrient deficiencies. Nutritional status and growth should be monitored in all patients following dietary restriction.

## MEDICAL THERAPY

### Proton Pump Inhibitor Therapy

Many adult and pediatric patients will show a histologic response with PPI therapy. A meta-analysis and systematic review of 33 published studies (188 pediatric participants; 431 adult participants), found improvement

in symptoms in 60.8% of patients (95% CI 48.3 - 72.2 %). Histologic remission was noted in 50.5% of participants (95% CI 42.4% - 58.7). The authors did note significant heterogeneity amongst the studies with a publication bias in studies reporting histologic response, indicating that some caution is needed when interpreting the meta-analysis findings[23]. There is no clear recommendation in the literature on PPI dosing, although a prospective study of adult patients, found that the majority of patients who achieved histologic remission on 40 mg omeprazole b.i.d. for 8 weeks, stayed in histologic remission when the dose was reduced to 40 mg daily[24].

The potential mechanism of action of PPI therapy in esophageal eosinophilia (in addition to anti-secretory activity) has been explored. A multicentre study of the EoE transcriptome which included genes for eosinophil chemotaxis (CCL26 (eotaxin-2)), mast cells (CPA3) as well as barrier molecules (DSG1) and tissue remodelling genes (POSTN) showed that the inflammatory molecular signature was nearly completely reversible with PPI therapy25.

Given the relative safety profile and ease of use, some patients may prefer this therapy prior to trying swallowed topical steroids or elimination diets[3].

## Swallowed topical steroids

Swallowed budesonide (typically a nebule is used to make a viscous suspension) and swallowed fluticasone (from a metered-dose-inhaler) have been shown to be effective in the treatment of both pediatric and adult patients[26-28]. A double-blind, double-dummy trial comparing swallowed fluticasone with swallowed viscous budesonide found similar efficacy with both medications[29]. To increase contact time of the medication with the esophageal mucosa, patients should not eat or drink for 30 minutes after the dose but may want to rinse out their mouth to help prevent esophageal candidiasis.

Suggested doses for swallowed topical steroids have been proposed in the 2011 consensus recommendation for adult and pediatric patients[7]:

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| Budesonide: Children < 10 years, budesonide 1 mg per day; for those over 10 years and adults, 2 mg per day was recommended. |
| Fluticasone: Children 88 to 440 µg 2 to 4 times per day was suggested; Adult dosing 440 to 880 µg twice daily. |

Technique: Puff a single puff directly (without use of a spacer-device) into the mouth and swallow. Do not breathe in until the dose is swallowed. After 15 seconds a second puff is administered. A typical dosing regimen is 2 puffs (250 µg per puff) swallowed twice per day. The patient should not eat or drink for 30 minutes after the dose.

Duration of therapy: There is no clear guideline on treatment duration or dosing for the use of swallowed topical steroids in the long-term. The literature shows that when treatment is stopped, symptoms and histologic activity are likely to recur.

More recently trials of an orodispersible form of budesonide have been performed in adult patients, for both induction and maintenance therapy[30,31]. The maintenance trial showed that rates of remission at 48 weeks were 73.5% and 75%, for the 0.5 mg twice daily and 1 mg twice daily dosing, respectively. The rate of clinic-histologic remission was almost 60%, and the rate of histologic remission was just over 90% in patients treated with orodispersible budesonide, 1mg b.i.d. for 6 weeks, in comparison with placebo[32]. Approximately 16% of patients developed oral candidiasis. This medication has become the first approved treatment for EoE and is now available for adult patients in Canada.

