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## **Eosinophilic esophagitis: pathophysiology, diagnosis, and management**

Short title: Eosinophilic esophagitis: pathophysiology, diagnosis, and management

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### **Abstract**

Eosinophilic esophagitis (EoE) is a multifactorial esophageal inflammation, with a genetic predisposition, which combines a deficient esophageal mucosal barrier, an abnormal immune reaction to environmental allergens mediated by Th2 interleukins, immediate esophageal lesions and dysmotility, with secondary remodeling and fibrosis. Symptoms include reflux, abdominal pain, and food impaction, with a variation according to age. Fibroscopy shows major and minor endoscopic and histologic criteria, with a mucosal count  $\geq 15$

eosinophils/high power field (Eo/hpf). A new entity has been defined, where gastroesophageal reflux disease (GERD) and EoE share responsibility: the PPIs-sensitive form of EoE (PPI-REE). Children with fibroscopy showing  $\geq 15$  Eo/hpf need a second endoscopy following 8 weeks of PPI treatment. EoE has a strong association with other atopic disorders. Allergy testing (specific IgE blood test and skin prick tests [SPTs]) identifies patients at risk of anaphylaxis (14.8% of cases). The dietary therapy is based on a 4- to 12-week elimination test followed by endoscopy to check the disappearance of eosinophilic infiltration. The “dietary approaches are the amino-acid-based formula, the allergy testing-based targeted diet, and the six-food elimination diet (empirical elimination of milk, wheat, soy, eggs, peanut/nuts, and fish/seafood). A recent first-line trial elimination of milk has been suggested, with wheat as a second elimination, if necessary. Dietary therapy allows remission and catch-up growth in 65% of cases. Swallowed topical steroids (budesonide in viscous gel or fluticasone propionate for nebulization) are an alternative, for which efficacy varies according to clinical and/or histological criteria and with relapses occurring at dosage tapering. Their use may be restricted by side effects, such as oral and/or esophageal candidiasis. The impact on long-term bone health and growth is unknown. Maintenance therapy is not standardized and is team-dependent, combining or not elimination diets and long-term steroids. The long-term risk of EoE is esophageal stenosis (25%) and endoscopic dilation may be repeated. Biotherapies have shown isolated histological improvement without significant clinical efficacy.

**Key words:** eosinophilic esophagitis, pathophysiology, diagnosis, management

## 1. Introduction

Eosinophilic esophagitis (EoE) was first described in 1978 and its pathology and phenotype defined by Atwood et al. in 1993 [1] and Straumann et al. in 1994 [2]. Its prevalence, currently 1–5 out of 10,000, was shown to increase from 0.7 to 1.3 out of 10,000 between 2000 and 2003 in an English study [3]. Younger children, 0–4 years old, show a reverse trend [3], probably due to better recognition and screening. Males (Caucasian) are three times more affected than females.

## **2. Pathophysiology**

Briefly, EoE occurs in individuals with a genetic predisposition, in whom gastroesophageal reflux disease (GERD), food allergy, and alterations of the epithelial barrier and possibly of the microbiota combine to allow food allergens to penetrate the epithelium and activate receptors and inflammatory cells, including eosinophils. The latter secrete toxic granules and cytokines, inducing chronic inflammation, tissue damage, and fibrosis.

### **2.1. The alteration of the esophageal wall**

During EoE, abnormal immune processes lead to esophageal inflammation with immediate esophageal lesions, and secondarily remodeling and fibrosis [4].

#### **2.1.1. *Immune processes***

The presence of intraepithelial eosinophils, usually absent from the esophageal lamina propria and submucosa, defines EoE [5]. Eosinophils are recruited from the blood pool with local chemotaxis. They initiate and maintain the inflammatory response, acting as antigen-presenting cells (APCs), recruiting T cells, orienting Th2 differentiation, recruiting and activating mast cells and basophils [5]. They secrete the eosinophilic peroxidase (EPO), the

eosinophilic cationic protein, and the major binding protein (MBP), a M2 muscarinic receptor antagonist, causing direct cell damage and esophageal dysmotility, which increases the contractility of smooth muscle cells. The symptomatology of EoE is more correlated with the local amount of EPO than with the number of eosinophils [5]. Mastocytes exhibit an increased number and degranulation in the esophageal epithelium, suggesting the involvement of immediate hypersensitivity (immunoglobulin E (IgE)-mediated) [5]. They take part in eosinophilic activation and esophageal dysmotility and remodeling, with the onset of fibrosis [5]. Their protease secretion pattern and the increased expression of carboxypeptidase A3 and tryptase might be specific to EoE [5]. Langerhans cells, the APCs of the keratinocyte layer, interact with antigens at the beginning of the pathological cascade. They express FcεRI, correlated with the Th2 response level in atopic pathologies [5]. Basophils express the receptor of thymic stromal lymphoprotein (TSLP), a basophil proliferation factor with a complex role, inducing a Th2 immune response, increasing basophils and APC recruitment and promoting atopic dermatitis and asthma [4].

