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EOSINOPHILIC ESOPHAGITIS: REVIEW ARTICLE

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Abstract: Eosinophilic esophagitis (EEo) is a chronic, inflammatory, immunological, antigen-mediated esophageal disorder characterized clinically by esophageal symptoms and histologically by an eosinophilic infiltrate demonstrated by biopsy of the esophageal mucosa. It most commonly affects males and individuals with a positive family history of the disease, and affects all age groups. Atopic predisposition is observed, with the majority of patients showing allergic symptoms typical of asthma, allergic rhinitis, eczema and IgE--mediated food allergy. The aim of the study is to describe Eosinophilic Esophagitis.
Keywords: eosinophilic esophagitis; digestive endoscopy; biopsy; epidemiology.

DEFINITION OF EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis (EEo) was first described in 1978 (LANDRES; KUSTER; STRUM, 1978) and has been recognized as a disease since 1993 (VEIGA *et al.,* 2017). Currently, it is characterized by symptoms of dysphagia and/or food impaction in adults and feeding problems, abdominal pain and/or vomiting in children, with esophageal histology showing a minimum eosinophil count of 15 per high-power field (DHAR; *et al.,* 2022).

The disease has an important association with allergies and has recently been recognized as a late manifestation of atopic march (DALL'AGNOL; *et al*., 2021).

EPIDEMIOLOGY

OES is a clinical entity that predominantly affects male patients and a potential genetic component is suggested, observed by an increased familial incidence and greater frequency in Caucasians (DIAS *et al*, 2012). However, with regard to the relationship with Caucasians, most studies and case studies originate from the Western hemisphere, which may project a bias in this observation (SOARES, 2016). It affects all age groups, although it was first described in children, and more recently it has been increasingly diagnosed in children and adults (DIAS *et al.*, 2012).

Epidemiological data suggest that OES is currently the second most common cause of chronic esophagitis, after gastroesophageal reflux disease, and a frequent cause of dysphagia (DIAS *et al.*, 2012), with prevalence currently approaching that of Crohn's disease and ulcerative colitis in the pediatric population (A BORDEA *et al.*, 2013).

The increased prevalence of OES has been correlated with the increased prevalence of atopy, with the majority of patients manifesting other allergic symptoms, (A BORDEA *et al.*, 2013) including asthma, allergic rhinitis, eczema and IgE-mediated food allergy (MUIR, 2018), with at least 60% of patients presenting with atopic symptoms previously or at the time of diagnosis (BIEDERMANN *et al.,* 2021).

PATHOGENY

The etiology of OES is uncertain; however, it is known that there is an interaction between the genetic characteristics and environmental factors of each patient (VEIGA *et al.,* 2017). Several factors are related to the pathogenesis of this disease, including caesarean section, prematurity, antibiotics in childhood, food allergies, lack of breastfeeding or living in an area with low population density, suggesting that an alteration in the stimulation of the immune system at an early age is a predisposition to this pathology (SOARES, 2016).

The growing number of OES cases seems to be included in the context of the generalized increase in allergic pathologies, since the literature suggests that the lack of early exposure to certain microorganisms and the alteration of the microbiome may play an important role in the pathogenesis of OES, similar to what is described for other atopic diseases, such

as asthma and atopic dermatitis (SOARES, 2016). In this sense, atopic individuals show a greater genetic predisposition to develop OES, since aeroallergens and food allergens are constantly implicated in the pathophysiology of this disease clinical entity (NUNES, 2018). Furthermore, the fact that around 40 to 80% of patients with OES have a personal history and 60% have a family history of atopy (SOARES, 2016) firmly corroborates the immunological hypothesis.

The genetic context is strongly linked to EOS, which can alter the esophageal epithelial barrier, the recruitment of eosinophils by eotaxin and tissue remodeling linked to the development of fibrosis. The pattern of eosinophilic esophagitis follows a hereditary model: parents of children with the disease have a history of esophageal dysfunction 10% of the time and can contract the pathology 7% of the time (INAGE *et al.,* 2018).

PHYSIOPATHOLOGY

IMMUNITY

The presence of intraepithelial eosinophils in the oesophagus defines OES, as this luminal site is normally devoid of this cell type (VINIT *et al*, 2019).

