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REVIEW

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Eosinophilic esophagitis in children: current knowledge to open new horizons

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ABSTRACT

Eosinophilic Esophagitis (EoE) is a chronic immune/antigen-mediated condition which is also driven by genetic and environmental factors. It has been deeply investigated over the last years and its incidence is widely increasing in childhood. Although atopic diseases are closely linked with EoE, it does not recognize a classical IgE-mediate immune pathogenesis but it is rather a T helper type 2 inflammatory process. Familial clustering supports genetic predisposition in EoE and recent advances in understanding the genetic basis for EoE may eventually translate into targeted management of the disease. EoE diagnosis is based on clinical symptoms, micro, and macroscopic findings along with exclusion of gastroesophageal reflux disease (GERD) evidence. Management of the disease encompasses both dietary and pharmacological solutions that need to be specifically targeted on patients' history, clinical symptoms, and diagnostic evaluations. New therapies, currently not available in children, may represent the basis for future therapeutic options in the next years.

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Introduction

Eosinophilic esophagitis (EoE) is a relatively new diagnostic entity, having only been first reported in 1977 [1,2]. Since then it has become increasingly recognized as a cause of morbidity for children and adults. Due to the overlap in clinical features with common gastro-esophageal reflux disease (GERD), there is additional pressure on tertiary pediatric gastroenterology services to perform an endoscopy to exclude the diagnosis.

We carried out a review including the most pertinent manuscripts on "Pediatric Eosinophilic Esophagitis" present on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) over the last 25 years (1993–2018); papers were selected from RCTs, case reports, reviews, systematic reviews, cohort and case–control studies, and observational studies. Researched terms were "pediatric eosinophilic esophagitis" [all fields]; "eosinophilic esophagitis" and "children" [all fields]; "pediatric eosinophilic esophagitis" and "management" [all fields]; "pediatric eosinophilic esophagitis" and "treatment" [all fields]; "pediatric eosinophilic esophagitis" and "therapy" [all fields]; "pediatric eosinophilic esophagitis" and "diet" [all fields]; "pediatric eosinophilic esophagitis" and "probiotics" [all fields]; "esophageal eosinophilia" [all fields]; "pediatric GERD" [all fields]; "gastroesophageal reflux" and "children" [all fields].

This review aims to provide an update with recent advances on EoE in children and reflect on what remains unclear in this challenging condition.

Definition

According to the 2014 ESPGHAN Guidelines, EoE is defined as a chronic immune/antigen-mediated disorder of the esophagus with typical features represented by esophageal dysfunction and histologic finding of eosinophil-predominant inflammation [3].

Furuta et al. included in the definition of the disease the presence of esophageal and/or upper gastrointestinal (GI) tract symptoms in association with esophageal mucosal finding of >15 eosinophils in 1 high-power field in one or more biopsy specimens along with the exclusion of GERD evidenced by lack of responsiveness to high-dose proton pump inhibition (PPI) (up to 2 mg/kg/day) or normal pH monitoring study of the distal esophagus [4]. However, recent evidence in the adult setting have considered PPI therapy as a proper treatment for EOE rather than a diagnostic tool, therefore in the adult guidelines, PPI trial has not been included in the definition anymore [5].

Epidemiology

The incidence of EoE in children has been investigated by several studies with high variability in estimates. It is an emerging disease where reported incidence is increasing, though it is unclear to what extent this reflects increased diagnosis, and currently varies widely from 1 to 20 new cases

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per 100,000 inhabitants per year. Although all ages can be affected, the majority of patients present in childhood, adolescence, and adulthood under the age of 50 with a peak at 30–50 years [4–6]. Males are more commonly affected than females (M/F ratio of about 3:1) [4]. A recent study reported a prevalence between 1 and 5 per 100,000 persons in the United States and Europe [7]. Another study suggests that EoE prevalence estimates vary from region to region tending to be on the same order of magnitude in Western Europe, North America, and Australia though much lower in Japan and China. Interestingly, there are no reports from sub-Saharan Africa and India despite similarities in clinical presentation and molecular features, indicating an opportunity for future study of etiologic mechanisms that focus on environmental factors [8]. In a recent meta-analysis, data reported a higher prevalence in adults (43.4/100,000 (95% confidence interval (CI) 22.5–71.2)) than in children (29.5/100,000 (95% CI 17.5–44.7) [9–11]. The majority of epidemiological data on EoE originates from North America and Europe. The condition has been described in patients with a variety of ethnic backgrounds, but it remains to be established whether ethnic predilection accounts for the differences described above. Socioeconomic distribution and seasonal variation in EoE have not been systematically examined [4].

