Eosinophilic Esophagitis

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Eosinophilic Esophagitis

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List of Abbreviations

EoE – Eosinophilic Esophagitis

GERD - Gastroesophageal reflux disease

EGE - Eosinophilic gastroenteritis

PPI -Proton pump inhibitor

APC - Antigen presenting cells

GMC-SF - Granulocyte macrophage colony – stimulating factor

TLRs - Toll Like Receptors

IL-4 – Interleukin 4

IL-5 – Interleukin 5

IL-13 - Interleukin 13

Th-2 - T-helper type 2

eos - Eosinophils

hpf - High Power Field

EGD - Esophagogastroduodenoscopy

NPO - Nil Per Os

NICU – Neonatal Intensive Care Unit

HICs - High Income Countries

LIMCs - Low Income Countries

NSAIDs – Non-Steroidal Anti-Inflammatory Drugs

APT - Atopy Patch Test

SPT - Skin Prick Test

TGF-β - Transforming Growth Factor Beta

CAPN14 - Calpain 14

HSV - Herpes Simplex Virus

FDA - Food and Drug Administration

BCG - British Society of Gastroenterology

AGA - American Gastroenterology Association

AGREE - Appraisal of Guidelines for Research and Evaluation

GRADE - Grading of Recommendations, Assessment, Development, and Evaluation

EREFS - Endoscopic Reference Score

I-SEE - Index of Severity for Eosinophilic Esophagitis

PPI-REE - Proton Pump Inhibitor-Responsive Esophageal Eosinophilia

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1. Summary

Eosinophilic Esophagitis

Zmarak Khan

There has been an extraordinary development in our understanding of eosinophilic esophagitis (EoE) over the last twenty years. This is a chronic immune system disorder that occurs when there is an increase in the numbers of eosinophils in the esophagus, leading to inflammation and symptoms such as chest pain and heartburn and most prominently, dysphagia which refers to food being stuck in the esophagus. It is usually linked to allergies such as food allergies and asthma. The diagnosis normally entails endoscopy and biopsy of the esophageal tissue for diagnosis. The treatment of this disease involves dietary control to avoid allergens, drugs like proton pump inhibitors (PPIs) or topical steroids and occasionally esophageal dilation. Initially, research focused on defining characteristics of the disease and the evaluation of its impact. Recent studies changed this tendency by identifying particular risk factors that could facilitate development of the disease. In this thesis we seek to solidify the current fundamental understandings of this disease, resulting in a comprehensive knowledge base. Furthermore, we present two in depth clinical cases, highlighting how their clinical presentations correlate with the current knowledge base of the disease. Moreover, the paper analyses different modalities of treatments effectiveness as well as implications of untimely therapy.

Key words: Eosinophilic esophagitis (EoE), diagnosis, treatment options, and biopsy findings.

2. Sažetak

Eozinofilni Ezofagitis

Zmarak Khan

U posljednjih dvadeset godina došlo je do izvanrednog napretka u našem razumijevanju eozinofilnog ezofagitisa (EoE). EoE je kronični poremećaj imunološkog sustava koji se javlja kada se poveća broj eozinofila u jednjaku, što dovodi do upale i simptoma kao što su bol u prsima i žgaravica, a najistaknutiji simptom je disfagija, koja se odnosi na osjećaj zaglavljenosti hrane u jednjaku. EoE je obično povezan s alergijama, poput alergija na hranu i astme. Dijagnoza EoE obično uključuje endoskopiju i biopsiju tkiva jednjaka kako bi se potvrdila prisutnost eozinofila.

Liječenje ove bolesti uključuje kontrolu prehrane kako bi se izbjegli alergeni, lijekove poput inhibitora protonske pumpe ili topičnih steroida te povremeno dilataciju jednjaka. U početku su istraživanja bila usmjerena na definiranje karakteristika bolesti i procjenu njenog utjecaja. Nedavne studije promijenile su taj fokus identificirajući specifične faktore rizika koji bi mogli olakšati razvoj bolesti.