The immune response in eosinophilic esophagitis is triggered mainly by ingested food allergens. These allergens lead to a type 2 T-helper cell response, and this pathway promotes the activation of cytokines, mainly interleukin IL-5 and IL-13. IL-5 participates in the maturation of eosinophils, and eventual migration to the esophageal epithelium (INAGE *et al*., 2018), and the increase in IL-13 leads to the production of specific proteins, especially eotaxin-3 via epithelial cells. Eotaxin-3 is a primary regulator of eosinophils in the gastrointestinal tract. In addition, IL-13 also induces proteases that damage the epithelial barrier and reduce the expression of adhesion molecules (PATEL; HIRANO; GONSALVES, 2021).

Eosinophils are recruited from the blood pool with local chemotaxis. They are responsible for initiating and maintaining inflammation, as they act as antigen presenters, recruiting T lymphocytes, guiding Th2 differentiation, recruiting and activating mast cells and basophils (DAVIS; ROTHENBERG, 2016). Eosinophils contribute to esophageal fibrosis by degranulating and secreting their proteins, such as basic protein (MBP) and fibrogenic growth factors such as TGF-β (CARVALHO *et al.,* 2019).

Mast cells show an increased number and degranulation in the esophageal epithelium, suggesting the involvement of immediate hypersensitivity (mediated by immunoglobulin E (IgE). They participate in eosinophil activation and esophageal dysmotility and remodeling, with the appearance of fibrosis. Their pattern of protease secretion and increased expression of carboxypeptidase A3 and tryptase may be specific for EEo. Langerhans cells, the APCs of the keratinocyte layer, interact with antigens at the beginning of the pathological cascade. They express FceRI, which correlates with the level of Th2 response in atopic pathologies. Basophils express the thymic stromal lymphoprotein (TSLP) receptor, a basophil proliferation factor with a complex role, inducing a Th2 immune response, increasing basophil and APC recruitment and promoting atopic dermatitis and asthma (VINIT *et al*., 2019).

The immune response is mainly mediated by Th2 interleukins (IL), IL-4, IL-5 and IL-13. IL4, secreted by Th2 cells, natural killers (NK) and TSLP-dependent basophils promotes the differentiation of virgin T cells into Th2 and B cells ending with IgE secretion. Overexpression of esophageal IL 13 by Th2 cells increases the expression of chemokine ligand 26 (CCL26), eotaxin 3 and periostin,

eosinophil recruitment from the circulating pool and expression of calpain 14 (CAPN14) responsible for the production of STAT6 and IL-33. It also increases the survival of T cells and decreases the local expression of desmoglein-1 (DSG1), filaggrin and epidermal differentiation complex (EDC), altering the epithelial barrier. IL-5, an eosinophil and mast cell differentiation and survival factor secreted by eosinophils, activates TL and mast cells in chronic allergic reactions (VINIT *et al.*, 2019).

THE ROLE OF ALLERGIES

Previous studies have shown that aeroallergens can also exacerbate OES, since the diagnosis of OES seems to increase during the spring and summer pollen seasons (DALL'AGNOL; *et al.*, 2021). One study showed that more than 90% of the OES patients analyzed had a history of atopy, with concomitant asthma, rhinoconjunctivitis, atopic dermatitis or IgE-mediated food allergy (CARVALHO *et al.*, 2019). Therefore, the assessment and treatment of diseases concomitant atopic diseases can optimize patient management and improve quality of life (PATEL; HIRANO; GONSALVES, 2021).

OES is associated with a high total IgE level and sensitization to food allergens (75%), mainly milk, often associated with egg, wheat and soy. In short, although IgE sensitization is common, OES is not merely an IgE-mediated food allergy and may involve complex mechanisms involving the innate and adaptive immune system (VINIT *et al.* 2019).

GENETICS

The study of the genetics and etiology of eosinophilic esophagitis has led to the conclusion that there is a repeated genetic profile in affected patients, and this pattern is called the EEo transcriptome. This profile contains several hundred differentially expressed genes (*"upregulated"* or *"downregulated"*), with the most expressed gene being the eotaxin-3 gene, whose expression is induced by IL-13 (RYU *et al.,* 2020) with a 53-fold increase when compared to control groups (NUNES, 2018). In addition, other genes such as thymic stromal lymphopoietin (TSPL) and calpain 14 (CAPN-14) are overexpressed, disrupting the esophageal barrier and exacerbating inflammation. Genetic studies to date have been concerned with identifying locations of risk genes for EEo and their role in the development of the disease (RYU *et al.,* 2020).