The immune response is mainly mediated by Th2 interleukins (IL), IL-4, IL-5, and IL-13. IL4, secreted by Th2 cells, natural killers (NK), and TSLP-dependent basophils promote the differentiation of naive T cells into Th2 and B cells ending with IgE secretion [5]. IL-13 esophageal overexpression by Th2 cells [5] increases chemokine ligand 26 (CCL26), eotaxin 3 and periostin expression, eosinophilic recruitment from the circulating pool, and calpain 14 (CAPN14) expression responsible for STAT6 and IL-33 production. It also increases T cell survival [6] and decreases the local expression of desmoglein-1 (DSG1), filaggrin, and epidermal differentiation complex (EDC), altering the epithelial barrier [4,5]. IL-5, an eosinophil and mast cell differentiation and survival factor secreted by eosinophils, activates LT and mast cells in chronic allergic reactions [5].

### 2.1.2. *Esophageal lesions*

In esophageal biopsies, decreased desmoglein-1 expression and intercellular space widening [7] renders the esophageal barrier more permeable to antigens [8]. MBP and tissue growth factor (TGF $\beta$ ), proteins and mediators secreted by eosinophils [6], increase the secretion of tryptase and chymase, proteolytic enzymes, contributing to extracellular matrix damage. Stimulation of fibroblasts by MBP, TGF $\beta$ , and fibrosis is correlated with complete and irreversible esophageal remodeling. Smooth muscle cells (SMCs) present morphological changes, together with increased contractility and decreased contraction force, in relation with TGF $\beta$  and other eosinophil and mast cell mediators, causing dysmotility [8]. The deep esophageal remodeling with irreversible fibrosis is the main complication in EoE, key in the onset of dysphagia and brings to mind tissue remodeling in atopic dermatitis with lichenification and skin thickening as well as bronchial remodeling, dysmotility, and SMC constriction in chronic asthma [9].

## 2.2. The origin of esophageal wall alterations

During EoE, the inflammatory cascade is similar to that of chronic allergic diseases, with an aberrant Th2 response, the involvement of eosinophils, basophils, mast cells, IL-5, and IL-13, a major role for allergic sensitization, and potential cross-reactivity with highly conserved proteins such as profilin or PR10 [4,5]. EoE is classified as an allergic and disimmune disease (**Figure 1**).

### 2.2.1. *The role of allergy*

EoE is triggered by food, mainly milk (35%), often associated with egg (13%), wheat (12%), and soy (9%) [9]. Interestingly, EoE may be associated (14.8% of cases) with severe IgE-mediated reactions (urticaria, anaphylaxis) to some foods, mostly peanut, milk, and eggs [9]. Oral immunotherapy (OIT) to treat an IgE-mediated food allergy can induce iatrogenic

EoE in 2.7% of cases (with peanut, milk, and egg), with discontinuation allowing remission [10]. Atopic diseases are more prevalent in EoE than in the general population [11], manifested by asthma (37%), allergic rhinitis with seasonal changes (39%), and atopic dermatitis (13%) [12]. A history of atopy is present in two-thirds of patients [12]. The allergic mechanisms remain poorly understood: EoE is associated with a high total IgE level and with sensitization to food allergens (75%) and respiratory allergens (73%), but IgE-mediated mechanisms cannot account for all the changes observed [13]. During OIT, EoE obviously results from the contact between an allergen and an IgE-sensitized esophageal mucosa, whereas, in contrast, the “targeted” elimination diet of EoE, based on allergy testing, provides only partial clinical improvement [13]. Briefly, while IgE sensitization is common, EoE is not merely an IgE-mediated food allergy and may well implicate complex mechanisms involving the innate and adaptive immune system [13].

### *2.2.2. The complex relationship with gastroesophageal reflux disease*

GERD is the first differential diagnosis of EoE, which very often delays diagnosis. Pyrosis is present in about 30% of EoE patients, even though the prevalence of EoE is very low during isolated refractory pyrosis (1–4%) [14]. Also, during GERD, gastric acidity is thought to induce an alteration of the secondary epithelial barrier, which might trigger an eosinophilic infiltration of the esophageal mucosa, usually < 10 eosinophils/high power field (Eo/hpf) [15] and/or the passage of allergenic food molecules across the esophageal barrier, contributing to the development of a local allergic reaction [15]. Proton pump inhibitors (PPIs) reverse this epithelial dysfunction. GERD might also lead to EoE through an inflammatory mechanism mediated by cytokines, as suggested experimentally [16].

Esophageal biopsies are now considered mandatory in the presence of reflux symptoms refractory to PPIs [17].

### *2.2.3. The constitutional abnormalities of the esophageal wall*

EoE is more frequent during connective tissue disorders (Marfan's and Ehlers-Danlos syndromes), potentially the consequence of excessive stimulation of the TGF $\beta$  signaling pathway. EoE and autoimmune bullous dermatosis both exhibit a decreased expression of DSG1 in the epidermis and the esophageal epithelium [8]. EoE is frequent during Netherton syndrome (NS), a chronic skin inflammation with severe allergic manifestations, and is related to LEKTI protein loss of expression in stratified epithelia. In esophageal biopsies, LEKTI immunostaining appears normal or decreased in EoE, and negative in patients with EoE and NS. Thus, in esophageal stratified epithelium, LEKTI loss of expression could result in alterations similar to those observed in NS patients' skin [18].

### 2.3. The genetic background

The risk of developing disease in the EoE patients' family is 41% in homozygous twins, 22% in dizygotic twins, and 2.4% in siblings versus 0.055% in the general population [19].