U ovoj tezi nastojimo učvrstiti trenutno temeljno razumijevanje ove bolesti, stvarajući sveobuhvatnu bazu znanja. Nadalje, predstavljamo dva detaljna klinička slučaja, naglašavajući kako njihovi klinički prikazi koreliraju s trenutnim saznanjima o bolesti. Osim toga, rad analizira učinkovitost različitih modaliteta liječenja kao i implikacije nepravovremenog terapijskog pristupa.

Ova teza doprinosi boljem razumijevanju eozinofilnog ezofagitisa, nudeći pregled trenutnog stanja istraživanja, identificirajući ključne faktore rizika i evaluirajući učinkovitost postojećih tretmana.

Ključne riječi: Eozinofilni Ezofagitis (EoE), dijagnoza, mogućnosti liječenja, i nalazi biopsije.

3. Introduction

Eosinophilic esophagitis (EoE) is an inflammatory, allergen-based chronic disease. Over the past two decades, there has been a gradual increase in its incidence. The increase in EoE may be explained by the increased frequency of esophageal biopsies and overall recognition of this entity by physicians (1). Unlike gastroesophageal reflux disease (GERD) and eosinophilic gastroenteritis (EGE), which can affect the entire gastrointestinal tract, EoE exclusively involves the esophagus (1). Initially thought to be a manifestation of GERD, patients with EoE were found to show other symptoms when physicians began detecting the disease in the mid-1990s. The constellation of these symptoms which include dysphagia, food impaction, and angina-like chest pain with meals and the fact that the condition would not respond to acid suppression therapy nor fundoplication surgery led to the conclusion that this condition differed from GERD and EGE (2).

In addition to symptoms such as dysphagia, vomiting, abdominal pain and chest pain or heartburn, this condition manifests with failure to thrive and inability to develop solid food tolerance in children (2). The main symptoms in adults are related to fibrosis and constricting and narrowing of the esophageal tract (2,3), which results in food impaction and regurgitation (2,4). When a patient presents with such signs and has an esophageal biopsy exhibiting a minimum of 15 eosinophils per high power field (eos/hpf) in the absence of additional illnesses like achalasia or GERD that could also be linked to esophageal eosinophilia, a diagnosis of EoE is suspected (2,5)

It is of importance to note that the symptoms of EoE may at times overlap with symptoms of GERD or EGE, making diagnosis challenging for physicians. Esophageal biopsies are common modalities in the diagnosis of EoE. Biopsies are achieved through esophagogastroduodenoscopy (EGD) and histologically examined (Figure 1), and prior to advancements, a proton pump inhibitor (PPI) trial was initiated to rule out GERD, but this is now considered inappropriate in the diagnostic procedure. Now, esophageal biopsies are an essential part of the diagnostics of this disease. Regarding treatment of EoE, there is no concrete medical cure that exists as of now however, treatment normally consists of PPIs and application of topical corticosteroids such as fluticasone and budesonide (6). Foodstuffs can be eliminated from the diet such as dairy items, wheat, soy, and eggs, inferring that the disease may be food antigen related. Often, amino acid therapy is also used. Amino acid therapy leads to less eosinophilic inflammation and is the most effective diet for the condition

with the response being satisfactory and thus it is the first line of treatment used in children (6).

The purpose of this thesis is to shed light on two highly interesting cases of EoE. It aims to provide a description of their clinical manifestations, the diagnostic methods employed, and the treatment methods that were implemented. Furthermore, we strive to conduct a comprehensive review of existing studies to facilitate an enhanced understanding of the disease. In this next section of the dissertation, we present two patients who had been diagnosed with EoE and discuss the pathologic evolution of their condition. The first case presents an acute complication in which the patient developed a bout of dysphagia and was presented to the emergency department with food bolus impaction. The second case displays a more chronic course of the disease including initial presentation and diagnosis with eventual admission to the emergency room with esophageal laceration. Both cases show the life-threatening complications of EoE if left untreated.

