Eosinophilic Esophagitis in Children: Clinical Findings and Diagnostic Approach

Arianna De Matteis¹, Giuseppe Pagliaro², Vito Domenico Corleto³, Claudia Pacchiarotti⁴, Emilio Di Giulio³, Maria Pia Villa⁴, Pasquale Parisi⁴, Francesca Vassallo⁴, Chiara Ziparo⁴ and Giovanni Di Nardo⁴,*

¹Department of Translational Medical Science, Section of Pediatrics, University Federico II, Naples, Italy; ²Pediatric Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy; ³Endoscopy Unit, Sant’Andrea University Hospital, Sapienza - University of Rome, Rome, Italy; ⁴NESMOS Department, School of Medicine & Psychology, Sapienza - University of Rome, Sant’Andrea University Hospital, Rome, Italy

Abstract: Eosinophilic esophagitis (EoE) is an emerging chronic immune and antigen-mediated clinicopathologic disease. During the last 2 decades, the incidence of this condition in children has increased significantly, thanks to practitioners for creating the awareness and higher use of diagnostic endoscopy. We have analysed paediatric literature on EoE focusing on the epidemiology, pathophysiology, clinical findings and diagnostic approach.

EoE is pathogenically related to a Th2 inflammation characterized by a mixed IgE and non-IgE-mediated reaction to food and/or environmental agents. This leads to esophageal dysfunction and remodeling accompanied by subepithelial fibrosis. EoE can be presented with several range of gastrointestinal symptoms, including regurgitation, vomiting, feeding difficulties or feeding refusal in infants and toddlers, as well as heartburn, dysphagia and food bolus impaction in older children and adults. The diagnostic suspicion is based on the presence of chronic symptoms of esophageal dysfunction and esophageal eosinophilia characterised histologically by a significant eosinophilic infiltration of the esophageal mucosa (>15 eosinophils per high powered field). In this review, we will provide an update on clinical presentation and diagnostic approach to EoE in children. We emphasized on the relevant aspects of the new clinical condition termed “PPI responsive esophageal eosinophilia”, as entities distinct from EoE and the role of PPI trial in the diagnostic workup, therefore we proposed a new diagnostic algorithm.

Keywords: EoE, gastroesophageal reflux disease, proton pump inhibitors, subepithelial fibrosis, dysphagia, gastrointestinal.

1. INTRODUCTION

Eosinophilic esophagitis (EoE) is an emerging chronic immune and antigen-mediated clinicopathologic disease, affecting both children and adults. This condition is characterized by severe eosinophil-predominant inflammation into the esophageal epithelium resulting in esophageal dysfunction. EoE was first described as a disease entity in 1995 by Kelly et al. [1]. Over the last decade, EoE has become increasingly recognized with an incidence considered to be similar to that of Chron’s disease [2]. In 2007, a multidisciplinary group of experts published the first consensus guidelines on the diagnosis and treatment of EoE [3], which was updated in 2011 [4] and recently revised in 2017 [5].

Here, we will revise new insights on clinical presentation and diagnostic approaches to EoE in children. Specifically the increasing incidence, the new clinical conditions (such as PPI responsive esophageal eosinophilia) and the revaluation of the role of PPI in the diagnostic workup, will be addressed.

2. EPIDEMIOLOGY

In recent years, the incidence and prevalence of eosinophilic esophagitis (EoE) in children and adults, have increased significantly [6]. A recent systematic review showed that population-based prevalence of EoE in children is 19.1 cases per 100.000 children/year [7], with a wide geographic variation from 2.3 in Denmark [8] to 50.5 per 100.000 children in the United States [9]. Likewise, the population-based incidence varies among the Westernised countries, with over-all incidence rate estimates of 5.1 per 100.000 children/year [7]. Possible biases of these variations may depend
on the studied population, study design and diagnostic criteria for EoE. Population-based data on the epidemiology of EoE in developing countries are scarce. There is a predominance of EoE among male patients [7, 9-11] with a male to female ratio of 3:1 in both children and adults [4]. The increasing of incidence and prevalence, during the last few decades, may be explained with improved recognition of EoE, more awareness of practitioners and higher use of diagnostic esophagogastroduodenoscopy (EGDS) with biopsies in children. Data showing that increasing incidence closely matches the increase in endoscopy volume and biopsies rates supported this hypothesis [12, 13]. Further factors may affect the increasing frequency of EoE such as a change in food allergens, increasing aeroallergens and other environmental factors, the decrease of H. pylori and microbiome changes [10].