Genetic factors may alter the esophageal epithelial barrier, the recruitment of eosinophils by eotaxin-3, and tissue remodeling linked to the development of fibrosis. EoE follows a hereditary model: parents of EoE children have a history of esophageal dysfunction (10%) and can contract EoE (7%) [20]. The EoE "transcriptome" comprises 574 genes expressed differently in tissues of affected and healthy children [20]. Their various roles illustrate the complexity of EoE pathophysiology: Ig and class switching, mast cells



(carboxypeptidase 3A), IgE receptor (FC $\epsilon$ RI), and tryptase- $\alpha$  (TPSAB1). The transcriptome can be elicited by the treatment of esophageal epithelial cells with IL-13 [21]. As filaggrin is part of EDC, a functional loss associated with single nucleotide polymorphisms (SNPs) results in epithelial barrier damage and increased antigen exposure. The eotaxin-3 gene, which allows eosinophil recruitment within esophageal mucosa, has the strongest transcriptome expression, 53 times more than in controls [19]. In mice, the absence of eotaxin-3 receptor protects from EoE [20]. A TSLP (whose receptor is located on both X and Y chromosomes) SNP augments the Th2 response. An SNP is associated with an increased risk of EoE in males [20]. No gene has been found yet to explain the role of GERD in EoE. A TGF $\beta$ 1 gene promoter SNP is associated with the appearance of binding sites for transcription factors, responsible for esophageal dysmotility and predisposition to asthma.

The role of epigenetics is supported by a twin cohort analysis [22] showing the importance of environmental factors (81.0%) compared to heritability (14.5%) in phenotypic variability. Some early environmental exposures, including antibiotic therapy in the 1<sup>st</sup> year of life, increase the risk of EoE [23].

### **3. Clinical diagnosis**

EoE is manifested by digestive symptoms and associated with allergic cutaneous or respiratory (asthma, rhinoconjunctivitis) manifestations [24,25]. In infants, feeding difficulties, irritability, vomiting, and regurgitations can lead to failure to thrive and alteration of general status [24]. Children complain of nausea, vomiting, epigastric abdominal pain, and dysphagia [25]. Adolescents and adults have varying severity of dysphagia in the foreground, without any impact on the general status. Chest pain or GERD symptoms may be associated [24], and food impaction is frequent (in contrast with children) owing to the progressive evolution towards esophageal stenosis [24].

The symptoms that characterize EoE are nonspecific, so that its frequency is underestimated. EoE often develops more than 4 years before being diagnosed [25]. As children grow up, they accommodate to dysphagia by eating more slowly, chewing more, avoiding solid foods and using liquids to swallow [26]. Food impaction is the first emergency consultation for adolescents. Differential diagnoses should not, however, be overlooked: reflux is a dominant manifestation in EoE, so that GERD and esophageal achalasia are essential differential diagnoses, as well as cow's milk protein allergy associated with reflux but no eosinophilic disorder. Other differential diagnoses include celiac disease, inflammatory bowel diseases, and eating disorders.

#### **4. Esophagogastroduodenoscopy (endoscopy)**

Endoscopy is key for EoE diagnosis.

##### **4.1. Endoscopic and histological criteria**

Endoscopy shows characteristic but nonpathognomonic morphological abnormalities, classified into major and minor criteria [27] (**Figure 2**): 1) mucosa edema (disappearance of the esophageal vascular frame); 2) exudate (60%), minimal (grade 1) or severe, blocking the endoscope progression (grade 2); 3) longitudinal furrows (70–80%); 4) circular esophageal rings or "pseudo-tracheal" aspect (70%); and 5) esophageal stenosis (30%), responsible for food impaction and dysphagia [28]. Esophageal friability may lead to secondary dissecting EoE (10%). A macroscopically normal esophageal mucosa is seen in 10–25% of cases.

Esophageal biopsies (two to four) in the proximal, medium, and distal esophagus, are mandatory for diagnosis [29] and must be carried out during any upper endoscopy, even with a normal macroscopical appearance. Five biopsies bear 100% sensitivity compared to 55%

with a single biopsy [30]. Histological signs are also classified into major and minor criteria (**Figure 2**). The major but nonpathognomonic criterion is defined with a mucosal count of  $\geq 15$  Eo/hpf ( $\times 40$  magnification) in the microscope [29]. Minor criteria include basal zone hyperplasia with papilla hyperplasia, eosinophilic micro-abscesses, eosinophil degranulation and surface desquamation, and lamina propria fibrosis [12].

#### 4.2. The role of PPIs in the diagnosis of EoE and PPI-sensitive EoE

The presence in biopsies of  $\geq 15$  Eo/hpf strongly suggests EoE, but eosinophilic infiltration is now considered to potentially result from GERD alone. Thus, children with symptoms suggesting EoE and  $\geq 15$  Eo/hpf at first endoscopy need to go to a second endoscopy following 8 weeks of PPI treatment. The second endoscopy confirms EoE if there are still  $\geq 15$  Eo/hpf, even if symptoms have decreased or disappeared [31]. This scheme is now becoming more complicated. Based on 2007 recommendations, EoE was diagnosed on the association of typical clinical symptoms,  $\geq 15$  Eo/hpf at endoscopy and the absence of GERD (normal pH-metric tracing or lack of response to PPIs 2 mg/kg/day) [31]. Patients responding to PPIs were considered as having GERD, assuming that only GERD could respond to an antacid. However, the systematic PPI trial period in children with  $> 15$  Eo/hpf led to the detection of a new entity, the PPI-sensitive form of EoE (IPP-REE) [32]. In 2011, EoE was therefore redefined as an association of typical esophageal symptoms, histology with  $\geq 15$  Eo/hpf, only esophageal localization but also exclusion of other eosinophilia esophageal causes (including PPI-REE) and remission after elimination diet, topical corticosteroids, or both [33]. More recently, it appeared that allergy forms of EoE do respond to PPI, suggesting that GERD and allergy/inflammation both share responsibility in EoE, leading to a recommendation of systematic use of PPIs in the long-term treatment of EoE [34].

