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## **Understanding of Eosinophilic Esophagitis in Children - A Comprehensive Study on Epidemiology, Clinical Manifestations, Diagnosis and Innovative Treatment Modalities**

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## **Abstract**

### **Introduction:**

In the late 1960s, probable cases of eosinophilic esophagitis (EoE) emerged, initially linked to esophageal rings and congenital causes or gastroesophageal reflux disease (GERD). Doubts about the GERD association arose due to poor responses to antisecretory therapy. EoE is now a significant pediatric health concern, impacting 1 to 7 cases per 10,000 children.

### **Purpose of the Study:**

This study aims to comprehensively explore EoE's epidemiology, etiology, subtypes, clinical manifestations, diagnostic methods, and treatment modalities.

### **Materials and Methods:**

The study employs a cross-sectional analysis of pediatric EoE patients, utilizing endoscopic evaluation and histological assessment. Three distinct EoE subtypes are identified based on pathogenic characteristics. Clinical manifestations, diagnostic methods, and treatments, including endoscopy, are examined.

### **Results:**

Clinical manifestations span a broad spectrum in the pediatric population. Diagnostic methods include endoscopy, esophageal manometry, impedance-pH monitoring, capsule endoscopy, and string tests. Three distinct EoE subtypes are identified with unique characteristics. Treatment modalities involve dietary management, proton pump inhibitors, topical corticosteroids, biologic therapies, allergen immunotherapy, and endoscopic interventions.

### **Conclusion:**

Formerly associated with GERD, EoE is now a significant pediatric health concern. The study underscores the importance of comprehensive diagnostic approaches and diverse treatment modalities, including promising biologic therapies and allergen immunotherapy. Understanding these aspects is crucial for effective management and improved outcomes in patients.

Key words: ***Eosinophilic esophagitis EoE; Pediatric patients; Clinical Manifestations; Diagnostic methods; Treatment methods; Biological therapy.***

## **Epidemiology**

In the late 1960s and early 1970s, there were reports of the first cases of probable eosinophilic esophagitis.<sup>16-18</sup> Initial accounts, primarily from the 1990s, detailed individuals with numerous esophageal rings, which were linked to either a congenital cause or gastroesophageal reflux disease.<sup>16, 19-24</sup> Based on the finding that patients with ringed esophageal biopsies had basal zone hyperplasia, papillary lengthening, and intraepithelial eosinophils (findings that are observed in patients with documented reflux disease) the association with gastroesophageal reflux disease (GERD) was postulated. As many of the patients did not respond to antisecretory therapy or showed objective reflux on a 24-hour pH study, a thorough examination of these reports has cast doubt on the association with GERD.<sup>19, 25</sup> Nowadays, increasingly recognized as a significant pediatric health concern, EoE's prevalence has surged, with estimates ranging from 1 to 7 cases per 10,000 children<sup>1</sup>. Boys are more commonly affected than girls, and the condition often emerges in early childhood or adolescence.<sup>2</sup>

## **Etiology**

Though the precise cause remains elusive, EoE is believed to stem from an immune-mediated response to allergens. Genetic predisposition and environmental factors contribute to an aberrant immune response, resulting in an excessive presence of eosinophils in the esophagus<sup>3, 4</sup>. IgE tests specific to allergens and/or skin prick tests indicate that most patients have evidence of food allergen and aeroallergen sensitization.<sup>26</sup> Seasonality is another common complaint among EoE patients, and wintertime (when outdoor aeroallergen levels are at their lowest) is when fewer cases are diagnosed.<sup>27-29</sup>

## **Subtypes**

Three distinct subtypes of eosinophilic esophagitis have been identified based on pathogenic characteristics. Three distinct endotypes were identified in a cross-sectional study that evaluated adult and pediatric patients with active eosinophilic esophagitis using a diagnostic panel of 96 molecular targets, endoscopic evaluation, and histological assessment. These endotypes each had unique features.<sup>15</sup>

1. The mild subtype EoE1 had a normal-appearing esophagus and mild changes in histology, endoscopy, and molecular testing.
2. EoE2: An inflammatory endotype characterized by a steroid-refractory phenotype, greatest expression of inflammatory cytokines, and genes that respond to steroids.
3. EoE3: This fibrostenotic endotype is linked to a narrow-caliber esophagus and is distinguished by highly severe endoscopic and histological features, as well as low expression of genes involved in epithelial differentiation.