Etiology

EoE pathogenesis is a highly active area of research. It is an immune-mediated inflammatory disorder with genetic and environmental drivers, including microbial exposure [11]. Between 50% and 80% of patients with EoE have a family or personal history of atopic diseases such as food allergy, asthma and allergic rhinitis, and the evidence indicates that it has a familial association, with nearly 10% of parents of EoE patients having a history of esophageal strictures and about 8% having biopsy-proven EoE [9,12]. However, unlike these conditions, EoE does not seem to be a classic IgE mediated immune response rather it is a T helper type 2 cell (Th2) predominant inflammatory process triggered by allergens. Adaptive T cell immunity, driven by Th2 cells and involving IL-13, IL-5, and IL-15 expression, appears to play a major role in the pathogenesis of EoE [13]. Moreover, the epithelial barrier abnormalities in EoE are caused by a combination of genetic, environmental and immunological factors, and may allow enhanced allergen penetration and systemic allergen sensitization [14]. Candidate gene like CCL26 (Eotaxin-3), FLG (Filaggrin), TSLP (Thymic Stromal Lymphopoietin) and TSLP receptor (TSLPR) gene, CAPN14 and ANKRD27 gene, and other are considered important in the pathogenesis of the disease (Table 1) [12,15–17]; and these recent advances in understanding the genetic basis for EoE may eventually translate into targeted management of the disease [18]. Another important factor in the pathogenesis of EoE is considered gut microbiota. Gut microbiota composition embraces a wide-ranging of bacteria divided in species and strain which differ throughout the GI tract with Bacteroidetes and Firmicutes representing the largest phyla compared to the relatively less common Proteonacteria, Acinobacteria, Fusobacteria and Verrucomicrobia. Gut microbiota contributes to the stimulation and maturation of the immune system; therefore, a disequilibrium in the gut flora may alter these processes [19].

Recently, a group from Philadelphia [20] used 16S rRNA gene sequencing showed a distinctive microbiota signature in active EoE compared to non-EoE controls with more abundant Proteobacteria in the EoE cohort while Firmicutes in non-EoE controls. Another study [21] found that bacterial load was increased in both EoE and GERD patients compared to normal subjects, and EoE patients with active inflammation showed an increase in Hemophilus compared to control subjects with a normal esophagus or GERD. Consistent with Benitez et al. [20], the microbiota in untreated EoE patients showed a shift from a Gram-positive population (Firmicutes) to an increase in Gram-negative bacteria (Proteobacteria).

Moreover, dysregulation of the brain–gut–microbiota axis, which is the cross-talk between the central nervous system (CNS), the gastrointestinal tract and its microbiota, may play a role in the pathophysiology of EoE as it has been already associated with several GI diseases such as inflammatory bowel disease, food antigen-related adverse response, peptic ulcer, and GERD [19].

Overall, it is established that there is a specific microbiome signature associated with EoE though it appears to be less dietary responsive than colonic microbes. It is yet to be established whether manipulation of the microbiome will be a clinical strategy as it has been already described in functional gastrointestinal disorders (FIGDs) where probiotics were successfully used for prevention and treatment [22,23].

Macroscopic and microscopic findings

Oesophagogastroduodenoscopy (OGD) with multiple esophageal biopsies is considered the gold standard diagnostic technique. Biopsies are performed throughout the esophagus as well as gastroduodenal tract to rule out concomitant framework eosinophilic gastroenteropathy.