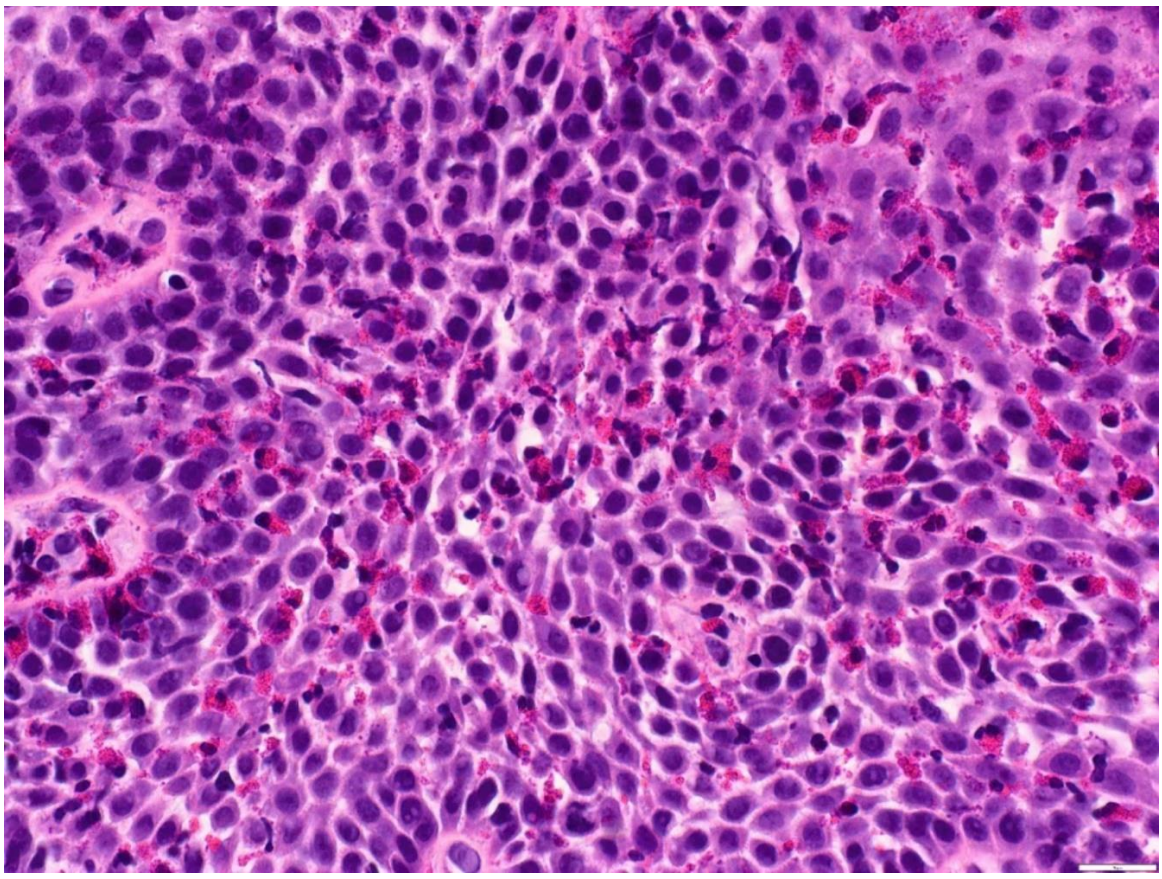
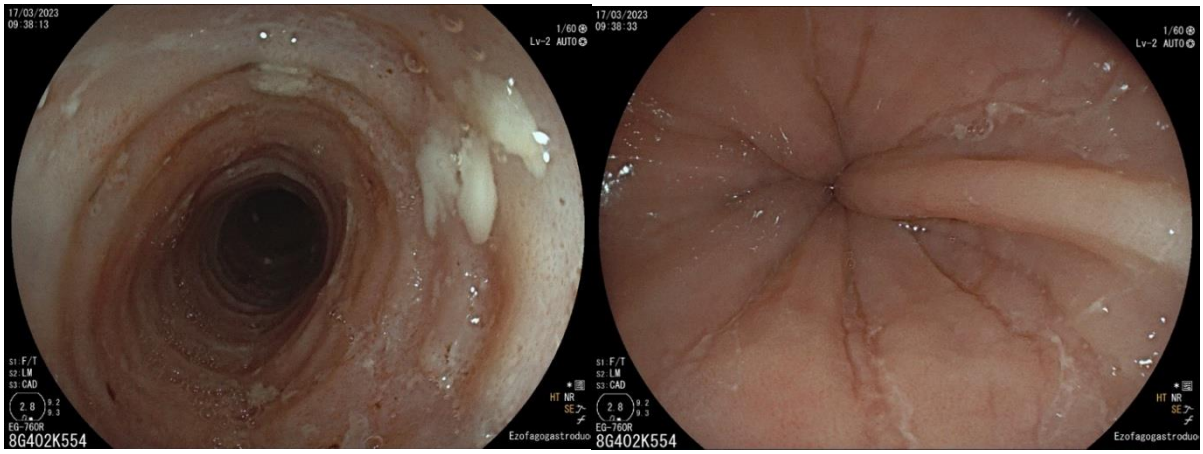