### **Clinical Manifestations**

A broad spectrum of nonspecific symptoms encompassing heartburn, nausea, vomiting, difficulty in feeding, and failure to thrive, can impact the pediatric population. Conversely, dysphagia and instances of food impaction are more prevalent among adolescents and adults. Nevertheless, individuals may manifest comparable symptoms across various age cohorts, such as persistent reflux symptoms.

Over the long term, inconspicuous adaptive behaviors, including deliberate consumption at a slower pace, meticulous chewing, subdivision of food into smaller portions, application of sauces to facilitate lubrication, ingestion of liquids to attenuate food consistency, and avoidance of challenging items such as pills, meats, and breads that are prone to induce dysphagia, may result in the underestimation of symptoms. Patients may develop apprehension associated with dining in public settings due to the perceived difficulty in eating.

Boerhaave's syndrome, an infrequent manifestation of eosinophilic esophagitis, materializes when the esophagus undergoes spontaneous rupture subsequent to vigorous retching following food impaction.<sup>30</sup>

### **Diagnostic Methods**

#### **Endoscopic View**

Endoscopy is pivotal for diagnosing EoE. In the course of endoscopy, it is imperative to procure biopsies from the distal esophagus, along with either the mid or proximal esophagus.<sup>32</sup> The diagnostic efficacy of biopsies in identifying eosinophilic esophagitis is contingent upon the quantity of biopsies acquired. Esophagogastroduodenoscopy (EGD) reveals characteristic findings such as linear

furrows, white plaques, and concentric rings in the esophageal mucosa.<sup>6</sup> Furthermore, a predominant majority of patients exhibit a minimum of 15 eosinophils per high-power field (at peak value) in at least one biopsy specimen.<sup>31</sup> Endoscopic biopsy confirms eosinophilic infiltration, a hallmark of EoE.<sup>7</sup>

On the other hand, it is crucial to note that the presence of esophageal eosinophilia in isolation, devoid of corresponding clinical manifestations, does not suffice for the definitive diagnosis of eosinophilic esophagitis.

### **Esophageal Manometry**

Esophageal manometry assesses muscle contractions, providing insight into motility disorders and esophageal coordination.<sup>9</sup>

### **Impedance-pH Monitoring**

This method evaluates acid exposure and detects non-acid reflux events, offering a comprehensive assessment of esophageal function.<sup>10</sup>

### **Capsule Endoscopy**

While not routine, capsule endoscopy captures images as it passes through the digestive tract, potentially offering a less invasive diagnostic tool for EoE.<sup>11</sup>

### **String Test**

Involving a gelatin capsule attached to a string, this test provides an alternative diagnostic approach by assessing esophageal mucosal changes.<sup>12</sup>

### **Morphological Changes and Eosinophil Levels**

Roughly 50 to 60 percent of individuals diagnosed with eosinophilic esophagitis exhibit heightened serum IgE levels exceeding 114,000 units/L.<sup>33,34</sup> Peripheral eosinophilia is also observed in patients, although it tends to be of a generally mild nature.

### **Serial Biopsies**

Serial biopsies during treatment provide dynamic insights into changes in eosinophil levels, aiding in therapeutic monitoring and assessing treatment efficacy.<sup>13</sup>

## **Treatment Modalities**

### **Dietary Management**

Elimination Diets: The potential for an efficient non-pharmacological treatment is what makes the dietary approach appealing. Removing specific allergens identified through testing can alleviate symptoms.<sup>15</sup> However, eliminating particular irritants and following elemental diets come with a risk of nutrient deficiencies and can be challenging for patients and their families. Cost, convenience, ease of compliance, and patient/family preference are other significant factors that could affect the choice. Furthermore, after quitting the diet, relapses are common.

### **Pharmacotherapy**

#### **Proton Pump Inhibitors (PPIs)**

Proton pump inhibitors (PPIs) represent a primary therapeutic approach, alongside dietary adjustments and topical glucocorticoids.

In the case of patients undergoing PPI treatment, it is recommended to initiate the therapy for a duration of eight weeks. The standard protocol involves commencing with a once-daily full-dose PPI for most patients, and if there is an absence of symptom amelioration after four weeks, escalation to a twice-daily regimen is advised. Alternatively, the initiation of PPI with a twice-daily dose is considered as another dosing regimen.

After an eight-week course of PPI treatment, patients undergo assessment for symptomatic improvement<sup>8</sup>. For those who exhibit a positive response, the PPI therapy should be sustained at the minimum effective dose necessary for symptom control. Some patients, particularly those with a history of food impaction, tight esophageal stricture, or below 18 years of age, routinely undergo upper endoscopy. In contrast, endoscopy is extended to others to ascertain histologic response.