The higher incidence of EoE in esophageal atresia (EA) patients has been ascribed to a possible genetic association, impairment of esophageal mucosal barrier function by acid refluxate, and prolonged exposure to acid suppressive medication [35]. Since GERD is considered as one of the most frequent gastrointestinal tract complications in EA patients, PPIs are recommended as the first-line therapy to prevent recurrent stenosis [36]. Recommendations for diagnosis and treatment of EoE in the general population should be followed in EA patients, with closer monitoring of clinical and histological symptoms refractory to PPIs to avoid delayed diagnosis (**Figure 3**).

#### 4.3. Repeated endoscopic procedures

Endoscopy confirms the diagnosis of EoE and remission following treatment [15], allowing, depending on the treatment option chosen, iterative reintroduction of foods or decreased topical steroids. However, no strategy has been established yet for endoscopy during long-term follow-up. American guidelines recommend systematic and repeated endoscopic procedures following any food reintroduction or steroid decrease ( $\geq 4$ –6 weeks after each therapeutic change), but do not encompass the long-term follow-up [28]. European recommendations suggest endoscopy in case of reappearance of symptoms, especially during food reintroduction, but not in asymptomatic patients [29].

#### 4.4. Allergy testing

EoE is an atopic disease with a strong association with other atopic disorders, but allergy assessments remain debated since EoE is based on IgE and non-IgE-mediated mechanisms. A specific IgE blood test and skin prick tests (SPTs) explore IgE-mediated reactions. Their predictive values fluctuate with age and clinical history [37], and their sensitivity and specificity are low, especially for milk [9]. Allergy testing still remains important, identifying patients at risk of anaphylaxis (14.8% of cases). Identifying respiratory

allergens responsible for allergic rhinitis enables better control of an atopic background [37]. Atopy patch tests (APTs) explore non-IgE-mediated allergy. They are not recommended alone in EoE because of lack of sensitivity, specificity, and predictive value [37].

## **5. Diagnostic procedures currently being tested**

During EoE, the constant need for endoscopy has prompted the search for less invasive methods for EoE diagnosis and monitoring. During the "esophageal string test," esophageal secretions adhere overnight to a thread ingested and assess eosinophil degranulation markers [38]. The "Cytosponge" is a digestible gelatin capsule comprising compressed mesh attached to a string, which is infiltrated by contact with esophageal eosinophils when removed from the stomach [39]. These are not currently validated, although the first results are encouraging.

MicroRNA expression is deregulated in tissue during EoE, and the expression profile differentiates EoE patients and controls [40]. This deregulation is largely reversible in patients in remission under topical steroid treatment, suggesting the future use of plasma microRNAs as biomarkers.

## **6. Dietary management of EoE**

### **6.1. Food elimination principles**

Dietary therapy is based on a 4- to 12-week elimination test followed by endoscopy to check for the disappearance of eosinophilic infiltration and by food reintroduction every 4–6 weeks, using first the least potentially allergic food [28,29]. Clinically, dietary therapy allows catch-up of failure to thrive and induces a histological remission in about 66.3% of cases [28]. Dietary support is essential to ensure maximum adherence, avoid cross-contamination and

nutritional deficiencies, taking into account the social impact of a long-term elimination diet in adolescents [28].

## 6.2. The three dietary therapy approaches

In 1995, Kelly et al. first suggested an elemental diet, an *amino acid (AA) formula*, supplied (Neocate®) for 6 weeks in ten refractory GERD children, with a significant reduction in eosinophilic infiltration and a clinical remission for at least 6 months [41]. This elemental diet is the most effective and induces a clinical benefit in 7–10 days and a histological remission of 95–98% in 4–5 weeks [28,29]. It is usually better tolerated in malnourished patients without any ionic disturbance or weight loss [42]. Its poor palatability, a source of poor compliance, often requires nasogastric tube feeding and may enhance orality disorders in infants [42]. The reintroduction of foods is slow and selective, implying a long follow-up with repeated endoscopies, with a social and economic impact [28].

*The targeted diet*, based on SPTs and APTs, depends on clinical history [43], addresses five to seven foods [9] even though an elementary diet is often suggested when more than three foods are involved. Clinical and histological efficacy after 6 weeks varies from 77% [44] to 45.5% [43], underlining low positivity and reproducibility and a lack of validation [45]. Remission is higher when associated with a systematic milk elimination (75%) [9]. Multiple allergies make it long to set up and low compliance is common. The younger children are, the more food sensitization exist and therefore achievement difficulties [9]. This targeted elimination diet is not recommended despite personalized elimination and better quality of life.

*The Six-Food Elimination Diet (SFED)* is the empirical elimination of milk, wheat, soy, eggs, peanut/nuts and fish/seafood, most commonly responsible for EoE [46]. Because of 82% efficacy, lower cost and short duration, SFED seems more adequate than the elementary diet [28,45]. Owing to poor adherence and the risk of nutritional deficiencies, authors tend to promote more simple elimination diets such as the Four-Food Elimination Diet (FFED) excluding milk, wheat, eggs, and soy in children (60%) [43,47].

