

Eosinophilic Oesophagitis in Children: Disease Modulation by Topical Steroids

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Abstract

Purpose of review Eosinophilic oesophagitis (EoE) is a chronic inflammatory disease, and effective treatment for paediatric EoE is still evolving. There is no consensual standard therapy for adults or children, as evolving concepts still need to be properly validated and there has been continuous update from published trials. This paper summarizes the current knowledge about inflammatory background and corticosteroid therapy in paediatric eosinophilic oesophagitis.

Recent findings There are some effective therapies in EoE treatment, and currently, the use of PPI may be considered as the first-line treatment, as a sub-group of EoE patients can be responsive to them. However, a considerable proportion of patients will not respond both clinically and histologically or will recur. Various dietary options and topical steroids are valid alternatives.

Basic research has shown that corticosteroids downregulate inflammation and prevent remodelling, reducing the long-term complication rate, mainly related to stenosis.

Corticosteroids are effective and safe especially if delivered in a viscous solution (budesonide, fluticasone). New formulations may be available soon thereby sparing the need for home-made manipulations. Clinical remission and the possibility to maintain treatment for long periods without serious side-effects make this option attractive in paediatric patients that have the prospect of long-term disease.

Summary Corticosteroids are effective as induction and maintenance therapy and can be used safely in long-term therapy in childhood, leading to sustained remission.

Active research will provide further evidence to consolidate outcome and length of treatment.

Introduction

Eosinophilic oesophagitis (EoE) is a complex inflammatory disease. It was first described 20 years ago in a group of infants with reflux-like symptoms that resolved after empirical diet exclusion treatment [1]. Knowledge about disease presentation, endoscopic features and therapeutic options has evolved rapidly in the past decades.

The ancient concept of reflux disease in young children with biopsy findings of eosinophils in the oesophagus has evolved to the current understanding of a disease characterized by a chronic immune response that occurs in a susceptible host of any age. Although it affects all age groups, the clinical picture may vary according to the age of presentation. In younger patients, EoE may present as feeding difficulties, vomiting and failure to thrive, whereas in older children and adults, it may present as non-specific epigastric or chest pain, dysphagia and food impaction [2••].

The current approach for diagnosis and characterization of this disorder includes the endoscopic appearance of the mucosa, objective histological evidence of inflammation involving eosinophils (oesophageal eosinophilia of ≥ 15 eosinophils per high-power field on haematoxylin and eosin stain at $\times 400$ magnification on light microscopy) and, when indicated, studies showing impaired motor function.

The most important endoscopic findings seen in a typical patient (an adolescent with dysphagia) are oesophageal rings (causing a tracheal appearance), longitudinal mucosal furrows and white exudates that can involve the entire oesophagus (Fig. 1). In other patients, however, endoscopy can be normal [2••, 3••].

Epidemiological studies have attempted to estimate disease prevalence in different populations. In developed countries, there is a rising incidence parallel to what is seen with other inflammatory diseases, such as inflammatory bowel disease. A recent published systematic analysis showed an overall prevalence of 22.7 cases per 100,000 inhabitants/year with slightly lower numbers in children (19.1 cases), but the lack of large population studies in paediatrics may lead to underestimation of the number of cases, as they may present later as young adult patients [4•].

In the paediatric population, it seems that both incidence and prevalence have been rising in the two last decades, with annual increases between 12 and 56% [5, 6]. This increase was initially thought to reflect a higher level of clinical suspicion and accurate diagnosis but that was not confirmed in recent studies.



Fig. 1. Food impaction and visible trachealization of the oesophageal wall. *Longitudinal furrows* are also present as a sign of oedema of the oesophagus. *White nodules* on the oesophageal mucosa correspond to eosinophil abscesses.

Inflammatory changes in the mucosa and eosinophil recruitment strategies are being investigated. Guidelines on effective treatment options have

been published but much is still in progress and there have been frequent updates on mucosal immunologic findings in EoE.

Eosinophilic oesophagitis as an inflammatory disease

Food allergies can be classified into those that are IgE-mediated, those that are mediated by both IgE-dependent and IgE-independent pathways (mixed) and the ones that are entirely IgE-independent.

In non-IgE-mediated food allergic disorders, multiple inflammatory cells and cytokines play a role in immune pathogenesis. EoE is an immune-mediated disorder with specific cytokine and inflammatory pathways but has some common features with allergy in the gastrointestinal tract [7].

