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State of the art

Eosinophilic esophagitis in adults: A distinct form of food allergy

Œsophagite à éosinophiles chez les adultes : une forme distincte de l'allergie alimentaire

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1. Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disorder defined symptomatically by esophageal dysfunction and histologically by esophageal eosinophil-predominant inflammation [1]. Despite being characterized first as a distinct clinicopathological disorder 20 years ago, EoE has just recently become recognized as the most prevalent cause of chronic esophageal symptoms in children and young adults.

Since the seminal report in 1995 showing complete reversal of refractory eosinophilic esophagitis attributed to gastrointestinal reflux disease in 8 children after an elemental diet for 6 weeks [2], it is now well established that EoE is a disease predominantly, but not exclusively, triggered by food allergens. However, this disorder is currently believed to be a distinct form of food allergy, combining IgE- and non-IgE-mediated mechanisms. In addition, the role of standard food allergy skin testing has been shown to be less than optimal to detect causative foods in EoE patients, especially in adults [3]. This review aims to summarize the most relevant clinical, therapeutic and immunoallergic information on EoE from the perspective of a gastroenterologist with special dedication to EoE.

2. EoE from childhood to adulthood: an evolving entity from IgE to IgG4?

EoE is an immune disorder mediated by CD4T lymphocytes where an antigen induces inflammatory cell infiltration with

a cascade of Th2 interleukins (IL-5, IL-13) and chemokines (eotaxin-3). The process is frequently pan-esophageal and accompanied by histological remodeling, including submucosal fibrosis and angiogenesis, which translates clinically into esophageal rigidity, dysmotility and symptoms of dysphagia [4].

Generally, patients with EoE are atopic and tend to be polysensitized to both foods and aeroallergens, with children having more food sensitization and adults having more aeroallergen sensitization, consistent with the natural history of allergy. Accordingly, initial interest in allergy mechanisms in EoE first focused on IgE-mediated allergy. However, serum IgE levels do not correlate with symptoms or histology in EoE patients, and predictive values of serum and skin food allergy testing are poor in adults and, to a lesser extent, in children. In addition, omalizumab, an anti-IgE monoclonal antibody has shown limited benefit for treating pediatric and adults EoE patients [4,5].

In a recent study, esophageal tissue from two EoE patients who had had an esophagectomy displayed granular deposits of IgG4 and abundant IgG4-containing plasma cells [5]. The authors suggested that EoE in adults may be IgG4-mediated rather than IgE-induced allergy. Interestingly, there have been reports of EoE onset during oral immunotherapy trials for milk, egg, peanut and pollen [6–8]. This clearly suggests that the mechanism of food allergy in EoE is not IgE-dependant but, instead, it involves a cellular process. Fortunately, the first meta-analysis on this issue showed that new-onset EoE occurs just in 2.7% of the patients undergoing oral or sublingual immunotherapy for food allergy [9].

Overall, these studies raise the possibility of EoE switching from an IgE type allergy to an IgG4 type allergy as patients become adults. This mechanism may also explain the development of EoE after oral immunotherapy. Nevertheless, it is

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Table 1

Evolving consideration of PPI responsiveness in patients with esophageal eosinophilia compatible with EoE over the past eight years.

2007 Consensus Guidelines	2011 Consensus Guidelines	2015
PPI responsiveness is equivalent to GERD	PPI responsiveness neither confirms GERD nor excludes EoE	PPI-REE might be a subphenotype of EoE
A pathological pH monitoring is equivalent to either response to PPI therapy or GERD	PPI responsiveness might occur either with normal or pathological pH monitoring	PPI-REE and EoE share both genotypical and phenotypical features
GERD, as an acid-related disorder, is the only showing response to the acid suppressing ability of PPI therapy	PPI-REE is a new phenotype referring to patients with suspected EoE achieving complete remission on PPI therapy	PPI therapy in PPI-REE downregulates allergic inflammation, in a similar way to steroids in EoE

EoE: eosinophilic esophagitis; GERD: gastro-esophageal reflux disease; PPI: proton pump inhibitor; PPI-REE: proton pump inhibitor-responsive esophageal eosinophilia.

also plausible to speculate that a few adults might retain IgE reactivity and lack an IgG4 response, like some cases of failure of IgG4 antibodies to develop in patients undergoing allergen immunotherapy. In this regard, a recent study reported the high efficacy of an IgE-targeted diet in selected adult Spanish patients with IgE sensitization [10].