*The milk elimination diet*, based on the major role of milk, has been suggested more recently, at least as a first step, with a histological remission reaching 65%, higher in younger patients and those with lower eosinophilia before milk elimination [48]. SPTs and APTs have a low sensitivity for milk in contrast with its strong involvement in EoE [29]. Wheat is ranked second after milk, with efficacy during gluten elimination [43].

### 6.3. Varying practices around the world

Elimination diets for 8–12 weeks are currently considered efficient in inducing clinical and histological remission [29,45]. The first-line therapy tends to be the SFED in North America. In Europe, the 4-week AA diet is recommended when EoE occurs with poly-allergy and/or impossibility or inefficiency of several eliminations [28,29,42,43], and the targeted diet is adapted to strong clinical suspicion and sensitization proven with allergy testing [29].

## **7. Steroid drug therapy**

Topical steroids are budesonide in viscous gel or fluticasone propionate in nebulizer, which are swallowed instead of being inhaled. Swallowed steroid therapy requires water mouthwash after each intake, without consumption of any solid or liquid food in the following

30 min [28,29]. Swallowed steroids can be used alone or mixed with an excipient (**Table 1**) [28,29]. The efficacy of each treatment varies according to the clinical and histological criteria used: improvement of dysphagia and histological response in 52–86% of cases with the budesonide, and heterogeneous clinical improvement and histological response in 15–62% with fluticasone. The only meta-analysis comparing budesonide and fluticasone shows similar results, both clinical (71%) and histological (51%) [49]. Budesonide in viscous form seems more efficient (lower Eo/hpf count), probably because of increased contact time between the drug and the esophageal mucosa [50]. Ciclesonide was used after failure of fluticasone and diet [29]. The main side effect of oral steroids is oral (1%) and/or esophageal (5–30%) candidiasis without associated adrenal insufficiency [28,29]. Prolonged corticosteroid therapy (3–6 months) may induce adrenal insufficiency, 43% with budesonide [51], 10% with fluticasone [52]). There are no data about bone health and long-term growth.

Because of numerous side effects and relapse when tapering the doses, systemic steroids (1–2 mg/kg/day; maximum, 40 mg) are restricted to severe dysphagia, weight loss, esophageal stenosis, the need for a rapid action, and other treatment failures. The intravenous route may be used when oral intake is impossible [29]. Clinical improvement is observed in less than 1 week, and histological remission in 4 weeks [29].

In the absence of current consensus for the first-line treatment option in France, a nonexhaustive survey collected the therapeutic management of EoE in several hospital centers in Paris, Lille, and Grenoble. The results are reported in **Table 2**.

## **8. Endoscopic dilation**

Endoscopic dilation is needed in case of severe stenosis or persistent dysphagia [28,29], mainly using an inflatable balloon. Esophageal mucosa is fragile, easily dilacerated,



with frequent post-procedure pain (75%), despite a low risk of perforation (< 1%) [28]. Iterative dilatations may be needed.

## **9. Progression and long-term treatment**

### **9.1. Progression from childhood to adulthood**

The main risk of EoE is esophageal stenosis (25%), but the progression of EoE probably encompasses different phenotypes. On one hand, EoE might be a progressive disease, beginning with dietary difficulties during childhood, worsening until esophageal narrowing and food impaction in adolescents. On the other hand, EoE might manifest according to different phenotypes that have their own symptoms and begin at different ages [12]. A follow-up study (2.8 years [0.18–5.61]) reported by Assa'ad et al. evidenced recovery in 14% of cases, relapse in 52%, and persistence in 34% [53]. EoE seems to neither threaten life expectancy, nor present a risk of esophageal metaplasia (Barrett's esophagus or adenocarcinoma), and mucosal destruction is known [28]. However, no comprehensive long-term follow-up study from childhood to adulthood is available.

### **9.2. Treatment goal: remission versus refractory EoE**

The goal of the treatment is to obtain clinical and histological remission [28,29]. A scoring system might help, but no existing score has been validated. One clinical score evaluates the daily impact of multiple symptoms or their binary disappearance/persistence (heartburn/regurgitation, chest/abdominal pain, nausea/vomiting, anorexia/early satiety, dysphagia, food impaction, nocturnal awakening, gastrointestinal bleeding) [54]. Another score is based on dysphagia with the Mayo Dysphagia Questionnaire [54]. Histological remission criteria also vary ( $\leq 1$  Eo/hpf,  $\leq 5$ ,  $\leq 7$ ,  $\leq 15$ ) [28,54]. Esophageal eosinophils

persist in some patients who become asymptomatic, for whom long-term treatments are discussed according to the severity of the initial symptoms, the patient's age, morphological esophageal abnormalities or the patient's and parents' wishes [17]. Based on these uncertainties, one might underline that the main treatment goal is the prevention of stenosis [28,29], the other objectives being the prevention of food impaction and the maintenance of a satisfactory quality of life [28,29].

The persistence of EoE observed at control endoscopy after 2 months of swallowed steroids might be explained by their modalities of administration (inadequate dosage, technique, or lack of compliance), fibrosis or stenosis, a persistent stimulation by inhaled or food allergen, or genetics (the overexpression of microRNAs could reduce IL-13 inhibition on the corticosteroid receptor) [55]. Treatment options include increasing topical steroid doses, combining the steroid with the elimination diet, and performing endoscopic dilations on demand [28].