The involvement of epigenetics has been little studied, and among the current knowledge, as mentioned in this review, we highlight biochemical studies involving a single nucleotide polymorphism in the CCL26 gene, which codes for eotaxin. This gene is highly expressed in esophageal epithelial cells of patients with EoE when compared to healthy individuals, and is strongly associated with eosinophil chemotaxis and tissue mastocytosis (SOARES, 2016).

The initial response to antigens is mediated by the release of IL-13, which recruits eosinophils through the release of eotaxin-3. Once activated in the oesophagus, the eosinophils release protein granules which, in addition to precipitating inflammation and their cytotoxic action on the oesophageal epithelium, increase the smooth muscle activity and cause the degranulation of mast cells and basophils (RUNGE; DELLON, 2015).

The involvement of epigenetics comes from the point of view that the lack of early expo-

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sure to microorganisms and the alteration of the microbiome create a "signature" that increases the likelihood of developing ESO, and this epigenetic-EEO interaction includes the modification of histones, DNA methylation and the post-transcriptional repression of microRNAs (miRNAs) (SHERRILL; ROTHENBERG, 2014). Initially, most of what is known about the involvement of epigenetics in EoS was obtained from biochemical studies of the promoter of the main EoS candidate gene, CCL26. In relation to histone modification and DNA methylation, post-transcriptional modification of the histone tail is a reversible mechanism, mostly acetylation and methylation, which causes altered accessibility to gene promoters located proximal or distal to the modified histone (SOARES, 2016).

In addition, DNA methylation occurs at the level of cytosine nucleotides located on cytosine-guanine dinucleotides (*CpG*). In addition to epigenetic regulation by histone acetylation, the CCL26 promoter is also controlled by DNA methylation, which occurs at the level of cytosine nucleotides located on cytosine-guanine dinucleotides and, like other epigenetic marks, is dynamically regulated (SHERRILL; ROTHENBERG, 2014).

Finally, miRNAs are small sequences of non-coding RNA that affect the expression of target genes at the post-transcriptional level. They act by repressing or inducing the degradation of messenger RNA (mRNA) by binding to complementary sequences in the 3' non-coding region of target mRNAs, forming double-stranded RNA molecules (HOLVOET; BLANCHARD, 2014). An ultra-specific set of miRNAs has been found to be dynamically altered in the esophageal mucosa of patients with EoE (SOARES, 2016), and are also different from the samples observed in controls and in patients with chronic and non-eosinophilic forms of esophagitis (SHERRILL; ROTHENBERG, 2014).

CLINICAL MANIFESTATIONS

The symptoms of eosinophilic esophagitis are diverse and vary with age (DALL'AGNOL; *et al.*, 2021). In general, the disease is non-specific and symptoms can be infrequent, not perceived as alarming and often confused with GERD symptoms (MENDONÇA; PINTO, 2020).

Currently, there are no symptoms or alterations on physical examination, biological markers or pathognomonic endoscopic findings of the disease and other causes of esophageal eosinophilia should always be excluded. OES is chronic and relapsing and the activity of the disease is highly variable, and there is usually an average period of 4.3 years between the onset of symptoms and diagnosis, which can vary between 1 and 13 years (SOUSA; COSTA; BARBOSA, 2013).

In children, the most common symptoms are epigastric pain, regurgitation, vomiting and chest pain, with little response to therapy with acid blockers and prokinetics (SUSSENBACH, 2006), as well as pharyngeal globus and anorexia, and less frequently symptoms such as growth retardation and hematemesis (SOARES, 2016).

Infants and pre-school children, especially under 2 years of age, most commonly present with feeding difficulties such as choking, asphyxia, refusal to eat, vomiting and poor weight-status progression (CANARIAS, 2018), and the frequency and severity of symptoms are often not related to the degree of esophageal eosinophilia found (SOARES, 2016). In addition, Otteson *et al* showed that certain recurrent ENT symptoms such as cough, dysphonia and hoarseness are common in the presentation of OES, corresponding to an average incidence of 46, 38 and 28% respectively (CANARIAS, 2018).

In older children and adolescents, we observe symptoms such as dysphagia, retrosternal burning and non-specific abdominal

pain (SOUSA; COSTA; BARBOSA, 2013), as well as symptoms of food impaction, nausea, GERD symptoms or selective dieting (VEIGA *et al.,* 2017).