3. Food allergy testing in adult EoE: getting patients mixed-up?

Currently, the efficacy of food allergy skin prick tests (SPT), serum IgE assays (intended to measure immediate hypersensitivity), and especially atopy patch tests (APT) (intended to measure delayed hypersensitivity) as guides for prescribing an elimination diet for adults with EoE has been extremely disappointing, with cure rates below 25% [11,12]. The first meta-analysis of dietary interventions for EoE showed that allergy testing-directed food elimination is the least effective dietary intervention (42%) compared to an elemental diet (90%) or to a six-food empiric elimination diet (72%) [13]. It is important to be aware of several remarks on this question:

- allergy testing for foods may be more useful in the pediatric population, especially for children under 6 years of age;
- the negative predictive values for foods generally tend to be superior to the positive predictive values, with the exception of milk, which is the most common food trigger in EoE;
- the results of skin testing might be influenced by cross-reactivity with environmental allergens.

Current data for a pediatric population come largely from the Children's Hospital of Philadelphia [14,15]; lacking high-quality studies, such data for children have not been duplicated. However, these results are at the very least questionable, since the final outcome reported (72% efficacy) was made up of three different dietary interventions: skin testing-guided elimination, a cow's milk elimination diet (due to a poor negative predictive value) and an elemental diet for those children for which the diet was thought to be too restrictive.

4. PPI-responsive EoE: not simply gastroesophageal reflux disease

The first Consensus Guidelines report on EoE, published in 2007, proposed the following diagnostic criteria:

- symptoms of esophageal dysfunction, mainly dysphagia/food impaction;
- esophageal eosinophilic infiltration (>15 eos/HPF);
- either absence of response to proton pump inhibitor (PPI) therapy or demonstration of normal esophageal acid exposure on pH monitoring [16].

Therefore, it was suggested that either a response to PPI therapy or increased esophageal acid levels on pH monitoring were consistent with gastroesophageal reflux disease (GERD), which ruled out EoE. The basis for this recommendation was that GERD, as an acid-related disorder, was the only disease that could respond to the acid-suppressing ability of PPI treatment. The first prospective series on PPI therapy, published in 2011, reported that up to 50% of patients with an EoE phenotype (dysphagia/food impaction and >15 eos/HPF in esophageal biopsies) achieved complete remission [17]. Clinical, endoscopic and histological findings after PPI therapy showed no difference between responders and non-responders, and responsiveness to PPI therapy was documented in patients with either normal or abnormal pH monitoring results. Since then, several prospective series have confirmed that 33% to 50% of patients with suspected EoE are as having PPI-responsive esophageal eosinophilia (PPI-REE). This new phenotype, first recognized in the 2011 updated guidelines for EoE, identifies patients who seem to have EoE but achieve complete remission on PPI therapy. Unlike GERD, recent studies on esophageal biopsies have shown that PPI-REE and EoE remain indistinguishable even with gene expression of Th2 chemokine (eotaxin-3) and cytokines (interleukin (IL) (IL-5) and IL-13) and a 94-gene molecular panel, termed the EoE Diagnostic Panel (EDP) [18,19]. Furthermore, PPI therapy has been shown to down-regulate Th2 allergic inflammation and EDP in PPI-REE patients in a way similar to what topical steroids do in EoE patients [18,19]. Considerations of responsiveness to PPI therapy evolving over the past 8 years are summarized in Table 1. Current evidence draws attention to the evidence that EoE and PPI-REE are genetically and phenotypically indistinguishable, therefore questioning whether PPI-REE and EoE are two different diseases. It may be counterintuitive to define PPI-REE by its response to PPI therapy rather than by its genetic, phenotypic and mechanistic characteristics, which are similar to those of classic EoE. For example, we do not define asthma as bronchial eosinophilic inflammation, based on responsiveness to corticosteroids, and call it asthma when step-up therapy is needed. As such, it is tempting to consider EoE as a disease

in which PPI therapy might be the first step in treatment, diet and steroids representing a step-up therapy. There is also concern that the term PPI-REE might be replaced by PPI-responsive EoE.