### 9.3. Long-term diet and/or steroids

There is no standardized maintenance therapy and no study comparing options, so each medical team works within its own habits. Liacouras et al. described steroid and elimination diet treatment in 381 pediatric patients [56]. Systemic steroids were efficient but clinical symptoms and eosinophils reappeared when therapy was discontinued. Swallowed steroids exhibited an incomplete clinical and histological response and early recurrence. Dietary therapy exhibited a high rate of remission with at least 9 months of follow-up, 95% for the elementary diet and 97% for the AA solution, suggesting a spontaneous improvement in a non-negligible percentage of patients, when compared with the 60% remission after 2

months of dietary therapy. A complete cure with disappearance of food allergy and return to normal feeding is actually possible.

In 562 patients, with 3.2 years of follow-up [1-14], the association of PPIs, diet, treatment of rhinitis or asthma, and swallowed steroids was rapidly replaced by dietary therapy after normalization of biopsies [12]. There was no remission with topical steroids. In 2% of patients, complete remission allowed normalization of the diet and removal of all drug treatment: this group had the lowest number of food allergies (2.4 foods versus 6.9 for the other patients). In 6% of patients, tolerance had developed for one or more allergenic foods. Complete remission and tolerance rates are lower (8%) than in IgE-mediated food allergies (from 20% for peanut to 80% for milk).

In a cohort of 97 patients followed up for 29.2 months, remission was observed in 67% of cases with dietary therapy and in 56% with topical steroids, increasing to 78–80% following two rescue treatment periods [57]. Rescue treatments encompass elemental, targeted, or empirical diet, swallowed steroids selected according to clinical history, physician practices, and patient preferences and may induce remission after a first or second treatment failure. Alleviating the elimination diet to a less stringent restriction can also improve adherence.

A study analyzed the result of more than 24 months of long-term swallowed steroids (fluticasone) and showed the decrease of eosinophils, histological abnormalities and fibrosis, endoscopic morphological abnormalities, and symptoms [58]. This treatment did not affect growth and was almost free of serious side effects (3/54 esophageal candidiasis).

#### 9.4. Long-term PPIs

Recent findings progressively incur a shift in therapy, through the systematic use of PPIs, which was not the standard of care in previous studies. Using a long-term treatment with PPIs for 6.7 years, without any swallowed steroids or dietary elimination, symptoms disappeared in 26 out of 38 patients and improved in 12 [59]. There was no progression to food impaction or fibrosis even though eosinophilic inflammation mostly persisted.

## **10. Biotherapy, a treatment for the future?**

Biotherapies (monoclonal antibodies) have shown no significant clinical efficacy in EoE treatment.

The anti-IL-5 antibody Reslizumab (four injections over 3 months) induced histological but not clinical improvement [60]. Mepolizumab (anti-IL-5 antibody) has never completely eradicated eosinophils in young children and adolescents [61]. Findings were similar in two adult studies on Mepolizumab [62,63]. QAX576 (anti-IL-13) carried out for 6 months in 23 adults with PPI-resistant EoE [64]. Dupilumab (anti-IL-4), which modulates IL-4/IL-13 signaling, is under investigation. Omalizumab (anti-IgE humanized monoclonal antibody) is efficient in eosinophilic gastritis and duodenitis, but not in severe EoE as assessed by clinical symptoms in children and adults [65]. After two anti-TNF $\alpha$  injections in 2 months, symptoms improved in two patients and worsened in the third one, without any change of Eo/hpf number [66]. Montelukast and chemoattractant receptor expressed on Th2 cell (CRTH2) receptor antagonists did not demonstrate significant clinical efficacy.

## 11. Conclusion

EoE is a multifactorial esophageal inflammation that includes IgE-mediated and nonmediated food allergies. Knowledge in EoE pathophysiology has increased for the last few years, emphasizing the role of GERD and the need for PPIs as the first-line treatment. There is currently no agreement on the treatment option to be adopted following the latter, to prevent stenosis (**Figure 3**). Elucidating the exact pathophysiological mechanisms will allow the development of new diagnostic and therapeutic approaches.

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**Figure 1:**

- *Title:* Pathophysiology of eosinophilic esophagitis (EoE)
- *Legend:* Food allergens penetrate the permeable esophageal barrier, interact with the antigen-presenting cells (APCs), driving an immune response mediated by Th2 interleukins (IL), IL-4, IL-5, and IL-13 secreted by Th2 cells, increasing eotaxin 3, recruiting and activating eosinophils, basophils, and mast cells, inducing fibrosis with fibroblast stimulation and dysmotility with smooth muscle cell (SMC) constriction.

**Figure 2:**

- *Title:* Endoscopic and histological features of eosinophilic esophagitis (EoE)
- *Legend:* A, mucosal edema; B, longitudinal furrows; C, fixed rings; D, stricture; E, normal esophagus; F, eosinophilia; G, basal zone hyperplasia; H, eosinophilic microabscesses. Endoscopic pictures: Dr. Jérôme Viala. Histologic images: Prof. Patrick Barbet, Prof. Dominique Berrebi.