In adults, the most frequent symptom is dysphagia for solids, and many of them report the need to adapt their eating habits over time in order to minimize symptoms (SOARES, 2016). In addition, the sensation of a "*bolus*" in the throat (SOUSA; COSTA; BARBOSA, 2013), food impaction and esophageal dysmotility can also occur, suggesting involvement of the muscular layer of the esophageal wall (CANARIAS, 2018).

The symptoms of atopic diseases are frequently observed in the adult population and in the pediatric population, however, in the former they are less prevalent (SOARES, 2016).

For a more detailed assessment, the doctor should obtain data such as a history of vomiting, reflux, food impaction, feeding difficulties, heartburn or abdominal pain, as well as a history of atopic disease, a family history of impaction, esophageal dilation or eosinophilic gastrointestinal disease (MENDONÇA; PINTO, 2020).

Finally, the symptoms are sometimes underestimated as a result of the patient's accommodation to the symptoms, such as eating slowly, chewing carefully, cutting the food into smaller pieces, associating food with sauces, drinking liquids to better dilute the food and avoiding pills and consistent foods that cause discomfort (VEIGA *et al.,* 2017).

DIAGNOSIS

According to the latest consensuses, the presence of symptoms of esophageal dysfunction, associated with mucosal biopsies showing at least 15 eosinophils per high magnification field after excluding secondary causes of esophageal eosinophilia, is necessary for diagnosis (VEIGA *et al.,* 2017).

ENDOSCOPIC ASPECTS

When OES is suspected based on symptoms, esophagogastroduodenoscopy (EGD) is useful in assessing other potential causes of esophageal eosinophilia and obtaining esophageal biopsies (VEIGA *et al.,* 2017). EDA can be normal in 7 to 18% of cases or show changes in the esophageal mucosa, such as transverse rings or grooves, longitudinal erosions, edema, friability, whitish plaques, narrowing and even esophageal polyps, as well as other abnormalities (GIRARDI *et al.,* 2015). In addition, chronic remodeling is represented by restrictions, characterizing the aspect "crepe paper esophagus", in which linear lesions occur in response to minimal trauma (FURUTA; KATZKA, 2015).

The endoscopic pattern is different in children and adults. Children more often have a normal-looking esophagus or plaques or edema are observable, while adults have rings and stenoses more commonly; thus, this difference supports the concept that some aspects are the result of inflammation (edema, plaques, furrows), while others are characteristic of fibrosis and chronic inflammation (rings, stenoses, narrowing) (SOARES, 2016).

HISTOLOGICAL ASPECTS

In eosinophilic esophagitis there is an infiltration of eosinophils in the epithelium that can be detected with standard hematoxylin-eosin staining (NUNES, 2018). Esophageal inflammation in OES has a diagnostic threshold of at least 15 eosinophils per high magnification field in at least one esophageal site. This criterion allows for a certain standardization of the diagnosis, but it is still somewhat arbitrary and needs to be complemented by the clinic (PATEL; HIRANO; GONSALVES, 2021).

In addition, there are other histopathological changes associated with EoS, including eo-

sinophil density, eosinophil surface stratification, eosinophilic microabscesses, basal layer hyperplasia, dilated intracellular spaces, surface epithelial alterations, dyskeratotic cells and, if the subepithelial tissue is analyzed, fibrosis of the lamina propria (PATEL; HIRANO; GONSALVES, 2021). There are also no substantial histological differences between children and adults.

It is valid to state that none of the findings mentioned above are pathognomonic of EEo and the diagnosis cannot be made based on histological evidence alone (VINIT *et al*., 2019).

Esophageal biopsies in the proximal, middle and distal esophagus are mandatory for diagnosis and should be performed during any upper digestive endoscopy, in the context of dysphagia, food impaction or the presence of other symptoms (SAILLEN *et al*., 2014). In order to increase diagnostic accuracy, it is recommended that at least 4 fragments of biopsies of the mid-proximal and distal esophagus (DALL'AGNOL; *et al*., 2021). Studies show that performing six biopsies increases sensitivity to 99% (VEIGA *et al*. 2017).

Oesophageal biopsies obtained by traditional methods take samples of the epithelium and rarely take tissues deeper than the lamina propria, which limits the characterization of OES to the mucosa. However, rare esophagectomy samples from patients with OES have shown transmural eosinophilic inflammation (SOARES, 2016).

To rule out other gastrointestinal diseases that also have eosinophilic infiltrates, it is important to perform a biopsy of the esophagus, stomach and duodenum, especially at the first endoscopy (VEIGA *et al*., 2017).