5. Topical steroid therapy: the best is yet to come

The best studied steroidal medications are fluticasone, dispensed from a metered-dose inhaler, and budesonide, administered either as a viscous slurry or as a nebulized vapor. Due to a lack of drugs approved for EoE, “off-label” drugs, designed for other allergic diseases, such as asthma or rhinitis, are still being used to treat patients with EoE. As for inhalers, the medication used without a spacer is usually puffed into the mouth twice daily with the breath being held and then it is swallowed with a minimum amount of water to minimize pulmonary deposition and the risk for candidiasis. A liquid formulation of fluticasone designed for intranasal delivery (nasal drops), which just needs to be swallowed, might be a valid alternative as well. The oral viscous budesonide preparation requires mixing this medication with multiple packets of sucralose; 3–5 mg of sucralose per 2 mL of aqueous budesonide are usually required to achieve the desired thickened consistency to make the viscous solution which is to be swallowed twice daily.

For all topical steroids, administration should be after meals, and patients should not eat or drink anything for 30–60 minutes after swallowing the drug. Doses of fluticasone typically range from 440 to 880 mcg/day for children and from 880 to 1760 mcg/day for adults. Recent findings suggest that an initial dose of 1760 mcg/day might be optimal for all age groups [20]. The usual dose of budesonide ranges from 1 mg/day for young children to 2 mg/day for adolescents and adults. All of these practical considerations are summarized in Table 2.

In a multitude of studies both of these steroidal drugs have demonstrated efficacy in treating EoE [20]. However, the efficacy rates have varied enormously (especially for fluticasone), ranging from 30% to 80%. About 25%–40% of EoE patients are currently considered to be refractory to topical steroids, including fluticasone and budesonide [20]. In a recent milestone randomized controlled trial, different formulations of a topical steroid (nebulized and viscous preparations of budesonide, 1 mg twice daily for 8 weeks) were first compared in a cohort of adult patients [21]. The authors found that complete histological remission was significantly higher in the oral viscous budesonide group than in the swallowed nebulizer solution group (64% vs. 27%, $P=0.09$). Of note, nuclear scintigraphy showed that overall drug mucosal contact time (measured with a tagged radiocontrast agent) was significantly longer (48,900 vs. 19,200, $P=0.005$) in patients treated with the oral viscous budesonide than those treated with the nebulizer solution, and this difference was much higher in the distal esophagus (18,100 vs. 3800, $P=0.001$) [21]. Therefore, this study pointed out that the frequency of histological remission improvement was directly related to higher mucosal contact time, which highlighted the importance of appropriate drug delivery methods in the treatment of EoE. A recently published randomized, double-blind, placebo-controlled phase II trial showed outstanding results for

Table 2

Considerations for use of topical steroids in clinical practice.

Fluticasone can be puffed into the mouth during a breath hold from a metered-dose inhaler, and then swallowed, or either with a liquid formulation designed for intranasal delivery (nasal drops).
Doses for fluticasone typically range from 440 to 880 mcg/day in children and 880 to 1760 mcg/day in adults. According to recent trials, an initial dose of 1760 mcg/day might be more effective for all patient age groups
Budesonide is usually dispensed in a viscous solution, made by mixing this medication with multiple packets of sucralose, an artificial sweetener. This formulation is termed oral viscous budesonide. The usual dose ranges from 1 mg/day in children to 2 mg/day in adolescents and adults
All topical steroids should be given twice daily (after breakfast and after dinner or at bedtime) and patients should not eat or drink anything for 30–60 minutes after swallowing the drug
Endoscopy to monitor response histological response on topical steroids should always be performed after a 6–12-week treatment period.
Patients taking budesonide should not ingest grapefruit or its juice since they inhibit the CYP3A enzyme pathway, responsible for the high first-pass effect of budesonide
Infectious esophagitis (candida, herpes) should be considered as causes of either sudden/unexpected odynophagia and/or dysphagia in EoE patients on topical steroid therapy
Long-term management with topical steroids is yet to be determined. An approach where the dose is progressively decreased to the lowest dose that keeps the disease in remission seems reasonable until more safety and efficacy data are available

the first novel budesonide formulations specifically designed for EoE (budesonide effervescent tablets and oral viscous solutions) [22]. After only a 2-week course of this treatment, histological remission (<15 eos/HPF) occurred in 100%, 94.7% and 94.7% of the budesonide groups and in 0% of the placebo recipients ($P<0.0001$); a majority of the patients (80%) preferred effervescent tablets. Yet again, this study emphasizes the importance of a specific drug delivery system as the key factor for responsiveness to topical steroids in EoE. Consequently, it seems that the best is yet to come in this field. When there is responsiveness to topical steroid therapy, maintenance anti-inflammatory therapy is recommended for all patients to prevent disease recurrence and esophageal fibrotic remodeling, even though this strategy is yet to be defined. Concerns about long-term safety of topical steroids, especially regarding adrenal suppression and bone metabolism in children, should be investigated in future studies.