**Figure 3:**

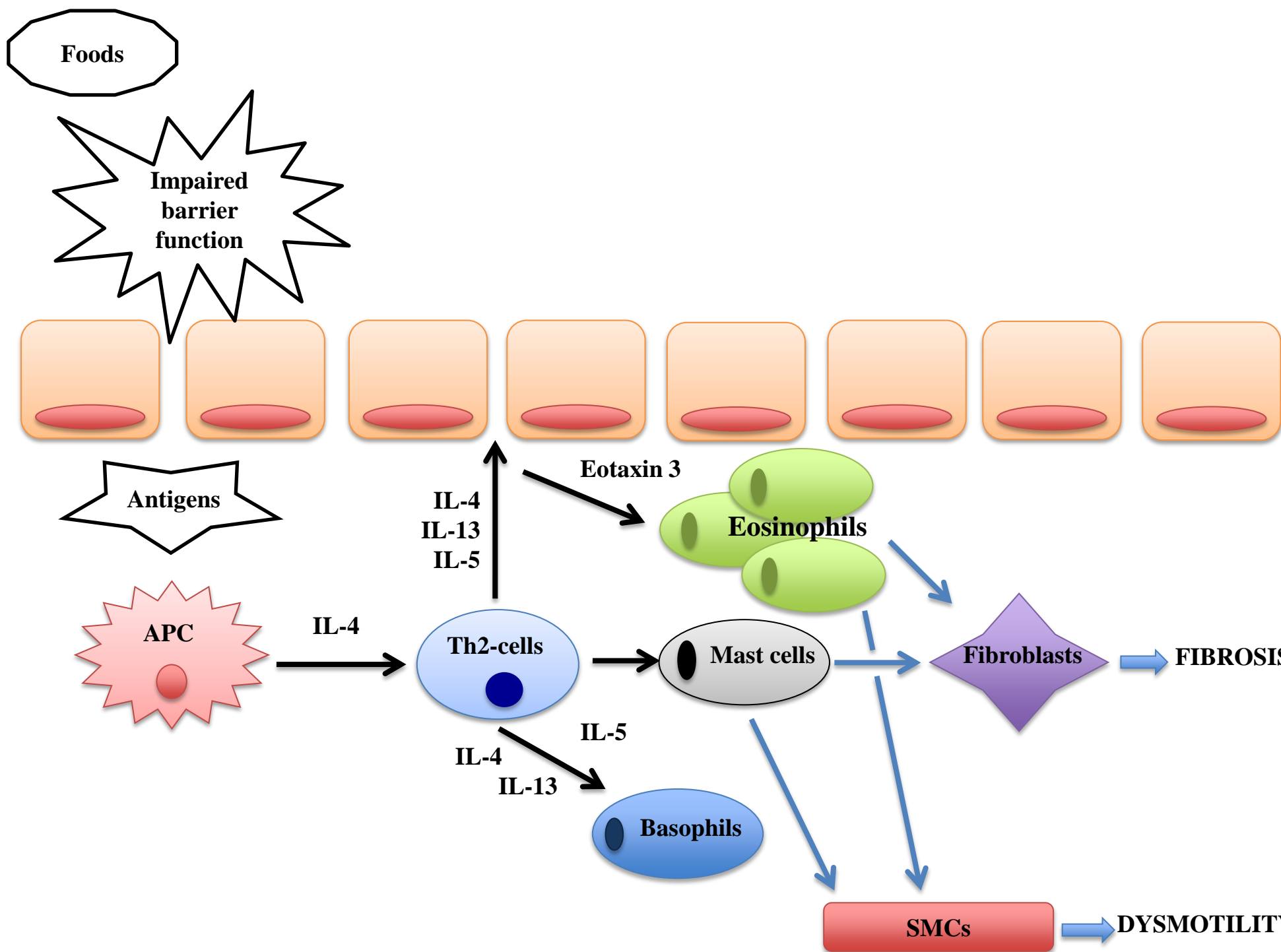
- *Title:* New therapeutic management of eosinophilic esophagitis (EoE)  
PPI: Proton pump inhibitor

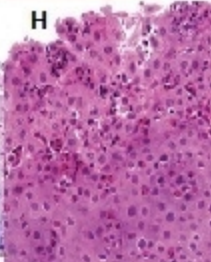
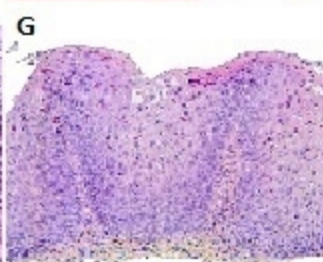
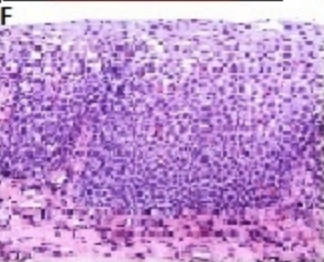
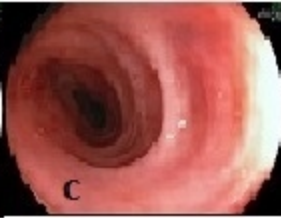
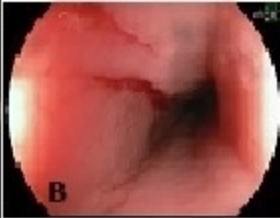
**Table 1:**

- Title: Swallowed steroids in eosinophilic esophagitis (EoE): doses, duration, and possible excipients.