3. PATHOPHYSIOLOGY

In the last years, there has been a rapid advancement in understanding the mechanisms involved in EoE generally attributed to an interplay between genetic, immunologic and environmental factors [14]. EoE is now considered as a chronic atopic disorder, histologically characterized by a dense epithelial eosinophilic infiltrate. Pathogenically related to a Th2 inflammation characterized by a mixed IgE and non-IgE-mediated reaction to food and/or environmental agents, which is driven [15, 16] by Thymic Stromal Lymphopoietin (TSLP) secreted by esophageal epithelial cells under the influence of genetic predisposition [17].

The role of TSLP as a strong inducer of a Th2 response is well-known and it has been linked to atopic diseases [18, 19]. TSLP is similar to IL-7 and regulates host adaptive immune responses through dendritic cells and T-cell interactions. Rothenberg et al. found an association between a single nuclear polymorphism (SNP) in the gene encoding TSLP and the risk for EoE [17]. In addition, Sherill et al. identified a significant association between an SNP located in the TSLP receptor and male EoE patients [20]. Another identified risk factor linked to EoE is a polymorphism in eotaxin-3 that is a chemokine and a potent eosinophil and mast cell chemoattractant [21]. The most recently described is an SNP located in the proximity of CAPN 14, a gene specifically expressed in esophagus and upregulated by Th2 cytokines [22]. However, a recent study, focusing on the risk of developing EoE in monzygotic and dizygotic twins, suggests a minor genetic contribution in favor of more relevant environmental factors [23].

Environmental exposures such as birth by cesarean section, premature delivery, antibiotic exposure during infancy, food allergy, lack of breastfeeding, lack of early exposure to microbes and altered microbiome can create an epigenetic signature that may increase the risk for EoE onset [24-26].

In most patients, food has been identified as a trigger of EoE inflammation with non-IgE-mediated mechanism [27, 28] and his role is supported by the response to dietary elimination of food antigens and relapse with the reintroduction of similar food antigens [29, 30]. However, the role of aeroallergens still remains unclear.

Most studies have shown that EoE inflammation has the typical characteristics of Th2 atopic inflammation. Esophageal biopsies and blood samples of patients with active EoE, have high levels of Th2 prototypical cytokines and chemokines such as interleukin IL-5, IL-4, IL-13, IL-5, TSLP, eotaxin-3 secreted by the typical cells involved in allergic inflammation: mast cells, T cells, basophils, invariant natural killer T cells (iNKTs) [4, 31-33].

Eosinophils are pathognomonic of EoE inflammation in the absence of GERD and although they represent the histologic mark of the disease [4], do not guarantee the EoE pathogenesis being most likely a consequence of the local Th2 inflammation. Recent clinical trials with antibodies against IL-5, which is the most important eosinophils growth factor, have shown a partial reduction of esophageal inflammation, and minimal symptomatic relief in patients with EoE [34, 35].

Finally, the esophageal epithelium plays a major role in EoE by promoting a local Th2 inflammation. As for atopic dermatitis, EoE patients have an altered epithelial barrier function [36], and a down-regulation of proteins associated with barrier function (filaggrin and zonulin-1) [37] and adhesion molecules (desmoglein-1) [4], that favors antigen penetration and sensitization. Altered epithelial permeability can lead to a permissive environment that enhances antigen presentation, which in turn leads to recruitments of eosinophils and pro-inflammatory cytokines [38, 39].

The major long-term consequence of chronic inflammation in EoE is esophageal remodeling followed by the development of irreversible structures. Aeces et al [40] observed basal thickening and increased vascular activation in untreated patients with EoE, associated with high levels of TGF-β 1 that stimulates myofibroblast differentiation and extracellular matrix remodeling [41, 42].

4. CLINICAL FINDINGS

Eosinophilic esophagitis (EoE) can affect individuals at any age and clinical presentation depends on the patient’s abilities to report symptoms associated with esophageal dysfunction [43-45]. Symptoms can be present for a long time (mean of 3-5 years) before reaching a diagnosis of EoE, especially if the disease appears progressively [46].

In pediatric population, vomiting, abdominal pain, dysphagia and bolus impaction are the most prevalent symptoms (Table 1) [43, 44, 47-65].

Clinical features of EoE are also different based on the age of children (Table 2). In toddlers and infants, the most frequent symptoms are feeding difficulties and failure to thrive (median age 2.8 years); vomiting and sleeping disturbance are also described. In EoE, vomit rarely appears before 6 months of life; it’s sporadic and not associated with meals, as in the case of food protein-induced enterocolitis or IgE-mediated food allergy [66]. School-aged children are present with nausea, vomiting, regurgitation and abdominal pain. In a study that included 43 patients with EoE [67], 100% of children under 7 years presented these symptoms. Abdominal pain in this age is mainly epigastric [66].
## Table 1. Symptoms and signs of EoE in children.