According to Shah et al., at least three esophageal biopsy specimens taken from different parts of the esophagus are needed to achieve a diagnosis of EoE in 97% of patients DA QUI IN POI 22 diventa 24 [3,24]. According to Gonsalves et al. [25], one biopsy specimen has a sensitivity of only 55%, whereas five biopsies increase this to 100%. To maximize diagnostic sensitivity, it is, therefore, recommended that at least 2–4 biopsies should be taken from both the proximal and distal esophagus [26]. It is useful to take at least 4–5 biopsies (1–2 per portion esophageal) to reach a sensitivity diagnostic up to 90–95% [4]. Several endoscopic features have been described in esophagus of patients with EoE such as longitudinal furrowing, friability, edema, longitudinal shearing, narrow caliber esophagus, esophageal rings, a thickened and sometimes pale mucosa with linear furrows and white exudates “crêpe paper mucosa,” and less often, narrowing of the caliber of the esophagus [4]. These features are associated with changes in motility and esophageal peristalsis, which are thought to give rise to dysphagia. Although none of these can be classified as pathognomonic features

Table 1. Genetics of EoE (GWAS-discovered loci).

Locus	Gene	Product	SNP with effect allele	Function	Susceptibility to other allergic disorders
1q21.3	*FLG*	Filaggrin	Loss-of-function variants	The major protein component of the keratohyalin granules of mammalian epidermis with a role in skin barrier function	Atopic dermatitis and eczema
7q11.2	*CCL26*	Eotaxin-3	rs2302009	Chemokine inducing eosinophils and basophils migration	Atopic dermatitis
5q22.1	*TSLP*	Thymic Stromal Lymphoprotein	rs3806932	B cell-stimulating factors (increased basophil response)	Allergic skin inflammation
Xp22.3; Yp11.3	*TSLPR*	Thymic Stromal Lymphoprotein Receptor	rs36133495	Member of the type I cytokine receptor family	Atopic dermatitis
12q13.3	*STAT6*	Signal Transducer and Activator of Transcription 6	rs324011	Signal transducer and activator of transcription	Allergic sensitization, total serum IgE levels and eosinophilia
11q13.5	*EMSY*	Chromosome 11 Open Reading Frame 30 (*c11orf30*)	rs55646091	Transcriptional regulator	Allergic sensitization, multiple allergic/inflammatory phenotypes
2p23.1	*CAPN14*	Calpain 14	rs77569859	Member of the caplain family (intracellular calcium-activated cysteine protease)	No
19q13.11	*ANKRD27*	Ankyrin Repeat Domain-containing protein 27	rs3815700	Regulate endosome dynamics and Regulates the proper trafficking of melanogenic enzymes to melanosomes in melanocytes	No

of EoE, one or more of the above endoscopic aspects may be strongly suggestive of this disease, in the presence of clinical symptoms. Conversely, some studies have reported that an absence of endoscopic alterations does not exclude the diagnosis of EoE [4]. Stenosis or reduction of the esophageal caliber is more serious and advanced lesions, secondary to eosinophilic prevalent inflammation, collagen deposition and resulting fibrosis. Mucosal erosions or ulceration are not characteristic of EoE and are more indicative for GERD, Crohn's disease, or other diagnoses [3]. The main microscopic features are represented by dense eosinophilia of the esophageal mucosa, basal zone hyperplasia, lamina propria fibrosis, and sometimes eosinophilic microabscesses (Figure 1) [27]. The presence of an increased number of eosinophils in the esophageal epithelium which is a mucosa that is typically devoid of eosinophils is the histologic hallmark of EoE [7]. Available data indicate that a number of sinopeosinophils per field represent a histological diagnosis of EoE in correlation with the clinical picture [3]. Other microscopic features, but not pathognomonic, include an aggregate of eosinophils or microabscess and eosinophil layering along the luminal surface, dilated intracellular spaces, rete-peg elongation, basal-cell hyperplasia and numbers of inflammatory cells including lymphocytes, mast cells, and basophils [7]. It should be noted, however, that the size of a high-power field has not been standardized. This may alter the sensitivity/specificity of the lower threshold of diagnosis at 15 eos/per field. Furthermore, it should be considered that diagnostic biopsies are predominantly epithelial and may underestimate deeper disease activity as eosinophil recruitment begins within the subepithelial compartment [3].