6. Empiric elimination diets: the way forward in clinical practice

As mentioned above, a recently published meta-analysis on dietary interventions for EoE recently showed that allergy testing-directed food elimination is the less effective dietary intervention (42%), compared to elemental (90%) or six-food empiric elimination diets (72%) [13]. An elemental diet is the most effective intervention, but it is not feasible in clinical practice. Aiming at overcoming the impracticability of elemental diets and the low sensitivity and specificity of allergy testing in identifying EoE food triggers, the alternative of empirically eliminating the six foods most commonly associated with food allergy in children (e.g., milk protein, soy, egg, wheat, peanut/tree nuts, and seafood), was first evaluated by Dr.

Table 3
Summary of the most common food triggers identified through individual food reintroduction and endoscopy after response to either six- (SFED) or four-food (FFED) empiric elimination diets.

First author, year of publication, country	Diet patients design	Histological remission	Responders undergoing food reintroduction	One food trigger	Two food triggers	Three or more food triggers	Most common food triggers
Kagalwalla, 2011, US	SFED Children Unicenter	74%	36/46 (78%)	72%	8%	8%	Cow's milk 74% Wheat 26% Egg 17%
Gonsalves, 2012, US	SFED Adults Unicenter	74%	20/37 (54%)	85%	15%	(>1 food trigger)	Wheat 60% Cow's milk 50%
Lucendo, 2013, Spain	SFED Adults Unicenter	72%	49/49 (100%)	36%	31%	33%	Cow's milk 62% Wheat 29% Eggs 26% Legumes 24%
Molina-Infante, 2014, Spain	FFED SFED Adults Multicenter	54% 72%	22/28 (78%)	45%	45%	0%	Cow's milk 50% Eggs 36% Wheat 31% Legumes 18%
Kagalwalla, 2015, US	FFED Children Multicenter	71%	19/39 (49%)	74%	21%	5%	Cow's milk 68% Egg 26% Wheat 21%

Kagalwalla, a pediatrician from Chicago [23]. This diet, the so-called six-food elimination diet (SFED), achieved a significant improvement of both esophageal inflammation and symptoms in most of the children (74%). These results have been fully confirmed in adults in the US and Spain [24,25]. However, an SFED is quite restrictive and is hampered by the large number of endoscopies after individual food re-introduction challenges used to identify specific food triggers. Of note, the most common causative foods identified after a response to SFED are cow's milk, wheat, egg and soy/legumes, with a negligible role for nuts, fish and seafood [24–26] (Table 3). In addition, the majority of patients (65%–85%) responsive to SFED were found to have just one or two causative foods identified after six food challenges and endoscopies. As such, some dietary restrictions and subsequent endoscopies after six food challenges may not be necessary and there might be room for optimizing and simplifying dietary interventions.

In this regard, a four-food elimination diet (FFED) (i.e., a SFED which allows consumption of nuts, fish and seafood) has been developed recently and is being used in the first prospective multicenter studies on elimination diets for EoE. This dietary approach has shown notable results in adults (54%) [27] and, to a higher degree, in children (70%) [28]. A single food trigger was found in 45% of the adults [27] and in 71% of the children [28]. The causative foods identified through individual re-introduction are summarized in Table 3. Collectively, available data on empiric elimination diets hint at a different profile of culprit foods between children and adults, with a narrow spectrum of culprit food allergens in children (especially cow's milk) and a broader spectrum in adults. Of note, cow's milk is the most common causative food in all age groups. Likewise, legumes were detected to be important food triggers of EoE in only 20% of Spanish adults, but not at all in American adults, which may be due to a geographical factor related to dietary differences; for example, in Spain the intake of legumes, such as lentils, chickpeas and beans is common. This novel FFED provides

several advantages, such as limiting unnecessary dietary restrictions and improving patient adherence, shortening the overall time to complete the food re-introduction process and reducing the number of endoscopies. Whether more simplified dietary schemes (one, two or three elimination diets including cow's milk, wheat and eggs) would benefit from the aforementioned advantages and also be cost effective (especially in children) and more convenient should be investigated in high quality prospective multicenter studies.