| Study (Number of Patients) [ref.] | Food Impaction | Abdominal Pain | Dysphagia | Chest Pain | Heartburn | Vomiting |
|----------------------------------|---------------|---------------|-----------|------------|-----------|----------|
| Mansoor E. et al., 2016 (1250) [48] | 48%           | -             | 29,6%     | 8,8%       | 4%        | 16%      |
| Fahey L. et al., 2017 (36) [49]  | 13,8%         | 30,5%         | 16,6%     | -          | -         | 30,5%    |
| Assa’ad et al., 2007 (89) [50]   | 6,7%          | 24,7%         | 15,7%     | 6,7%       | 21,3%     | 59,5%    |
| Gill R et al., 2007 (44) [51]    | -             | 55%           | -         | -          | 39%       | 43%      |
| Weiler T et al., 2014 (50) [52]  | -             | 40%           | 22%       | -          | -         | 74%      |
| Kubik et al., 2017 (251) [53]    | -             | 57%           | 43%       | -          | -         | 49%      |
| Bohm et al., 2017 (58) [54]      | 3%            | 53%           | 33%       | 2%         | 19%       | 24%      |
| Vigier et al., 2017 (28) [55]    | 46%           | 11%           | 32%       | -          | 21%       | 42%      |
| Homan et al., 2015 (30) [56]     | -             | 19%           | 33%       | -          | -         | 43%      |
| Prasad GA et al., 2009 (23) [44] | 21,7%         | 30,4%         | 60,9%     | -          | 17,4%     | 43,5%    |
| Gomez Torrijos et al., 2017 (35) [58] | 20%       | 31%           | 51%       | 8,5%       | 6%        | 20%      |
| Alves Marcelino et al., 2018 (25) [57] | 52%       | -             | 56%       | -          | 40%       | 32%      |
| Sun MF et al., 2017 (22) [59]    | -             | 41%           | -         | -          | -         | 45%      |
| La Orden Izquierdo et al., 2018 (254) [60] | 22%       | -             | 23,6%     | -          | -         | -        |
| Saeed et al., 2018 (37) [61]     | 21,6%         | -             | 56,7%     | -          | -         | 48,6%    |
| Rodrigues et al., 2013 (43) [62] | 28%           | 58%           | -         | -          | 30%       | 53,5%    |
| Rezende ER et al., 2014 (35) [63] | 11,4%         | 51,4%         | 28,5%     | -          | -         | 71,4%    |
| Kapel et al., 2008. (42) [43]    | -             | 31%           | 26,2%     | 4,8%       | -         | -        |
| Hoofien A et al., 2018 (410) [64] | 24,4%         | 9%            | 38%       | 9,2%       | 9%        | 14,3%    |
| Romano C et al., 2014 (23) [65]  | 43%           | 35%           | 65%       | 22%        | -         | 43%      |

## Table 2. Main symptoms of EoE based on age (revisited by Carr et al. 2019).

| Infant/Toddlers | Children | Adolescent/Adults |
|-----------------|----------|-------------------|
| Failure to thrive | Dysphagia | Dysphagia |
| Food refusal | Food impaction | Food impactions |
| Vomiting | Choking/gagging with meals | Food avoidance |
| Choking with meals | Abdominal/chest pain | Intractable heartburn |
| Sleep disturbance | Throat pain | Regurgitation |
| - | Vomiting/regurgitation | Retrosternal pain |
| - | Nausea | Chest pain |
| - | Sleep disturbance | - |
| - | Decrease appetite | - |

Mainly in infants, toddlers or young children EoE can be present with GERD like symptoms, such as heartburn, regurgitation and vomiting. As demonstrated in some studies [68, 69], there are cases of PPI refractory GERD that underwent fundoplication without clinical improvement, some of these patients receive a post-operative diagnosis of EoE. The misdiagnosis of EoE in GERD like symptoms patients can be related to the lack of routine esophageal biopsies as part of the standard preoperative evaluation before anti-reflux surgery.
In adolescents, the most common symptoms are dysphagia, heartburn, food impaction and chest pain. The prevalence of EoE among EGDS performed in children with esophageal food impaction and/or dysphagia is high (63-88%) [70-72], so children with these presenting symptoms should be rapidly tested with EGDS and multiple esophageal biopsies. A study [43] evidenced an increasing prevalence of EoE in patients with dysphagia; moreover, they were more likely to have higher eosinophils peak mucosal counts. Furthermore, the incidence of EoE in patients having these symptoms is probably underestimated, because biopsies are not always performed. Food impaction is a gastrointestinal emergency, requiring endoscopic intervention to remove the impacted food: considering the close link with EoE biopsies during endoscopic disimpaction are recommended. Food impaction is often associated with acute severe retrosternal or chest pain. When symptoms do not respond to medical treatments for GERD, EoE should be strongly considered [69]. Chest pain, which is spasmodyc, can be severe enough to lead patients to seek emergency evaluation and lead to cardiac evaluation [66]. Dysphagia in children is not always related to esophageal anatomical damage, but also it can be related to secondary esophageal dysmotility [43].