The hallmark of EoE is the accumulation of eosinophils in oesophageal mucosal biopsies with signs of active involvement of these cells in the inflammation, as expressed by micro abscesses and degranulation. The chronic inflammation may evolve to sub-epithelial fibrosis, increasing dysmotility and stenosis [8, 9]. Histologic identification of one biopsy with elevated eosinophil count (>15/hpf) at any level of the oesophagus is a sign of inflammation and supports diagnosis. Effective treatment should lead to tissue eosinophil normalization.

A substantial proportion of paediatric EoE patients have evidence of food and/or aeroallergen hypersensitivity with personal history of asthma or rhinitis and use of therapy to alleviate those symptoms.

Murine studies using an experimental model of EoE showed elevation in CD4 and CD8 T cells in mice with induced EoE and found no oesophageal inflammation after nasal allergen stimulation in T cell-deficient mice, which suggested a role for Th2 signalling in EoE [10].

It is well known that children with EoE and rhinitis often have seasonal variation of oesophageal symptoms and mucosal eosinophilia and that is usually linked to the worsening of their respiratory disease, but that depends on the specific sensitization [11].

More than 2% of alimentary proteins reach Peyer's patches of the small bowel and other lymph tissue without any degradation. The stimulation of dendritic tissue and subsequent stimulation of IL-10 production and of FOXP3 cells lead to alimentary tolerance [7, 12]. When this tolerance pathway is disrupted, the imbalance between Th-2 inhibition and stimulation leads to a chronic inflammatory response.

Since the first description of the condition, EoE and alimentary sensitization have been linked, and it has been demonstrated that elemental diet normalizes eosinophil infiltration in paediatric patients with EoE [13]. The empirical elimination of six foods (milk, wheat, soy, fish, nuts and egg) led to normalization of the oesophageal mucosa in several studies both in adult and paediatric patients [14••]. Mucosal stimulation by food protein allergens may have a role to start and perpetuate the inflammatory pathway in oesophageal tissue [15].

The Th2 immune response is not only an inflammatory cell process. There are specific roles of eosinophils, mast cells and dendritic cells of the *lamina propria* revealing complex connected pathways.

Mast cells are linked to a general allergic response in the gastrointestinal mucosa. They are downregulated by IL-10 and Treg cells in gut *lamina propria* overexpressed when there is any imbalance in this pathway [7]. However, in EoE, mast cells are related to eosinophils as they are directly stimulated by major basic protein (MBP) secreted after eosinophil degranulation. MBP directly increases smooth muscle reactivity [16] and triggers degranulation of mast cells and basophils [17]. Mast cells and eosinophils are linked and their activation leads to inflammation of the oesophageal mucosa [18–20]. Activated eosinophils and mast cells generate lipid mediators that stimulate smooth muscle contraction, increased vascular permeability and mucous secretion as well as production of TGF-beta which mediates collagen deposition and fibrosis that are associated to later oesophageal remodelling [21, 22]. This process may occur in parallel to eosinophil activation. A recent study showed that IL-13 produces oesophageal remodelling and stimulates remodelling-associated gene expression in a manner independent of eosinophil activation [23].

Eosinophils are the main players even in the absence of other cells involved in inflammation [24]. In fact, a subset of patients does not have atopic disease or response to food elimination. Eotaxin-3 is induced in EoE patients of all age groups regardless of the allergic condition of the patient, and it has a powerful effect on eosinophil recruitment. Its gene overexpression is seen in EoE patients and this gene expression is different in patients with reflux oesophagitis [10].

IL-5 is an important cytokine involved in eosinophil activation and leads to eosinophil expression in the mucosa. Human and murine studies have demonstrated this effect in EoE. Eosinophils can also secrete IL-5 which may perpetuate the inflammation cascade in the oesophageal mucosa [10, 23].

IL-13, traditionally associated to lung allergic disease also has a potential role in inflammation in EoE. In humans, pre-treatment with human neutralizing IL-13 (CAT-354) antibody has been shown to reduce IL-13-induced lung and oesophageal eosinophilia [25].