#### **Topical Corticosteroids**

Topical steroids can help control inflammation in the esophagus.<sup>13</sup> Fluticasone and budesonide stand out as the most extensively researched topical glucocorticoids within the literature.



Fluticasone propionate is administered through a metered dose inhaler by spraying into the patient's mouth, with subsequent ingestion. The optimal dosage remains undetermined. The standard approach to fluticasone propionate induction dosing is contingent upon the patient's age:<sup>30,35</sup>

- Children aged 1 to 11 years: 110 mcg/spray, administered in eight sprays daily, distributed across multiple doses. Patients are instructed to divide the total daily dose into two to four intervals.
- Children aged 12 years and older, as well as adolescents: 220 mcg/spray, administered in eight sprays daily, divided across multiple doses. Similar to younger children, patients are advised to distribute the total daily dose into two to four intervals.

Generally well-tolerated, fluticasone propionate treatment tends to elicit a prompt response in responsive patients, often within one to two days and certainly within one week.<sup>36</sup> It is noteworthy, however, that symptom improvement does not consistently align with the resolution of esophageal eosinophilia.

Fluticasone induction therapy spans four to eight weeks, followed by an evaluation of symptomatic response, particularly regarding dysphagia.<sup>8</sup> For responsive patients, repeat upper endoscopy is routinely conducted, especially for those with a history of food impaction, tight esophageal stricture, or below 18 years of age. In contrast, endoscopy is offered to other patients to ascertain histologic response.

### **Biologic Therapies**

**Anti-IL-5 Agents:** Monoclonal antibodies targeting IL-5, such as reslizumab, have shown efficacy in reducing eosinophilic infiltration and alleviating symptoms, marking a significant step forward in personalized treatment options.<sup>14</sup>

**Anti-IL-4/IL-13 Agents:** Dupilumab, targeting IL-4 and IL-13, is under investigation for EoE.

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### **Study on Dupilumab:**

Subcutaneous dupilumab was administered every two weeks to seven patients diagnosed with Eosinophilic Esophagitis (EoE), primarily presenting with asthma and/or Atopic Dermatitis (AD). At the commencement of dupilumab treatment, the median age was 15.8 years (interquartile range (IQR) 9.3–19.5 years), with 71%

being male. The median duration of EoE for these patients was 2.7 years (IQR 1.8–5.3 years). Prior to initiating dupilumab, all patients had undergone other EoE therapies, such as proton pump inhibitors (6 out of 7 patients), one or more swallowed topical corticosteroids (STCs) (7 out of 7), and dietary restrictions (6 out of 7). One patient had previously undergone four esophageal dilations alongside pharmacologic and dietary interventions. None of the patients had achieved healing (<15 eosinophils per high-power field) with previous treatments.

Before starting dupilumab, the median peak esophageal eosinophil count was 50 eosinophils per high-power field (IQR 48–95 eos/hpf). The most recent esophagogastroduodenoscopy (EGD) completed while on STCs or dietary restrictions revealed edema (4 out of 6 patients), rings (1 out of 6 patients), exudates (3 out of 6 patients), furrows (3 out of 6 patients), and strictures (1 out of 6 patients). At the follow-up EGD conducted after dupilumab initiation, the median peak esophageal eosinophil count was reduced to 2 eosinophils per high-power field (IQR 0–5 eos/hpf). Edema and exudate were observed in two patients, while no rings, furrows, or strictures were documented in any of the seven patients. The follow-up EGD took place a median of 5.3 months (IQR 4.6–9.8) after initiating dupilumab, during which all patients had discontinued STCs, and four of them had reintroduced one or more food groups into their diet. <sup>37</sup>

#### Patient demographics and characteristics

Patient no.	Gender	Dupilumab primary indication	Age at dupilumab initiation (y)	Previous therapies trialed	Predupilumab peak eos/hpf	Postdupilumab peak eos/hpf	Predupilumab endoscopic score (EREFS)	Postdupilumab endoscopic score (EREFS)
1	Male	Asthma	15.8	EoE: dietary restrictions, PPI, budesonide, fluticasone, mometasone	50	9	1 (1,0,0,0,0)	0

				e Asthma: Fluticasone/ salmeterol				
<b>2</b>	Fem ale	Asthma	18.7	EoE: Dietary restrictions, PPI, fluticasone, mometason e Asthma: Fluticasone	100	5	3 (1,0,1,1,0)	2 (1,0,1,0,0)
<b>3</b>	Male	Asthma	25.4	EoE: Dietary restrictions, elemental formula, PPI, budesonide, mometason e, esophageal dilations × 4 Asthma: Fluticasone/ salmeterol, budesonide /formoterol	>200	0	7 (1,2)	0
<b>4</b>	Male	Asthma, AD	9.5	EoE: PPI, mometason e	90	4	0	0