**Table 2:**

- *Title:* eosinophilic esophagitis (EoE) nonexhaustive survey in France.
- *Legend:* PPIs, proton pump inhibitors; MED, milk elimination diet; SFED, six food elimination diet; FFED, four food elimination diet; TFED, two food elimination diet (milk/wheat); TED, targeted elimination diet; AAS, amino-acid solution.





***1st Fibroscopy + biopsies***

**PPI 8 weeks**

Stenosis prevention  
(25%)

**PPI-REE (30-50%)**

***2nd Fibroscopy under PPI + biopsies***  
 $\geq 15 \text{ Eo/hpf}$

**PPI +**  
**-Elimination diet**

- . Amino-acid solution
- . Targeted diet
- . Six food elimination
- . Empirical milk elimination

**-Swallowed steroids**

- . Fluticasone
- . Viscous Budesonide

**-Both associated**

**-Endoscopic dilation**

**2<sup>nd</sup> Intention  
8 weeks**

Anti-IL-5, anti-IL-13, anti-IgE, Montelukast

**Biotherapy?**

***3rd Fibroscopy + biopsies***

**Long-term  
treatment?**

- PPI
- Swallowed steroids at efficient minimum dosages
- Elimination diet
- Both associated
- On-demand dilation

**!! Recurrence ↔ Fibroscopy !!**

	Swallowed steroids	Possible excipients
<b><i>Fluticasone</i></b>	<ul style="list-style-type: none"> <li>- 1-4 years: 88 µg/day</li> <li>- 5-10 years: 220 µg/day</li> <li>- &gt; 11 years: 440-880 µg/day</li> <li>- Adults: 880-1760 µg/day</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Sucralose:</b> 1 mg/2 mL for 5 g of Splenda® sucralose</li> </ul>
<b><i>Budesonide</i></b>	<ul style="list-style-type: none"> <li>- &lt; 10 years: 1 mg/day</li> <li>- &gt; 10 years or adults: 2 mg/day</li> <li>- <u>If no response:</u> <ul style="list-style-type: none"> <li>. &lt; 10 years: 2.8 mg/day</li> <li>. &gt; 10 years: 4 mg/day</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- <b>Alginic acid</b> (Gaviscon®)</li> </ul>
<b><i>Administration</i></b>	<ul style="list-style-type: none"> <li>- 2 times a day</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Dimeticone gel</b> (Polysilane®)</li> </ul>
<b><i>Duration</i></b>	<ul style="list-style-type: none"> <li>- 8 weeks (<math>\geq</math> 4 weeks and maximum 12 weeks)</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Amino-acid solution</b> (Neocate Nutra® 2.5cm<sup>3</sup>/mg of budesonide)</li> </ul>

	GASTRO-ENTEROLOGY					ALLERGOLOGY			
	Paris (Trousseau)	Paris (Necker)	Paris (Debré)	Lille (CHRU)	Grenoble (CHU)	Paris (Necker)	Paris (Ambroise Paré)	Lille (Saint Vincent)	Grenoble (CHU)
<b><u>Age</u></b> - Infants - Children - Adolescents	25% 25% 50%	20% 40% 40%	5% 35% 60%	10% 60% 30%	20% 30% 30%	10% 70% 20%	20% 40% 40%	0% 80% 20%	<i>For all:</i> < 10 pediatric patients
<b><u>Systematic PPIs</u></b>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<b><u>Elimination diets</u></b> - Infant - Children - Adolescents  - Allergologic tests  - Duration (months) - Surveillance fibroscopy  - Efficiency - Disadvantages	MED, SFED, TED TED, SFED TED, SFED  Yes  1.5-3 Yes  Yes Restrictive, Adolescents/infants	<i>For all:</i> AAS, TED, 2 FED  Yes  3 Yes  Yes Restrictive	MED, TED TED > SFED TED >> SFED  Yes  3 Yes  Incomplete Restrictive	<i>For all:</i> TED  Yes  3 Yes  Incomplete Restrictive	<i>For all:</i> TED  Yes  3 Yes  Yes Restrictive	<i>For all:</i> SFED <i>with</i> TED but fish  Yes  2 Yes  Yes Restrictive, Adolescents	TED, SFED TED, SFED If clinical evidence  Yes  3 Yes  Yes	<i>For all:</i> TED  Yes  2-3 Yes  Yes  Yes Restrictive, Adolescents	MED TFED, FFED, SFED TFED, FFED, SFED  With clinical symptoms  ≥ 1.5 Yes  Yes Restrictive, Adolescents
<b><u>Swallowed steroids</u></b> - Choice - Intake  - Efficiency - Disadvantages	Both Excipients/swallowed  Variable Intake difficulties, Candidosis	Budesonide Excipients  Yes None	Budesonide Gaviscon®, paste  Yes Dependency, Impregnation	Budesonide Sucralose  Yes Candidosis, Recurrence	Budesonide Maltose dextrin  Yes None	Fluticasone Swallowed  Incomplete Failure to thrive?	Fluticasone Swallowed  Yes	Fluticasone Swallowed  Yes Candidosis	Budesonide Sucralose  Unkown
<b><u>Therapeutic options after PPI failure</u></b>	1. Steroids 2. Diet (AAS)	1. Diet 2. Steroids	1. Steroids 2. Diet	1. Steroids 2. Diet	1. Steroids 2. Diet 3. Singulair: failure	1. Diet 2. Steroids +/- TED	1. Diet 2. Steroids	1. Diet 2. Steroids	1. Diet 2. Diet + steroids