Clinical symptoms

Clinical symptoms of EoE vary with age. Infants and toddlers present with a range of feeding difficulties including vomiting, regurgitation, and food refusal, sometimes resulting in failure to thrive. During childhood, there are more specific symptoms: vomiting and/or abdominal or retrosternal pain, therefore, GERD-like symptoms. During adolescence, the most frequent symptoms are also GERD symptoms, though dysphagia and food impaction are more prominent in EoE [3,28]. Peripheral eosinophilia (>700 cells/mm^3) can be found in children with EoE [3,29]. Furthermore, in children with EoE, specific immunoglobulin E (IgE) antibodies to foods which may (or may not) be the causative foods of the disease have been reported [3,27].

Differential diagnosis

Many diseases associated with esophageal eosinophilia, such as infectious esophagitis, esophageal achalasia, celiac disease, Crohn's disease, connective tissue disorders, graft-versus-host disease, drug hypersensitivity, and hypereosinophilic syndromes, should be excluded [4,26]. The main differential diagnosis for symptoms and histopathological findings is GERD (Table 2). However, it is not clear how to differentiate reliably EoE from GERD. The diagnosis of EoE should be

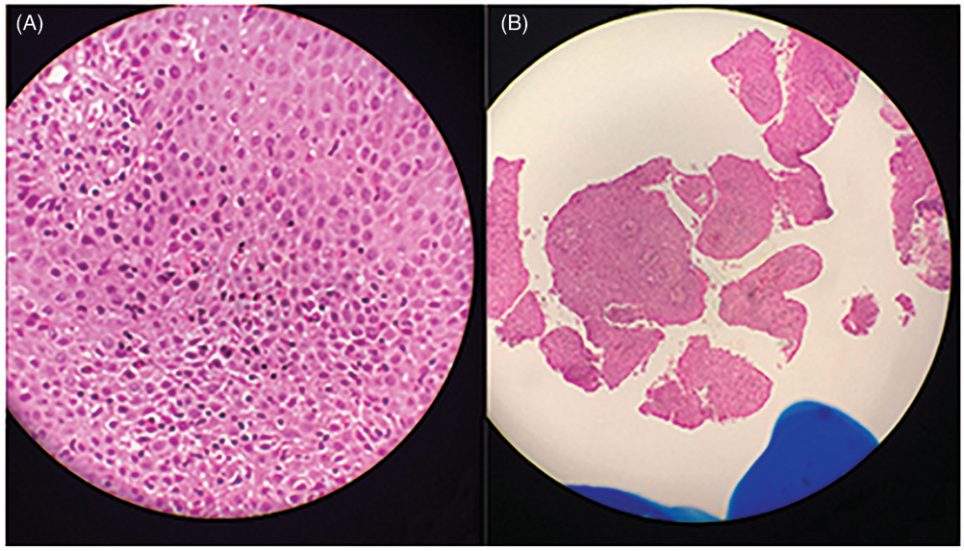

Figure 1. A and B: EoE histology – Superficial biopsy of oesophageal squamous epithelium in which there is a prominent eosinophilic infiltrate and patchy basal cell hyperplasia.Images gently given by Department of Pediatric and Perinatal Pathology, Addenbrooke's Hospital, Cambridge, UK.Patient consent for the use of images for teaching purpose given at the time of procedure.

Table 2. Differences between EoE and GERD.

	EOE	GERD
History of atopy	Common	Uncommon
Predominance m/f	3:1	1:1
Etiology	Immune-mediated inflammatory disorder	Acid reflux
Predominant symptoms	Dysphagia Food impaction	Regurgitation Retrosternal pain Heartburn
Macroscopic findings	Esophageal rings Edema Thickened mucosa Exudates furrows Narrowing of the caliber of the esophagus Strictures Normal findings (uncommon, <10%)	Erosions Ulcerations Normal findings (common)
Hystology	≥15 eosinophils per hpf (usually panesophageal) Basal zone hyperplasia Lamina propria fibrosis Eosinophilic microabcesses	< 15 eosinophils per hpf (usually limited to distal esophagus)
Diagnostic markers	Peripheral eosinophilia (700 cells/mm3) Specific IgE to food allergens Eosinophil-derived proteins in luminal secretions	Unknown
Diagnostic tests	Upper gastrointestinal endoscopy	Intraluminal impedance and esophageal pH monitoring Esophageal manometry Upper gastrointestinal endoscopy
Therapy	PPI Elimination diet Steroids	Antiacid drugs PPI H2 receptor blockers

EOE: eosinophilic esophagitis; GERD: gastro-esophageal reflux disease; hpf: high-power field; IgE: immunoglobulin; PPI: proton-pump inhibitors.

based on a combination of symptoms and histologic and endoscopic findings bearing in mind that no single feature is sufficient to establish a definitive diagnosis [30].