IL-33 is an interleukin usually associated with lung disease, atopy and eczema. Recently, murine and human experimental work showed IL-33 overexpression in children's eosinophilic oesophageal mucosa, without change in the serum levels (as usually occurs in lung disease). In this study, IL-13 knock-out mice inoculated with IL-33 had no changes after stimulation with this cytokine [26].

Therefore, it seems that both allergic stimulation and intrinsic Th2 pathways are involved in this inflammatory disorder.

Treatment of EoE

The treatment goals in EoE aim not only at clinical and endoscopic improvement, but also histologic remission. Histologic remission is defined as lowering eosinophil counts to less than 15 eosinophils per high-power field. The secondary endpoint of treatment is diminution of cumulative risk of stenosis.

a) Dietary approach

First cases of EoE were successfully treated with elemental diet [1], and it remains the most effective dietary treatment but its wide use is limited by acceptability and cost. The potential role of alimentary stimulation led to several studies based on the elimination diet and the response of the

oesophageal tissue. Several studies were conducted in children and adults with evidence of elevated remission rates after elemental diet [14••]. Prospective conducted paediatric studies also showed highest histological remission rate with elemental diet (96%) when compared to other dietary interventions [27].

Empirical elimination diet using the most common dietary triggers has also been used with good results. The six-food elimination diet (SFED) led to promising studies regarding induction of remission using nutritional manipulation—74% remission rates. However, in the paediatric scenario, this restrictive diet is difficult to maintain and requires close dietary monitoring to avoid nutritional imbalance. Food avoidance guided by allergen testing (PRICK, PATCH) has variable results. Some discrepancies between tests and results have been reported [28] although this approach may be successful in up to 78% of cases [14••, 29–31]. Other empirical less-restrictive approaches have been proposed [32, 33].

b) Protein pump inhibitors

Therapy with protein-pump inhibitors (PPIs) has been one of the successful therapeutic options. Initially, PPI-related benefit was thought to be associated with the reduction of acid reflux that might cause inflammation. Accepting that many patients with oesophageal eosinophilia might not have reflux, the term PPI-responsive oesophageal eosinophilia (PPI-REE) was then coined and considered to be a separate group different from gastro-oesophageal reflux disease (GERD) or EoE. However, recent studies have shown that PPI-REE patients have identical genetic, histological and clinical profiles to typical EoE so that PPI-REE is now being regarded rather as a sub-group of true EoE that responds to PPI, than a separate entity [3, 34, 35••].

Many EoE patients may benefit from PPIs through mechanisms that are not related to acid suppression. PPIs can inhibit Th2 cytokine-induced eotaxin-3 secretion in oesophageal epithelial cells, reducing eosinophil recruitment as shown by in vitro studies [36•, 37]. In children with EoE under PPI therapy, oesophageal specimens from patients who had improved with therapy showed a decrease in eotaxin-3 expression in the proximal oesophagus, suggesting an anti-inflammatory effect rather than mere acid suppression [38]. Other anti-inflammatory effects of PPIs include inhibition of immune cell functions, antioxidant properties, decreasing expression of cell adhesion molecules and decreasing inflammatory cytokines [39]. The transcriptome expression analysis in mucosa of EoE patients (an array of genes associated with eosinophilia, mastocytosis, tissue remodelling and impaired barrier function) was reversed in PPI-REE patients. PPIs have also been shown to have an anti-inflammatory role by regulating CCL26 transcription activity which modulates eosinophil chemotaxis [40].

PPIs are now being regarded as the first-line therapy due to significant efficacy, lower cost and easier compliance as compared to topical steroids or multiple elimination diets. Patients that have clinical and histological response are being considered PPI-responsive EoE patients meaning a sub-group of EoE rather than a separate entity [3••]. It is becoming accepted as the indicated induction therapy and some studies show efficacy of almost 50% of paediatric

patients. One prospective study revealed benefit in more than 75% of patients on long-course maintenance option [41].

c) Other anti-inflammatory agents and immune modulators

Omalizumab, an anti-IgE monoclonal antibody, has been used in children with atopic disease and eosinophilic oesophagitis but failed to induce remission despite improvement in atopic manifestations [42]. An open-label study using omalizumab showed reported benefit in 33% of patients, but only in those that had low peripheral eosinophil counts [43].