It is important to realize that children may develop long-term coping strategies to avoid symptoms, including taking small bites, eating slowly with excessive chewing, and drinking fluids after each bite [66]. The patients may also avoid certain kinds of food due to their not easy swallowing.

Children with EoE have a higher rate of atopy compared with normal children. The rates of asthma, allergic rhinitis and atopic dermatitis are approximately three times higher than the general population [73, 74].

Adolescents with EoE may be misdiagnosed as having eating disorders, because of symptoms of food-related anxiety, vomiting and food aversion.

EoE should be considered also in children with chest pain and cough that does not respond to aggressive asthma treatment [66].

Given the variability of the symptom patterns in EoE patients, the measurement of disease activity based on clinical symptoms remains a challenging task. As several clinical trials showed, there is a poor correlation between histological abnormalities and symptoms [75, 76]. A possible explanation for this discrepancy might be that symptoms can be caused not only by esophageal inflammation but also by fibrotic changes in esophageal motility even in the absence of inflammation, or even by psychological factors [77].

5. DIAGNOSIS

EoE diagnosis is difficult because clinical symptoms are variable and sometimes unspecific and the presence of esophageal eosinophilia can be found in several diseases.

The new diagnostic criteria for EoE are the result of the collaboration between paediatrics, gastroenterologists, allergo-immunologists and pathologists in order to identify clinical and histological characteristics useful for having a clinical suspicion associated with supports elements to confirm the diagnosis.

Guidelines of 2017 and recent updates on EoE showed that diagnostic suspicion is based on the presence of chronic symptoms of esophageal dysfunction and esophageal eosinophilia [5]. The absence of symptoms even in the presence of esophageal eosinophilia does not allow the diagnosis of EoE [78].

Accurate anamnesis can be useful for making the diagnosis of EoE: in addition to clinical symptoms and esophageal eosinophilia recently, independent predictors of EoE have been identified in order to distinguish it from other diseases, first of all, GERD.

The early age of onset of symptoms is more suggestive of EoE [79]. Up to 75% of patients with EoE have a personal or family history of atopic disease (asthma, eczema, allergic rhinitis or food allergies) [80].

Testing for allergic sensitization may be considered: skin prick test, blood testing for allergen-specific IgE or atopy patch testing are useful for making the diagnosis of allergy but they cannot identify EoE trigger and their positive predicted value remains poor [81].

If the clinical evaluation is suggestive for EoE, EGDS with biopsies examination has to be made. At least six biopsies should be taken from different esophageal segments, focusing on areas with endoscopic mucosal abnormalities [5]: a study demonstrated that six biopsies increase diagnostic sensitivity to 99% [82]. Hematoxilin-eosin staining is sufficient for histological assessment. The principal diagnostic element for the diagnosis of EoE is the presence of at least 15 eosinophils per high power field. Although GERD can increase eosinophilic infiltration in the distal esophagus, eosinophils associated with GERD generally occur at a lower density. Additional histological features consistently associated with EoE may include eosinophilic microabscesses (32-64,8% - defined as aggregates of four or more eosinophils in a cluster), basal zone hyperplasia (35-86,4% - more severe in patients with EoE than in those with GERD), dilated intercellular spaces, eosinophil surface layering and papillary elongation (75,6%) [3, 51, 58, 61, 83].

Endoscopy in EoE can be macroscopically normal, with a range from 4 to 23% [57, 58 61]. There are also some endoscopic characteristics associated with the diagnosis of EoE in order to support the diagnosis of EoE. In adults, their sensitivity range from 50% to 90% while in the pediatric population, it is not known. These findings include: fixed rings(6%) (Fig. 1), exudates(28,5%), furrows(21,6-80%) (Fig. 2), edema(26%)and mucosal alterations (Fig. 3).The presence of strictures in children is rare and less common than in adults. The alterations can be quantified using the EoE Endoscopic Reference Score (ERFES) [84] (Table 3).

In the case of esophageal eosinophilia, clinical evaluation and endoscopy allow to distinguish EoE from other diseases (Table 4). The diagnosis of EoE is confirmed if there are no other conditions that justify clinical symptoms and esophageal eosinophilia.
GERD is the main disease to consider differential diagnosis with EoE. They often have similar symptoms, and both clinic and endoscopic findings have the low sensibility and specificity [78]: they were felt to be mutually exclusive disorders where a response to PPI/pathologic pH exposure was consistent with GERD and non-response/normal pH confirmed EoE [84]. Nowadays, without a definitive method for defining GERD, no single test (including PPI trial) can exclude the presence of GERD.