TREATMENT

The goals of treatment are to relieve symptoms, improve histopathology, reverse existing disease and prevent future complications of the disease (PATEL; HIRANO; GONSALVES, 2021).

A widely used parameter of response to therapies is symptoms, but they cannot be used in isolation as a determinant of disease activity since the patient's lifestyle and diet can mask symptoms (SOARES, 2016).

The three main therapeutic options for OES, which aim to eliminate the allergenic stimulus, achieve symptomatic control and remission of disease activity, are diet, drugs and endoscopic dilation (DALL'AGNOL; *et al*., 2021).

Diet therapy is considered a first-line treatment strategy in adults and children (PATEL; HIRANO; GONSALVES, 2021). Three different dietary approaches are used: the diet of elimination of all food allergens, using an amino acid-based formula; the diet of food restriction guided by allergy tests (specific IgE research by skin prick or serum tests and patch test; and the empirical diet of elimination of six food groups most commonly known to trigger EoE: soy, egg, milk, wheat, nuts and seafood (VEIGA *et al.,* 2017). Such diets include food restrictions and are effective, however, most of the time because they are restrictive they are not well accepted by patients.

The aim of diet therapy is not to maintain a definitive restrictive diet, but rather to identify a limited number of specific eating triggers and customize a long-term maintenance diet (FURUTA; KATZKA, 2015).

Drug treatments that are primary therapy options for both children and adults include topical corticosteroids, the most commonly used being Fluticasone for 6 to 8 weeks or oral viscous Budesonide (SOUSA; COSTA; BARBOSA, 2013), which have the same

efficacy as systemic corticosteroids, although they have few side effects, except for the risk of oral candidiasis (SAILLEN *et al.*, 2014). Despite being effective and well tolerated, after discontinuation 50% of cases can recur (SOUSA; COSTA; BARBOSA, 2013).

As for systemic costicosteroids, such as Prednisolone, they should only be used in situations where urgent symptomatic relief is required: severe dysphagia, reduced esophageal caliber without indication for esophageal dilation due to risk of perforation, weight loss and inability to eat (SOUSA; COSTA; BARBOSA, 2013).

First-line treatment of EEo with PPI monotherapy is widely practiced (DHAR *et al.,* 2022), and can result in a significant improvement in symptoms and the rate of eosinophil infiltration in cases of esophageal eosinophilia. Regardless of the presence of associated gastroesophageal reflux, they have an overall histopathological response of 42% based on observational studies (SAILLEN *et al.,* 2014).

Esophageal dilation is an effective strategy for controlling dysphagia symptoms resulting from stenosis associated with OES, and can be used in adolescents and adults (FURUTA; KATZKA, 2015). However, it is associated with the risk of bleeding, perforation and chest pain (SOUSA; COSTA; BARBOSA, 2013).

A number of other agents have been studied to a limited extent in OES, but their efficacy has not been established and they are not recommended for use (SOARES, 2016). Some studies have shown histological efficacy with the use of monoclonal antibodies, such as anti-IL-5 Reslizumab, but they do not appear to have any effect on symptomatology (VEIGA *et al.,* 2017). Dupilumab, an anti-interleukin (IL-4) receptor monoclonal antibody, has been used to treat the disease treatment of chronic allergic diseases such as eczema and asthma. Targeting the IL-4 and IL-13 pathway has been considered a potentially useful strategy in the management of patients with OE (DHAR *et al.* 2022).

PROGNOSIS AND FOLLOW-UP

An endoscopy should be carried out after an initial course of 6 to 12 weeks to check the effectiveness of any pharmacological/ dietary therapy. However, it is valid to say that the follow-up of each patient must be individualized, and it is necessary to perform EDA every 3 months or if symptoms worsen, to follow up clinically, and to make nutritional and therapeutic adjustments and indicate new tests (SOUSA; COSTA; BARBOSA, 2013).

EEo is a chronic disease which, if left untreated, can lead to a reduction in patients' quality of life. However, periods of symptom remission can occur spontaneously or induced by dilation. Evidence to date indicates that eosinophilic esophagitis does not represent a pre-malignant disease and does not reduce life expectancy (VEIGA *et al.*, 2017).

REFERENCES

BORDEA, Ma; MOSTEANU, O; POP, Ta; GHEBAN, D; SEMASCA, G; MIU, N. **Eosinophilic esophagitis.** Gastro-Enterologica Belgica, [S.L], v. 76, p. 407-412, out. 2013.