Montelukast, a selective leukotriene D4 receptor antagonist, has been widely used for maintaining remission in asthma and has also been considered as a therapeutic agent for EoE. In a small study including 8 paediatric EoE patients, there was an improvement in symptoms but not in the histological inflammation of the oesophageal mucosa [44]. A prospective study showed no effect on corticosteroid sparing or remission maintenance in adult patients [45]. A randomized controlled trial (RCT) is ongoing regarding efficacy and safety of montelukast in EoE [46].

In two trials using anti-IL-5 antibody (reslizumab and mepolizumab), Spergel et al. reported significant reduction of intraepithelial oesophageal eosinophil counts in children and adolescents with EoE treated with reslizumab. However, improvements in symptoms were observed in all treatment groups and were not associated with mucosal changes. In the mepolizumab group, oesophageal inflammation was reduced and symptom scores were better at the end of the study [47–49].

Anti-IL 13 and anti-IL 4 α receptor (dupilumab) monoclonal antibodies have been studied in adults and there are ongoing RCTs assessing the efficacy and safety of these agents. There are currently no reports on the use of these drugs in children [46].

Anti-interleukin studies are still not available in most countries and these agents are very costly. Demonstration of clinical improvement and clarifying the indications to treat EoE with these agents require more studies and duplication of previously reported positive findings.

A recent meta-analysis of clinical trials regarding therapeutic strategies in paediatric EoE was attempted [50]. However, it was concluded that there is considerable heterogeneity of terms and endpoints in most published studies which limits the possibility of making strong recommendations based on those publications.

d) Corticosteroids

Despite its efficacy, treatment with PPIs may fail to induce remission in a considerable number of paediatric EoE patients [2••]. Therefore, alternative therapeutic options must be considered. Elimination diets as mentioned above also provide remission in a substantial group if the triggering food can be identified and compliance obtained.

An alternative medical treatment is the use of corticosteroids that modulate the immune response and decrease inflammatory mucosal cytokines [51]. They are widely used in the spectrum of inflammatory diseases and usually lead to an effective response with quick onset of action.

Corticosteroids decrease eosinophil counts in the oesophageal mucosa. Several studies show that T cell expression, mast cells and cytokine expression (IL-5, eotaxin-1/CCL11, eotaxin-3/CCL26) are also reversed after corticosteroid treatment [46, 52–55].

Gene expressions of mucosal IL-5 and IL-13 are decreased after treatment and so are remodelling molecules [55]. In adults, continuous treatment with steroids was associated with fewer impaction episodes in a 5-year period [51].

Systemic corticosteroids were initially used to treat paediatric EoE [56]. However, because of toxicity and systemic side-effects, their use is now reserved to severe or refractory cases. Currently, systemic steroids are not recommended for adult or paediatric patients [3••, 57].

Topical steroids (budesonide and fluticasone) have shown to be effective and lack most of the side-effects of systemic steroids, although not completely free from the risk of causing some degree of adrenal insufficiency [58].

A retrospective study in children assessed the effect of diet and steroids on oesophageal remodelling. Biopsies were taken before and after treatment. Elemental diet, six-food-elimination diet and topical corticosteroids all decreased remodelling scores significantly in 81.2, 72.8, and 68.2% of patients, respectively [59].

Lucendo et al. [60] studied 10 adult patients treated with fluticasone (400 µg twice daily) for 1 year. They found only insignificant reductions in sub-epithelial fibrosis and in the levels of genes of pro-fibrosing IL-5, TGF-β1 and FGF9 in cell cultures from oesophageal samples. Another study used oesophageal culture cells treated with steroids. Collagen and fibroblast transformation was prevented by the treatment, suggesting the possible reversion of fibrosis after treatment with steroids [61]. The inhibition of eotaxin-3 and the JAK-STAT6 pathway inhibitor expression by sub-epithelial fibroblasts pre-treated with steroids were not reproduced with omeprazole therapy suggesting a beneficial effect of PPI on the mucosa but not on collagen formation as opposed to steroids which affect both pathways [61].

Paediatric studies showed that topical steroids are easy to use and their efficacy is high when delivered in a viscous solution that can reach the oesophageal mucosa [62, 63]. Steroids should be given no less than 30 min before the next meal, drinks or mouth rinse to avoid fast clearance of the drug from the oesophageal mucosa.