**CONCLUSION**

Multiple prospective and retrospective studies found that esophageal eosinophilia (≥ 15 eos/HPF) in patients with symptoms and endoscopic sign suggestive of EoE responded to PPI therapy both in adults and children at a rate of 28-82% [78]. From 2011, diagnostic guidelines defined a new

| Findings                                    | Grade 0 | Grade 1                  | Grade 2                                      | Grade 3                                      |
|---------------------------------------------|---------|--------------------------|----------------------------------------------|----------------------------------------------|
| Major findings                              |         |                         |                                              |                                              |
| Fixed rings (concentric rings, trachealisation) | None    | Mild (subtle circumferential ridges) | Moderate (distinct rings that not impair passage of standard diagnostic endoscope) | Severe (distinct rings that do not permit passage of a diagnostic endoscope) |
| Exudates (plaques)                          | None    | Mild (lesion involving <10% of the esophageal surface area) | Severe (lesion involving >10% of the esophageal surface area) | - |
| Furrows (vertical lines)                    | Absent  | Present                  | -                                            | -                                            |
| Oedema (mucosal pallor)                     | Absent  | Present                  | -                                            | -                                            |
| Stricture                                   | Abset   | Present                  | -                                            | -                                            |
| Minor findings                              |         |                         |                                              |                                              |
| Crepe paper esophagus (mucosal fragility or laceration upon passage of diagnostic endoscope) | Absent  | Present                  | -                                            | -                                            |
Table 4. Condition associated with esophageal eosinophilia (revisited by Dellon 2018).

- Eosinophilic esophagitis
- Eosinophilic gastritis, gastroenteritis or colitis with esophageal involvement
- GERD
- Achalasia and other disorder of esophageal dysmotility
- Hyperesinophilic syndrome
- Crohn’s disease
- Infections (fungal, viral)
- Connective tissue disorders
- Hypermobility syndromes
- Autoimmune disorders
- Dermatologic condition with esophageal involvement
- Drug hypersensitivity reactions
- Pill esophagitis
- GVHD
- Mendelian disorders

Fig. (4). Diagnostic algorithm for diagnosis of EoE. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

condition termed PPI-responsive esophageal eosinophilia (PPI-REE) [4]. It is a debate if PPI-REE represents a subtype of EoE or GERD, but the latest updates tend to consider it a pattern of EoE. At baseline (prior to a PPI trial) patients with EoE and PPI-REE have similar clinical, endoscopic and histologic features [85, 86], in addition, RNA expression profiles were largely similar between EoE and PPI-REE but distinct from GERD [84]. Finally, patients with PPI-REE can also have a response to dietary elimination or topical steroid therapy.

The complex relationship between GERD and EoE and the identification of PPI-REE questioning the role of PPI trial for diagnosis of EoE, even if PPI trial potentially reduces the number of endoscopies required, helps concomitant GERD and provides a stepwise approach for EoE diagnosis [78]. Most recently, the response of esophageal eosinophilia to PPI has been defined as a treatment option for EoE rather than an exclusion criterion: therefore, we proposed a new diagnostic algorithm (Fig. 4).

**LIST OF ABBREVIATIONS**

| Abbreviation | Description |
|--------------|-------------|
| CAPN14       | Calcium-Activated Neutral Proteinase 14 |
| EGDS         | Esophagogastroduodenoscopy |
EoE = Eosinophilic Esophagitis
EREFS = Endoscopic Reference Score
GERD = Gastro-Esophageal Reflux Disease
HPF = High-Power Field
H. pylori = Helicobacter pylori
iNKTs = invariant Natural Killer T Cells
PPI = Proton Pump Inhibitor
PPI-REE = PPI-Responsive Esophageal Eosinophilia
SNP = Single Nuclear Polymorphism
TGFβ-1 = Transforming Growth Factor-β 1
Th2 = T helper 2
TSLP = Thimic Stromal Lymphopoietin

CONSENT FOR PUBLICATION
Not applicable.

FUNDING
None.

CONFLICT OF INTEREST
The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS
Declared none.

REFERENCES
[1] Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology 1995; 109(5): 1503-12. http://dx.doi.org/10.1016/0016-5085(95)90637-1 PMID: 7557132

[2] Dellon ES. Eosinophilic esophagitis. Gastroenterol Clin North Am 2013; 42(1): 133-53. http://dx.doi.org/10.1016/j.gct.2012.11.008

[3] Furuta GT, Lia courteous CA, Collins MH, et al. First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Sub-committees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology. 2013; 145(4): 1342-63.

[4] Lia courteous CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults J Allergy Clin Immunol 2011; 128(1): 3-20.