BIEDERMANN, Luc; STRAUMANN, Alex; GREUTER, Thomas; SCHREINER, Philipp. **Eosinophilic esophagitis: established facts and new horizons.** Seminars In Immunopathology, [S.L.], v. 43, n. 3, p. 319-335, jun. 2021. Springer Science and Business Media LLC. http://dx.doi.org/10.1007/s00281-021-00855-y.

CANARIAS, Alexandre Gomes. **Esofagite eosinofílica.** 2018. 22 f. Dissertação (Mestrado) - Curso de Mestrado Integrado em Medicina, Faculdade de Medicina Lisboa, Lisboa, 2018.

CARVALHO, Sara; COSTA, Célia; MARCELINO, João; DUARTE, Fáti Ma Cabral; BARBOSA, Manuel Pereira. **Esofagite eosinofílica numa consulta de alergia alimentar: caracterização e comparação entre idade pediátrica e idade adulta.** Brazilian Journal of Allergy And Immunology (Bjai), [S.L.], v. 3, n. 3, p. 301-308, 27 set. 2019. GN1 Genesis Network. http://dx.doi.org/10.5935/2526-5393.20190041.

DALL'AGNOL, Letícia; SOUZA, Phelipe; BERNHARDT, Claudia; FERRARI, Fangio. Esofagite eosinofílica: uma revisão narrativa. **Arquivos de Asma, Alergia e Imunologia,** Itajaí, v. 5, n. 2, p. 135-141, mar. 2021.

DAVIS, BP; ROTHENBERG, ME. **Mecanismos da doença da esofagite eosinofílica.** Pathol 2016; 11: 365-393.

DHAR, Anjan; HABOUBI, Hasan N; ATTWOOD, Stephen e; AUTH, Marcus K H; DUNN, Jason M; SWEIS, Rami; MORRIS, Danielle; EPSTEIN, Jenny; NOVELLI, Marco R; HUNTER, Hannah. **British Society of Gastroenterology (BSG) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults.** Gut, [S.L.], p. 1-29, 23 maio 2022. BMJ. http://dx.doi.org/10.1136/gutjnl-2022-327326.

DIAS, Eduardo Montagner; GUEDES, Renata Rostirola; ADAMI, Marina Rossato; FERREIRA, Cristina Targa. **Esofagite eosinofílica: atualização e contribuição da endoscopia.** Boletim Científico: de pediatria, Porto Alegre, v. 1, n. 1, p. 19-28, jun. 2012.

HOLVOET, Sebastien; BLANCHARD, Carine. **Genetic and molecular mechanisms leading to eosinophilic esophagitis.** Revista Espanhola de Enfermidades Digestivas, Madrid, v. 106, n. 4, p. 276-280, mar. 2014.

FURUTA, Glenn T.; KATZKA, David A. **Eosinophilic Esophagitis.** New England Journal of Medicine, [S.L.], v. 373, n. 17, p. 1640-1648, 22 out. 2015. Massachusetts Medical Society. http://dx.doi.org/10.1056/nejmra1502863.

GIRARDI, Fernanda; GOMES, Gabriela Delatorre; ORIBKA, Rafaela; SILVA, Lucas Baptista da; LUIZ, Ricardo Panico Rizzo; FEY, Augusto; KOTZE, Lorete Maria da Silva. **Perfil epidemiológico dos pacientes com eosinofilia esofágica no serviço de endoscopia digestiva alto vale.** Revista Caminhos, Rio do Sul, v. 6, n. 18, p. 23-30, jul. 2015.

INAGE, Eisuke; FURUTA, Glenn T.; MENARD-KATCHER, Calies; MASTERSON, Joanne C. **Eosinophilic esophagitis: pathophysiology and its clinical implications.** American Journal of Physiology-Gastrointestinal and Liver Physiology, [S.L.], v. 315, n. 5, p. 879-886, 1 nov. 2018. American Physiological Society. http://dx.doi.org/10.1152/ajpgi.00174.2018.

LANDRES, Richard T.; KUSTER, Gustavo G. R.; STRUM, Williamson B. **Eosinophilic esophagitis in a patient with vigorous achalasia.** Gastroenterology. Bethesda, p. 1298-1301. jun. 1978.