In the first description of the disease [31], GERD and EoE were considered mutually exclusive disorders and the first guidelines for diagnosis and management of EoE suggested that patient with esophageal eosinophilia who responded to PPIs or had abnormal acid reflux suffered from GERD instead of EoE [4,32]; however, the distinction is now felt to be less dichotomous. The inflammatory process of EoE may lead to a hypersensitivity to acid exposure, even in the absence of erosions, comparable with non-erosive reflux disease [3]. EoE and GERD are not mutually exclusive or may even exacerbate each other.

Selection of which children to perform endoscopy on is challenging and, currently, there are no specific biomarkers in routine practice. This is a field of active research and a recent study reported that the measurement of eosinophil-derived proteins in luminal secretions could be used to distinguish children with EoE from those with GERD [33].

Although endoscopy plays a key role in the diagnosis of GERD, if the clinical assessment is suggestive enough then empiric PPI therapy may be used. However, endoscopy it is required for diagnostic uncertainty, "red flag" symptoms (e.g.

dysphagia), when symptoms do not respond to empiric PPI therapy, and before starting corticosteroids [34].

Management

The target of EoE's therapy is the achievement and maintenance of clinical and histological remission and also prevents iatrogenic damage caused by adverse effects related to pharmacological therapy and nutritional deficiencies caused by a long-term elimination diet [32,35]. The confirmation of remission can be done only be formally confirmed through an endoscopic revaluation before food reintroduction or drug titration. All intervention should be individually tailored: atopic patients mostly benefit from diet elimination, whereas non-atopic patients benefit most from steroid therapy [3,35].

Empiric treatment

According to the ESPGHAN Guidelines [3], in symptomatic children with histological findings of esophageal eosinophilia, a trial of PPIs is recommended for 8 weeks. A second OGD should be performed under PPI therapy in all children, even if symptoms are resolved. If histology is still suggestive of EoE and other causes of esophageal eosinophilia are unlikely, then the diagnosis of EoE can be made. If the first endoscopy is performed after an adequate trial of PPI, the diagnosis of EoE can also be made and specific treatment for EoE initiated.

Dietary solutions

There are three types of the elimination diet for patients with EoE: amino acid-based formulas (AAF), targeted elimination diet (TED), and empiric elimination diet (EED).

Although there are no randomized controlled trials, the available literature to date seems to assert that AAF is the most successful intervention [35]. AAF consists of food allergens complete removal, replaced with a hypoallergenic milk formula based on amino acids [36]. However, the use of this formula has advantages and disadvantages. In children, the resolution of characteristic symptoms such as vomiting, abdominal pain and dysphagia usually subsides between 8 d and 2 weeks from the introduction of hypoallergenic formula while the histological resolution has been reported in 4 weeks [37–39].

The use of AAF is, however, burdened by excessive cost and the frequent need for nasogastric tube delivery because of low palatability. To date, AAF is restricted to children with multiple food allergies or who does not respond to a strict elimination diet [35].

TED is indicated in those patients who have a suggestive history of food allergies with a positive test such as Skin Prick Tests (SPTs) and Allergy Patch Test (APT). Some EoE patients have multiple food allergies and it is sometimes difficult to identify the responsible food allergen through the common skin tests; often it is possible that the food allergen tested positive to the SPT or APT is not responsible for the disease. This can lead to the unnecessary elimination of foods [35]. However, it should be highlighted that an elimination diet based on a combination of SPT and APT was reported to achieve resolution of both symptoms and histological abnormalities in 77% of children with EoE [40].