[5] Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017; 5(3): 335-58. http://dx.doi.org/10.1177/2050620616689525

[6] Dellon ES, Hirano I. Epidemiology and Natural History of Eosinophilic Esophagitis. Gastroenterology 2018; 154(2): 319-32. http://dx.doi.org/10.1053/j.gastro.2017.06.067

[7] Arias A, Pérez-Martínez I, Tenias JM, Lucendo AJ. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther 2016; 43(1): 3-15. http://dx.doi.org/10.1111/apt.13441

[8] Dalby K, Nielsen RG, Kruse-Andersen S, et al. Eosinophilic oesophagitis in infants and children in the region of southern Denmark: a prospective study of prevalence and clinical presentation. J Pediatr Gastroenterol Nutr 2010; 51(3): 280-2.

http://dx.doi.org/10.1097/MPG.0b013e3181d1b107 PMID: 20512060

[9] Soon IS, Butzner JD, Kaplan GG, de Bruyn JC. Incidence and prevalence of eosinophilic esophagitis in children J Pediatr Gastroenterol Nutr 2013; 57(1): 72-80.

[10] Dellon ES, Jensen ET, Martin CF, Shahseen NJ, Kappelman MD. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol 2014; 12(4): 589-96.e1. http://dx.doi.org/10.1016/j.cgh.2013.09.008 PMID: 24035773

[11] Franciosi JP, Tam V, Lia courteous CA, Spigel JM. A case-control study of sociodemographic and geographic characteristics of 335 children with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2009; 7(4): 415-9. http://dx.doi.org/10.1016/j.cgh.2008.10.006 PMID: 19118642

[12] Syed AA, Andrews CN, Shaffer E, Urbanski SJ, Beck P, Storr M. The rising incidence of eosinophilic oesophagitis is associated with increasing biopsy rates: a population-based study. Aliment Pharmacol Ther 2012; 36(10): 986-98. http://dx.doi.org/10.1111/apt.12053 PMID: 22994460

[13] Vanderheyden AD, Petras RE, De Young BR, Mitros FA. Emerging eosinophilic (allergic) esophagitis: increased incidence or increased recognition? Arch Pathol Lab Med 2007; 131(5): 777-9. [PMID: 17483165

[14] D’Alessandro A, Esposito D, Pesse M, Cuomo R, De Palma GD, Sarnelli G. Eosinophilic esophagitis: From pathophysiology to treatment World J Gastrointest Pathophysiol 2015; 15(6):150-8.

[15] Inage E, Furuta GT, Menard-Katcher C, Masteron JCS. Eosinophilic esophagitis: pathophysiology and its clinical implications. Am J Physiol Gastrointest Liver Physiol 2018; 315(5): G879-86. http://dx.doi.org/10.1152/ajpgi.00174.2018 PMID: 30212252

[16] Cianferoni A. Wheat allergy: diagnosis and management. J Asthma Allergy, 2016; 29: 13-25.

[17] Rothenberg ME, Spiegel JM, Sherrill JD, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. Nat Genet 2010; 42(4): 289-91. http://dx.doi.org/10.1038/ng.547 PMID: 20208534

[18] Li M, Hener P, Zhang Z, Ganti KP, Metzger D, Chambon P. Induction of thymic stromal lymphopoietin expression in keratinocytes is necessary for generating an apoptotic dermatitis upon application of the active vitamin D3 analogue MC903 on mouse skin. J Invest Dermatol 2009; 129(2): 498-502. http://dx.doi.org/10.1038/jid.2008.232 PMID: 18650845

[19] Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. Nat Immunol 2002; 3(7): 673-80. http://dx.doi.org/10.1038/ni805 PMID: 12055625

[20] Sherrill JD, Gao PS, Stucke EM, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. J Allergy Clin Immunol 2010; 126(1): 160-5.e3. http://dx.doi.org/10.1016/j.jaci.2010.04.037 PMID: 20620568

[21] Blanchard C, Wang N, Stringer KE, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. J Clin Invest 2006; 116(2): 536-47. http://dx.doi.org/10.1172/JCI26679 PMID: 16453027

[22] Sleiman PM, Wang ML, Cianferoni A, et al. GWAS identifies four novel eosinophilic esophagitis loci. Nat Commun 2014; 5: 5593. http://dx.doi.org/10.1038/ncomms5593 PMID: 25407941

[23] Alexander ES, Martin LJ, Collins MH, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. J Allergy Clin Immunol 2014; 134(5): 1084-1092.e1. http://dx.doi.org/10.1016/j.jaci.2014.07.021 PMID: 25258143

[24] Jensen ET, Hoffman K, Shaeseen NJ, Genta RM, Dellon ES. Eosophageal eosinophilia is increased in rural areas with low population density: results from a national pathology database. Am J Gastroenterol 2014; 109(5): 668-75. http://dx.doi.org/10.1038/ajg.2014.47 PMID: 24667575

[25] Jensen ET, Kappelman MD, Kim HP, Ringel-Kulka T, Dellon ES. Early life exposures as risk factors for pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2013; 57(1): 67-71. http://dx.doi.org/10.1097/MPG.0b013e318290d15a PMID: 23518485

[26] van Nimwegen FA, Penders J, Stobberingh EE, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy J Allergy Clin Immunol 128(5): 948-55.2011;
Mulder DJ, Lobo D, Mak N, Justinich CJ. Expression of toll-like receptors and chemokines in healthy and inflamed mucosa: probing the role of eosinophils in the digestive tract. Inflamm Bowel Dis 2005; 11(8): 720-6.