MUIR, Amanda B. **Eosinophilic Esophagitis. Current Problems in Pediatric And Adolescent Health Care,** [S.L.], v. 48, n. 3, p. 99-101, mar. 2018. Elsevier BV. http://dx.doi.org/10.1016/j.cppeds.2018.01.006.

NUNES, Bruno André Puim. **Esofagite eosinofílica: uma revisão fisiopatológica.** 2018. 67 f. Dissertação (Mestrado) - Curso de Mestrado Integrado em Medicina, Universidade de Coimbra, Coimbra, 2018.

PATEL, Ronak V.; HIRANO, Ikuo; GONSALVES, Nirmala. **Eosinophilic Esophagitis: etiology and therapy.** Annual Review of Medicine, [S.L.], v. 72, n. 1, p. 183-197, 27 jan. 2021. Annual Reviews. http://dx.doi.org/10.1146/annurev- med-052819-023848.

RUNGE, Thomas M.; DELLON, Evan S. **Do We Know What Causes Eosinophilic Esophagitis? A Mechanistic Update.** Current Gastroenterology Reports, [S.L.], v. 17, n. 9, p. 1-17, 24 jul. 2015. Springer Science and Business Media LLC. http://dx.doi.org/10.1007/s11894-015-0458-9.

RYU, Seohyun; LEE, Keum Hwa; TIZAOUI, Kalthoum; TERRAZZINO, Salvatore; CARGNIN, Sarah; EFFENBERGER, Maria; SHIN, Jae Il; KRONBICHLER, Andreas. **Pathogenesis of Eosinophilic Esophagitis: a comprehensive review of the genetic and molecular aspects.** International Journal of Molecular Sciences, [S.L.], v. 21, n. 19, p. 7253, 30 set. 2020. MDPI AG. http://dx.doi.org/10.3390/ijms21197253.

SAILLEN, Élodie; CELLIER, Christophe; NANEIX, Anne-Laure; CANIONI, Danielle; BRUNEVAL, Patrick; POUCHOT, Jacques; GEORGIN-LAVIALLE, Sophie. **Esophagite à éosinophiles.** La Presse Médicale, [S.L.], v. 43, n. 1, p. 34-38, jan. 2014. Elsevier BV. http://dx.doi.org/10.1016/j.lpm.2013.03.012.

SHERRILL, Joseph D.; ROTHENBERG, Marc E. **Genetic and Epigenetic Underpinnings of Eosinophilic Esophagitis. Gastroenterology Clinics of North America**, [S.L.], v. 43, n. 2, p. 269-280, jun. 2014. Elsevier BV. http://dx.doi.org/10.1016/j.gtc.2014.02.003.

SOARES, Flávia Manuela Cardoso Rios. **Doença eosinofílica gastro- intestinal.** 2016. 80 f. Dissertação (Mestrado) - Curso de Mestrado Integrado em Medicina, Universidade de Coimbra, Coimbra, 2016.

SOUSA, Filipa; COSTA, Ana Célia; BARBOSA, Manuel. **Esofagite eosinofílica e alergia.** Ge Jornal Português de Gastrenterologia, [S.L.], v. 20, n. 1, p. 10-15, jan. 2013. Elsevier BV. http://dx.doi.org/10.1016/j.jpg.2012.07.013.

SUSSENBACH, Carolina Pelzer. **Esofagite eosinofílica: relato de cinco casos.** 2006. 38 f. TCC (Graduação) - Curso de Medicina, Universidade Federal de Santa Catarina, Florianópolis, 2006.

VEIGA, Fernanda Marcelino da Silva; CASTRO, Ana Paula Beltran Moschione; SANTOS, Cristiane de Jesus Nunes dos; DORNA, Mayra de Barros; PASTORINO, Antonio Carlos. **Esofagite eosinofílica: um conceito em evolução?** Arquivos de Asma, Alergia e Imunologia, [S.L.], v. 1, n. 4, p. 363-372, 2017. GN1 Genesis Network. http://dx.doi.org/10.5935/2526-5393.20170054.

VINIT, C.; DIEME, A.; COURBAGE, S.; DEHAINE, C.; DUFEU, C.M.; JACQUEMOT, S.; LAJUS, M.; MONTIGNY, L.; PAYEN, E.; YANG, D.D. **Eosinophilic esophagitis: pathophysiology, diagnosis, and management.** Archives de Pédiatrie, [S.L.], v. 26, n. 3, p. 182-190, abr. 2019. Elsevier BV. http://dx.doi.org/10.1016/j.arcped.2019.02.005.02.005.