The most common foods tested with SPT and APT include milk protein, egg, peanuts, soy, a variety of grains (wheat, rice, corn, rye, oats, and barley), meat, vegetables, and fruits. Due to the T_H2-nature of the inflammatory activity, even extensive allergy testing may return false-negative results, potentially leading to incomplete elimination diet of offending food antigens if these results are taken in isolation [3].

In children with gastrointestinal manifestations of cow's-milk protein (CMP) allergy, specific IgE tests results are commonly negative without excluding the diagnosis of CMP allergy [41,42]. CMP is a common food antigen and the leading cause of food allergy in infants and children younger than 3 years [43,44]; some studies suggested that it is often avoided from the diet in this age group, regardless of the results of specific IgE or SPT/APT testing.

Another strategy for EoE is represented by EED, which is based on the elimination from the diet of foods that, regardless of sensitization, are strongly correlated with EoE (soy, eggs, wheat, peanuts, fish, and shell-fish). This strategy in some studies showed a clinical and histological improvement in 74% of children [45]. Support from a pediatric nutritionist is essential for all significant elimination diets.

Diet efficacy

When children are treated with AAF, the second-look-endoscopy should be performed at 4 weeks after the resolution of symptoms. In cases of TED or EED, resolution of symptoms is usually delayed and repeating endoscopy should be performed at 8–12 weeks from the beginning of treatment strategy. In the case of histological remission, food reintroduction should be commenced with the least allergenic foods [40].

Some centers suggest a more invasive approach consisting of periodic repetition of endoscopies in order to ensure both clinical and histological resolution of the disease and also an endoscopy after the reintroduction of foods [35].

Drug therapy

Proton pump inhibitors (PPI)

Until recently, PPI has been considered a diagnostic-tool in the differential diagnosis between EoE and GERD. Lack of responsiveness to high-dose PPI along with clinical and esophageal (micro- and macroscopic) findings exclude GERD-associated esophagitis and confirm EoE [4]. Over the last few years, a new entity known as "proton pump inhibitor-responsive esophageal eosinophilia" (PPI-REE) has been used for patients who meet criteria for EoE but are also responsive to PPI therapy [6,46]. Despite this, recent evidences state that, in adults, PPI-REE and EoE are indistinguishable from one other, even at genetic levels; therefore, PPI therapy should be considered as a therapeutic agent rather than a diagnostic tool; however, it still remains unknown whether the esophageal immune response of patients with EoE who

respond to PPI therapy is triggered by GERD, food allergens or both [6]. Although this has been endorsed in adults, promising results also come from recent pediatric studies, with 70% of children with PPI-responsive EoE in histological and clinical remission after 1-year follow-up [47]. However, PPI-therapy should be still considered a diagnostic tool in children as the latest guidelines on EoE state that further studies are required to show whether the diagnosis of EoE can be assumed without PPI treatment, this because the proportion of children with esophageal eosinophil count of $\geq$ 15 eos/hpf that are responsive to PPI is unclear because only retrospective data on selected patients are currently available [3].

Steroids

Systemic and topical corticosteroids are both highly efficacious in inducing clinical and histological remission, even if systemic steroids are burdened with many side effects (hyperphagia, weight gain, and/or cushingoid features), and, for this reason, not recommended [6]. Studies show that clinical remission is achieved after 1 week from the use of oral steroids and histological remission after 4 weeks [48]. Due to the potential adverse effects of systemic steroids yet excellent results on remission, their relative benefits and disadvantages should be discussed in the case with parents [35]. The use of systemic corticosteroids is indicated when the patient has severe dysphagia, dehydration, weight loss, or esophageal strictures. In all other cases, topical steroids are the first line of treatment for EoE. The dose of prednisone for the resolution of symptoms and for the regression of histological alterations is 1–2 mg/kg/d with a maximum dose of 40–60 mg [35]. Topical fluticasone has given positive results on histologic remission without difference between resolution of symptoms, relapse, or timing of relapse [49]. Fluticasone propionate and the oral viscous budesonide (OVB) are the most commonly used topical steroids. Fluticasone propionate in the form of oral spray is recommended at a dosage of 88–440 mcg from two times to four times per day [26]. OVB in the form of preparation for inhalation is recommended at a dosage of 1 mg per day for children $<$ 10 years and 2 mg per day for children $>$ 10 years [26].