## Maintenance therapies

Eosinophilic esophagitis is a chronic condition which recurs when treatment is discontinued. Given the concern that untreated esophageal inflammation may lead to fibrostenotic disease, maintenance therapy may be considered[4]. For patients in whom triggering foods are identified, it is preferable to continue avoiding these foods. This is particularly helpful as it avoids the need for swallowed topical steroids, but can be difficult to adhere to, particularly in adult patients[33]. A few studies have explored ongoing use of swallowed topical steroids, showing higher remission rates in those continuing with therapy versus those who use placebo/ no medication[34,35]. The AGA-JTF guideline recommends that patients who achieve remission with topical steroid therapy **continue** with this treatment as maintenance[3]. Further guidance on dosing and use in children will be helpful in future publications.

### Adrenal Suppression

**Use of steroid therapy raises concern about the risk of adrenal suppression. Symptoms of adrenal suppression are non-specific and include nausea, lethargy, reduced responsiveness (i.e. altered level of consciousness) and can be life-threatening in an adrenal crisis.**

While there are guidelines for screening for adrenal insufficiency for asthmatic patients on long-term corticosteroids[36], no such guideline exits for patients with EoE receiving steroid therapy. For patients who continue on daily topical steroid therapy, clinicians may consider screening for adrenal suppression with an 8:00 am cortisol level, on an annual basis. Screening for adrenal suppression amongst EoE patients is not done consistently by treating physicians[37]. Several studies, often small, have shown reduced early morning cortisol and reduced ACTH stimulation tests in patients treated with prolonged use of topical corticosteroid[38,39]. Despite the potential risk of adrenal suppression, a larger study of 106 patients identified true adrenal insufficiency (post ACTH stimulation test) in just 5 patients, all of whom were on additional steroids for other atopic conditions. A larger number in the group had abnormal early morning cortisol levels at one point during follow up[40]. Nonetheless, given that corticosteroids are often used for prolonged periods or for repeated courses and considering that many patients will have other forms of steroid therapy for coexistent atopic conditions, it is important to be aware of this potential adverse effect, particularly as the consequences of a true adrenal crisis can be devastating.

### Endoscopic Dilation

For patients with a fibrotic stricture, dilations may be required. Dilations can be done via therapeutic endoscopy or with an interventional radiologist. A retrospective review of 509 patients at a single centre, found that 164 (32%) patients required a dilation over a 12-year follow-up period. More than one dilation was required in almost 60% of patients[41].

### Monitoring Treatment Response

Treatment response is determined with endoscopic and histologic re-evaluation. In children, this usually requires general anaesthesia. Repeated endoscopies are inconvenient for the patient and families and utilise hospital resources. Less invasive testing is being explored, and transnasal endoscopy, which does not require sedation, is being used at some centres in the United States for both pediatric and adult patients[42,43]. The scope is thin, measuring 6 mm, and adult patients have reported that a non-sedated transnasal endoscopy is more tolerable than a non-sedated standard endoscopy[44]. In children, the use of virtual reality goggles helps with tolerability of the procedure[45].

Other less invasive tests of disease activity include the esophageal string test and swallowed cytosponge. A multicenter study looked at a one-hour esophageal string test in adult (n=60) and pediatric (n=74) patients. Levels of various eosinophil-derived proteins obtained with the string were comparable with values obtained from mucosal biopsies. There was also good correlation with endoscopic mucosal appearance. The results obtained with the string test were able to distinguish 'active' versus 'inactive' eosinophilic esophagitis. Over 90% of parents and adult patients reported that they preferred the string test over the stand endoscopic procedure[46]. The cytosponge test is less invasive than a standard endoscopy and involves swallowing a gelatin capsule containing a mesh sponge. The test can be performed at the bedside. An adult study found that there was good correlation between eosinophil counts obtained from the sponge and from mucosal biopsies[47].

## FUTURE DIRECTIONS

Therapeutic approaches may change in the future. Biologic agents targeting cytokines involved in the EoE inflammatory pathway are currently being studied, as are novel formulations of existing therapies. Less-invasive monitoring methods, though not yet available in Canada outside of a clinical trial, are desirable. When choosing therapies, close collaboration with the patient and their family is important to facilitate joint decision-making and to increase the chance of adherence to the treatment plan.

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