Lior D, Narasimhan S, Michaylira CZ, Wang ML. TLR3-mediated NF-κB activation in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2014; 12(11): 1824-9.e1.

Kagawalla AF, Shah A, Li BU, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. J Pediatr Gastroenterol Nutr 2011; 53(2): 145-9.

Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental gastrointestinal diets in children and adolescents. J Allergy Clin Immunol 2012; 129(2): 456-63.

Assaad AH, Putnam PE, Collins MH, et al. A striking difference in the prevalence of eosinophilic esophagitis between children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol 2012; 129(2): 1815-23.e2.

Katzka DA, Tadi R, Smyrk TC, et al. Effects of topical steroids on tight junction proteins and spongiosis in esophageal epithelia of patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2014; 12(11): 1824-9.e1.

Lim DM, Narasimhan S, Muthiyula CŽ, Wang ML. TLR3-mediated NF-κB activation in human esophageal epithelial cells. Am J Physiol Gastrointest Liver Physiol 2009; 297(6): G1172-80.

Mulder DJ, Lobo D, Mak N, Justinich CJ. Expression of toll-like receptors 2 and 3 on esophageal epithelial cell lines and on eosinophils during esophagitis. Dig Dis Sci 2012; 57(3): 630-42.

Aceves SS, Ackerman SJ. Relationships between eosinophilic inflammation, tissue remodeling, and fibrosis in eosinophilic esophagitis. Immunol Allergy Clin North Am 2009; 29(1): 197-211.

Tomasek JJ, Gabbiani G, Hinz B, Chapronnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodeling. Nat Rev Mol Cell Biol 2002; 3(5): 349-63.

Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Eosinophilic esophagitis in pediatric eosinophilic esophagitis. J Allergy Clin Immunol 2007; 119(1): 206-12.

Kapel RC, Miller JK, Torres C, Aksoy S, Lash R, Katzka DA. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. Gastroenterology 2008; 134(5): 1316-21.
[62] Sorsor SA, Barawi M, Hagglund K, et al. Eosinophilic esophagitis in children and adolescents: epidemiology, clinical presentation and seasonal variation. J Gastroenterol. 2013; 48(1): 81-5. http://dx.doi.org/10.1016/j.jgastro.2013.03.001 PMID: 23642431

[63] Rezende ER, Barros CP, Yuan LH, Santos AT, Pinto RM, Segundo GR. Clinical characteristics and sensitivity to food and inhabitants among children with eosinophilic esophagitis. BMC Res Notes 2014; 7: 47. http://dx.doi.org/10.1186/1756-0500-7-47 PMID: 24443803

[64] Hoofien A, Dias JA, Malamisura M, et al. Pediatric Eosinophilic Esophagitis: Results of the European Retrospective Pediatric Eosinophilic Esophagitis Registry (RetroPEER). J Pediatr Gastroenterol Nutr 2019; 68(4): 552-8. http://dx.doi.org/10.1097/MPG.0000000000002215 PMID: 30540712

[65] Romano C, Chiaro A, Lucarelli S, et al. Mucosal cytokine profiles in paediatric eosinophilic oesophagitis: a case-control study. Dig Liver Dis 2014; 46(7): 590-5. http://dx.doi.org/10.1016/j.dld.2014.03.003 PMID: 24704289

[66] Liacouras CA, Spiegel J, Gober LM. Eosinophilic esophagitis: clinical presentation in children. Gastroenterol Clin North Am 2014; 43(2): 219-29. http://dx.doi.org/10.1016/j.gtc.2014.02.003 PMID: 24813511

[67] Rodrigues M, D’Amico MF, Patino FR, Barbieri D, Damiao AO, Sipahi AM. Clinical manifestations, treatment, and outcomes of children and adolescents with eosinophilic esophagitis. J Pediatr (Rio J) 2013; 89(2): 197-203. [Erratum in: J Pediatr]. [Rio J]. [5]. Sipahi, Aytan M]. [corrected to Sipahi, Aytan M]. [PMID: 23642431]. http://dx.doi.org/10.1016/j.jped.2013.03.001 PMID: 23642431