				Asthma: Fluticasone AD: Halobetasol 0.05%, tacrolimus 0.1%				
5	Female	Asthma	20.2	EoE: Dietary restrictions, PPI, mometasone Asthma: Budesonide/formoterol	33	1	1 (0,0,1,0,0)	0
6	Male	Asthma, AD	6.9	EoE: Dietary restrictions, elemental formula, PPI, mometasone, fluticasone Asthma: Fluticasone/salmeterol, budesonide, montelukast AD: hydrocortis	45	0	2 (1,0,0,1,0)	0

				one 2.5%				
7	Male	Asthma, 9.0 AD		EoE: Dietary restrictions, budesonide Asthma: Fluticasone AD: triamcinolone 0.1%, crisaborole, desonide	50	2	Not available	2 (1,0,1,0,0)

Patient no.	Conditions postdupilumab EGD	of Change in symptoms on dupilumab
1	Off STC and dairy reintroduction × 2 months	EoE: Dysphagia resolved, milk reintroduced Asthma: ICS discontinued
2	Off × 4 months	STC EoE: Dysphagia and food impactions resolved (previously daily dysphagia, impactions every 2 months) Asthma: no exacerbations (previously daily symptoms, frequent exacerbations)

3	Off × 9 months	STC	EoE: Dysphagia improved, no further dilations, multiple foods reintroduced. Asthma: Albuterol use decreased from 2-3×/week to <1×/month, ICS discontinued
4	Off × 2 months	STC	EoE: Heartburn improved Asthma: ICS weaned from daily to seasonal use, no albuterol use AD: fewer flares
5	Off STC and dairy reintroduction × 5 months		EoE: Dysphagia improved Asthma: Fewer exacerbations on ICS
6	Off × 18 months Dairy reintroduction × 2 months Egg reintroduction × 1 month	STC	EoE: Dysphagia, poor appetite, and abdominal pain resolved. Multiple foods reintroduced Asthma: No exacerbations, ICS dose decreased AD: No further flares
7	Off dairy and soy reintroduction × 19 months	STC,	EoE: Improved appetite and weight gain, dietary restrictions stopped. Asthma: ICS weaned to winter use only AD: Topical therapies discontinued

AD = atopic dermatitis; Eos/hpf = eosinophils per high-powered field; EREFS = edema grade 0–1, rings grade 0–3, exudate grade 0–2, furrows grade 0–2, stenosis grade 0–1; ICS = inhaled corticosteroid; PPI = proton pump inhibitor; STC = swallowed topical corticosteroid.<sup>37</sup>

This study identified seven pediatric and young adult patients with atopic conditions and Eosinophilic Esophagitis (EoE), all of whom exhibited histologic improvement in their EoE and positive responses in their asthma or Atopic Dermatitis (AD) following dupilumab treatment. Notably, these patients had previously shown resistance to swallowed topical corticosteroids (STCs), and many presented with relatively severe EoE phenotypes. This suggests promise for dupilumab as a potentially effective treatment approach for challenging-to-treat EoE cases.<sup>37</sup>

### **Allergen Immunotherapy**

Oral Immunotherapy (OIT): Desensitizing the immune system to specific allergens may be a promising avenue for EoE treatment.<sup>18</sup>

### **Endoscopic Interventions**

Dilation: In cases of severe strictures, esophageal dilation can be performed during endoscopy.<sup>13</sup>

Esophageal Stents: Temporary placement of stents may be considered for refractory strictures.<sup>16</sup>

### **Conclusions**

In conclusion, eosinophilic esophagitis in children poses a significant and growing health concern, necessitating a thorough understanding of its diverse facets. The surge in prevalence underscores the importance of continuous research and clinical exploration. The distinct subtypes identified shed light on the heterogeneity of EoE, paving the way for targeted and personalized treatment approaches. The broad spectrum of clinical manifestations emphasizes the need for a nuanced diagnostic process, incorporating various methods to ensure accurate identification. Treatment modalities, ranging from dietary management to cutting-edge biologic therapies, offer a spectrum of options, recognizing the complex nature of this disorder.

As our understanding of EoE continues to evolve, future research should focus on refining diagnostic criteria, exploring novel treatment avenues, and unraveling the intricate interplay of genetic and environmental factors. Collaborative efforts between clinicians, researchers, and families affected by EoE will be pivotal in

advancing knowledge and improving the quality of life for children grappling with this chronic inflammatory disorder.

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