Titration of these drugs should be commenced after confirmation of histological and clinical resolution of symptoms with a subsequent endoscopy at 4–12 weeks of drugs introduction [3].

Other therapies

Other drug therapies such as montelukast, a leukotriene receptor antagonist, biologic agents, immunomodulators such us Azathioprine (AZA) and 6-Mercaptopurine (6-MP) and sodium cromoglycate are not recommended for treating pediatric EoE at this time until further data is available [1].

Montelukast has been studied for the treatment of EoE but results are conflicting [50]. In 2017, an RCT compared maintenance therapy with montelukast versus placebo in a patient who was topical steroids responders and reported no differences in symptoms recurrence between groups [50,51]. Infliximab and Omalizumab targeting tumor necrosis factor and IgE, respectively, have not been effective in treating EoE [52]. Mepolizumab and Reslizumab (both IL-5 blockers) partially reduced esophageal eosinophilia but did not ameliorate esophageal fibrosis and demonstrated a poor symptom response. Reslizumab improved the histologic response but symptom response was no better than placebo [52,53]. AZA and 6-MP have been studied in a small court of patients who were refractory to steroids and after an initial response, they relapsed with recurrent eosinophilia when treatment was stopped [50,54].

Oral viscous sodium cromoglycate (cromolyn sodium) is a non-steroidal anti-inflammatory, mast cell stabilizer agent. A recent randomized, double-blinded, placebo-controlled trial conducted in a cohort of sixteen pediatric patients did not significantly decrease esophageal eosinophilia, neither symptoms more than placebo and only led to complete resolution in one patient [55].

Refractory disease

Refractory EoE can be defined as persistent eosinophilia with incomplete symptom resolution and persistent endoscopic findings after a PPI trial and after topical steroid treatment or dietary elimination [50]. Depending on the treatment modality, non-response to topical steroid or dietary elimination in EoE occurs in up to 50% of patients. Reasons for non-responding EoE may be non-adherence to therapy, incorrect dosing, errors in formulation or administration, ongoing allergen or food trigger exposure, inadequate dietary elimination and validity of original diagnosis [50]. In some cases, patients may be refractory to treatment because they have a stricture or a small-caliber esophagus which will likely need a series of dilatation in order to achieve an esophageal diameter that allows reasonable oral intake [30].

Management of refractory EoE consists in first maximizing the initial treatment and then to switch from topical steroids to dietary elimination or vice versa. If there is still no response, alternative treatments could be considered in selected patients including custom topical steroids, elemental formula, a short course of prednisone, immunomodulators, or montelukast. Even if combination therapy with corticosteroids and elimination diet has not been tested in a randomized, prospective manner, combination therapy may be considered as an option [50,52,56].

Conclusion

Pediatric EoE is increasingly becoming such as interesting field of study due to its worldwide diffusion. EoE pathogenesis is not still completely understood therefore further studies need to investigate whether immunological factors, genetics, and possibly the microbiota analysis may add knowledge to this complex multifactorial disease. Diagnosis has to take into account both clinical symptoms, macroscopic, and microscopic esophageal findings; however, the selection of children who need endoscopy still remains challenging for the clinicians. Treatment is helped by allergy

tests (SPT/APT) and encompasses dietary solutions and/or medications such as PPI and steroids. The administration of PPI is conflicting as considered a diagnostic tool in the latest pediatric guidelines and, controversially, a proper treatment in the adult ones given the high-rate of response in EoE patients treated with PPI. Topical steroids are considered the first line of pharmacological treatment with excellent results, oral steroids are, instead, indicated in severe disease or in patients not responding to topical steroids, due to their collateral side effects. Further RCTs will need to clarify whether emerging therapies, especially biologic agents, may be considered useful in a pediatric setting. Refractory EoE is common and usually needs therapy adjustment and reevaluation of patient history and risk factors. Pediatric EoE is a relatively new clinical entity which still needs research to cast light on its causes and pathophysiology in order to clarify and address current unmet needs routinely faced by clinicians in diagnosis and management of the disease.

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Disclosure statement

All authors declare that they have no conflict of interest. The data presented, the statements made, and the views expressed are solely the responsibility of the authors.

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