Home-made solutions containing sucralose, filtered honey, apple purée, elemental formula powder or food thickeners are currently used with good results. Budesonide oral viscous solution (OVB) has been tested with promising results [63–68]. Recommended OVB dosage for induction of remission ranges between 1 and 2 mg/day (adjusted to age) for 8 weeks but lowest dosage for maintenance of remission is not defined.

Topical fluticasone has been studied in the paediatric population with clinical and histological efficacy after 2 years of treatment [69–71]. Its efficacy has been demonstrated in a paediatric prospective trial showing higher remission rate with fluticasone than food elimination diet (mainly cow's milk proteins) [72]. Fluticasone can be used as a home-made viscous solution using liquid vials or an aerosolized metered device. When using the inhalation device, the drug can be directly swallowed prior to inspiration to avoid deposition of the drug into the airways.

Paediatric dosages range between 88 and 440 µg of fluticasone and 0.5–1 mg of budesonide in two or four daily doses, depending on the child's height [2••, 3••]. A commercial viscous budesonide solution ready-to-use is expected to become available on the market soon and may minimize the bias and errors of home-made solutions.

Systematic meta-analysis did not show significant advantage of one steroid over the other [50]. Dellon et al. showed that the oral viscous form of budesonide may have longer mucosal contact as evidenced by scintigraphy and greater efficacy in inducing histological remission when compared with the nebulized form of the same drug. This may be the reason for a slight beneficial effect attributed to budesonide [73, 74]. There are no paediatric RCTs to provide formal demonstration of the benefit of this drug.

Remission occurs within 8 weeks of therapy and recurrence may occur after treatment cessation. Despite the absence of studies demonstrating better long-term outcomes with continuous versus intermittent use of topical steroids, continuous treatment may prevent future remodelling and the tendency to stenosis which is inherent to EoE.

Clinical series evaluating symptom remission and overall quality of life as outcomes after treatment with topical steroids are scarce. As a result, histologic remission is the main endpoint utilized in clinical studies. However, it is questionable if oesophageal eosinophilia should be the sole primary endpoint. The progressive nature of the disease and the risk of severe oesophageal dysfunction and stenosis may limit quality of life [6], and long-term treatment must be seriously considered [75].

When used as a chronic treatment, systemic absorption of topical steroids seems to be very low and has a high tolerability. Oesophageal candidiasis has been described in up to 20% of patients, usually asymptomatic and with high-resolution rates after fluconazole treatment [3••]. Published studies are controversial about cortisol levels in children on chronic treatment with topical corticosteroids but there are no studies regarding the impairment of growth in children under long-term topical CCT therapy. Prospective studies have been conducted in a paediatric setting related to long-term steroid therapy in children with EoE, but mixed evidence on the risk of adrenal suppression has been provided [58, 76]. However, adrenal suppression was found when high doses of topical steroids were used [58, 76]. Close monitoring may be appropriate with the chronic use of topical steroids.

Recently, a new inhaled steroid—ciclesonide—has been studied in a small set of four patients. Ciclesonide is a pro-drug that is converted to the active metabolite desisobutyryl-ciclesonide in the lung and oesophageal mucosa and has less side-effect than usually observed with the use of other inhaled corticosteroids. The report showed a group of corticosteroid-resistant EoE patients that improved after topical ciclesonide treatment [77, 78].

In rare instances of oesophageal stenosis in paediatric patients, the inflammatory nature of the narrowing should be assumed and medical treatment must be prescribed even if endoscopic dilation is to be considered [57]. If stenosis persists, then endoscopic dilation may be performed with good results [79].

Summary statement

Eosinophilic oesophagitis is a chronic inflammatory disease that requires both induction and maintenance treatment. Although elimination diets may be effective, identification of the specific food is not easy and proper compliance may be irregular, especially in paediatric

patients. Medical alternatives include PPIs that may provide improvement in a substantial group of patients both by its acid-suppression action and direct anti-inflammatory properties. Topical steroids are also effective, although they currently require some adaptation for oesophageal deposition from the available preparations. New formulations may render these drugs more attractive for first-line treatment. Long-term use of topical steroids requires monitoring of growth and signs of adrenal suppression, although available data shows a safe profile.

Compliance with ethical standards

Conflict of interest

Marta Tavares declares that she has no conflicts of interest. Jorge Amil Dias reports personal fees from Abbvie, Ferring, Ferrer, Danone and Nestlé, outside the submitted work.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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