[68] Dellon ES, Farrell TM, Bozymski EM, Shaheen NJ. Diagnosis of eosinophilic esophagitis after fundoplication for ‘refractory reflux’: implications for preoperative evaluation. Dis Esophagus 2010; 23(3): 191-5. http://dx.doi.org/10.1111/j.1442-2050.2009.01019.x PMID: 19863640

[69] Rea F, Caldaro T, Tambucci R, et al. Eosinophilic esophagitis: is it also a surgical disease? J Pediatr Surg 2013; 48(2): 304-8. http://dx.doi.org/10.1097/MPG.0b013e3181e67072 PMID: 20975581

[70] Hurtado CW, Furuta GT, Kramer RE. Etiology of esophageal food impactions in children. J Pediatr Gastroenterol Nutr 2011; 52(1): 43-6. http://dx.doi.org/10.1097/MPG.0b013e3181ee7502 PMID: 21481025

[71] Cheung KM, Oliver MR, Cameron DJ, Catto-Smith AG, Chow CW. Esophageal eosinophilia in children with dysphagia. J Pediatr Gastroenterol Nutr 2003; 37(4): 498-503. http://dx.doi.org/10.109700005176-200310000-00018 PMID: 14508223

[72] Littreddy AR, Sink JR, Georg MW, Kitsko DJ, Simons JP. Association between Eosinophilic Esophagitis and Esophageal Food Impaction in the Pediatric Population. Otolaryngol Head Neck Surg 2018; 159(4): 750-4. http://dx.doi.org/10.1177/0194598118779049 PMID: 29807494

[73] Roy-Ghanta S, Larosa DF, Katzka DA. Atopic characteristics of adult patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2008; 6(5): 531-5. http://dx.doi.org/10.1016/j.cgh.2007.12.045 PMID: 18304887

[74] Simon D, Marti H, Heer P, Simon HU, Braathen LR, Straumann A. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. J Allergy Clin Immunol 2005; 115(5): 1090-2. http://dx.doi.org/10.1016/j.jaci.2005.01.017 PMID: 15867973

[75] Miehike S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut 2016; 65(3): 390-9. http://dx.doi.org/10.1136/gutjnl-2014-308815 PMID: 25792708

[76] Spiegel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol 2012; 130(2): 461-7.e5. http://dx.doi.org/10.1016/j.jaci.2012.05.021 PMID: 22743304

[77] Miehike S. Clinical features of Eosinophilic esophagitis in children and adults. Best Pract Res Clin Gastroenterol 2015; 29(5): 739-48. http://dx.doi.org/10.1016/j bj.2015.09.005

[78] Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis Proceedings of the AGREE Conference Gastroenterology. 15(4): 1023-22.

[79] Hirano I. Eosinophilic esophagitis and gastroesophageal reflux disease; there and back again. Clin Gastroenterol Hepatol 2011; 9(2): 99-101. http://dx.doi.org/10.1016/j.cgh.2010.11.001 PMID: 2170874

[80] Franciosi JP, Liacouras CA. Eosinophilic esophagitis. Immunol Allergy Clin North Am 2009; 29(1): 19-27. http://dx.doi.org/10.1016/j.iac.2008.09.001

[81] Carr S, Chan ES, Watson W. Eosinophilic esophagitis. Allergy Asthma Clin Immunol 2018; 12;14(Suppl 2): 58-.

[82] Nielsen JA, Lager DJ, Lewin M, Rendon G, Roberts CA. The optimal number of biopsy fragments to establish a morphologic diagnosis of eosinophilic esophagitis. Am J Gastroenterol 2014; 109(4): 515-20. http://dx.doi.org/10.1038/ajg.2013.463 PMID: 24445569

[83] Steiner SJ, Kernek KM, Fitzgerald JF. Severity of basal cell hyperplasia differs in reflux versus eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2006; 42(5): 506-9. http://dx.doi.org/10.1097/01.mpg.0000221906.06899.1b PMID: 16707971

[84] Dellon ES, Liacouras CA, et al. Summary of the updated international consensus diagnostic criteria for eosinophilic esophagitis: AGREE conference. Ann Allergy Asthma Immunol 2018; 121(3): 281-4. http://dx.doi.org/10.1016/j.anai.2018.05.035 PMID: 30030146

[85] Dellon ES, Speck O, Woodward K, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. Am J Gastroenterol 2013; 108(12): 1854-60. http://dx.doi.org/10.1038/ajg.2013.363 PMID: 24145677

[86] Warners MJ, van Rhijn BD, Curvers WL, Smout AJ, Bredenoord AJ. PPI-responsive esophageal eosinophilia cannot be distinguished from eosinophilic esophagitis by endoscopic signs. Eur J Gastroenterol Hepatol 2015; 27(5): 506-11. http://dx.doi.org/10.1097/MEG.0000000000000331 PMID: 25822858