7. Treating EoE: a practical algorithm

Similar to inflammatory bowel diseases, two different phenotypes have been described for EoE patients: inflammatory and fibrostenotic [29]. The natural history of this disease suggests that it may evolve from the former to the later. Currently, the most reliable end points of therapy are healing of mucosal inflammation and resolution of caliber abnormalities. PPI, dietary and topical steroid therapies target mucosal inflammation, whereas fibrostenotic complications should be treated by endoscopic dilatation. Both approaches should be combined when both clinical EoE phenotypes overlap. A follow-up endoscopy after an initial 6- to 8-week course of any therapy should be carried out to document any histological response. EoE appears to be a chronic disease affecting mainly young patients who require maintenance therapy to prevent esophageal fibrotic remodeling and subsequent stricture formation. Still, a long-term therapeutic strategy for EoE is yet to be elucidated. A practical algorithm for treating EoE is displayed in Fig. 1.

PPI therapy is now considered a formal pre-requisite before diagnosing EoE. PPI-REE, which is currently considered to be a sub-phenotype of EoE, is present in 30% to 50% of EoE patients. Furthermore, PPI is a safe drug with minor and infrequent long-term complications. As such, it should be considered the first-line therapy for EoE patients. This subset of patients will not need topical steroid or dietary therapy. As for patients

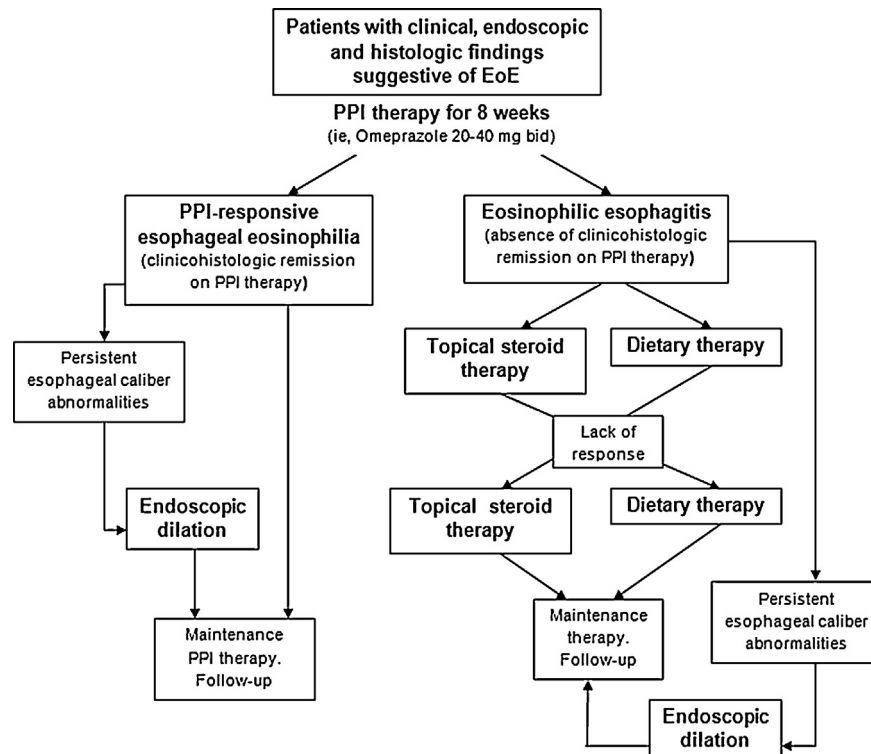


Fig. 1. Proposed therapeutic algorithm for EoE in children and adults.

unresponsive to PPI therapy, either topical steroids or dietary therapy are good choices for patients with mucosal inflammation and no esophageal caliber abnormalities. The choice of short- and long-term medical therapy (corticosteroids vs. dietary therapy) should be discussed with the patient and may depend on the age, the disease severity, the patient's lifestyle and preferences, the ability of the patient to continue the medication, treatment side effects and adverse impact on quality of life and family resources [29].

8. Anti-allergic drugs in EoE: they just don't make the grade

A plethora of new anti-allergic drugs, including montelukast (a leukotriene D4 receptor antagonist), OC000459 (an anti CRTH2), omalizumab (an anti-IgE monoclonal antibody), reslizumab and mepolizumab (anti-IL-5 monoclonal antibodies) and QAX576 (an anti-IL-13 monoclonal antibody), which are being studied in patients with other allergic diseases, are also being studied in patients with EoE [30]. All of these drugs have produced significantly much worse results in EoE patients, especially concerning symptom improvement, than PPIs, dietary regimes and topical steroids. Therefore, these drugs should only be considered for use in research studies and potentially for treatment of refractory EoE patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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