Figure 1. Appearance of an esophageal tissue sample taken via biopsy from a patient with EoE under microscope. (H&E, 400x) - marked epithelial infiltration by eosinophils, higher power. Note the aggregation of eosinophils.

4. Clinical Cases

4.1 Clinical case 1

A male aged 46 presented to emergency room with odynophagia following ingestion of vitamin tablets and hazelnuts few hours ago. The patient had a history of food bolus impaction once a year for the past 10 years. An emergency EGD was indicated, and thus the first endoscopic extraction was carried out. At 25 cm (about 9.84 in) from the frontal incisors an impaction of a large nut occluding the esophageal lumen was visualized. Several attempts were made to perform an extraction with a Roth net retrieval but without any success. Occasionally, an attempt to crush the hazelnuts with crocodile pliers was made, eventually latching onto the core and the lateral edge of the hazelnut, leading to extraction, revealing an underlying mucosa without any lacerations. The esophageal mucosa was slightly paler, showing submucosal concentric and longitudinal formations characteristic of EoE and a band of fibrosis at the gastroesophageal junction (Figures 2 a and b). Biopsies of the proximal esophagus and distal esophagus were taken and sent for pathohistological analysis.



Figures 2. a (left) and **b** (right)
(a) Concentric rings and White plaques can be seen lining the mucosa of the esophagus.
(b) linear furrowing and band of fibrosis can be seen at the gastroesophageal junction.

Histology of esophageal mucosa sample showed-multiple layers of squamous epithelium of incomplete thickness with scarce underlying stroma in some parts of the sample and with inflammatory infiltrates of mononuclear cells along with some eosinophils. More than 50 eos/hpf were found. The histological results based on the findings in the tissue samples taken from the patient verified to fit into the referring diagnosis of EoE by the competent pathologist. Esomeprazole therapy was initiated with a dosage of 2x40 mg per day.

Upon conducting a follow-up EGD the following year, the esophageal mucosa exhibited a pale coloration, along with notable submucosal concentric changes. Furthermore, a scar from the previous repair of a laceration caused by food impaction was identified at 25 cm from the incisor. Navigating through this particular region during endoscopy was achieved with some difficulty. Biopsies of the proximal esophagus and distal esophagus were taken and sent for pathohistological analysis.

The proximal esophageal biopsy revealed segments of stratified squamous epithelium with edema and a dense population of eosinophils within the epithelium, measuring up to 100 eos/hpf. Conversely, the distal esophageal biopsy exhibited a lower count of 60 eos/hpf. H. pylori was ruled out. The gastroenterologist recommended switching to budesonide after the endoscopic findings did not show improvement following the esomeprazole therapy. The initial budesonide dosage is 2x1mg a day for 6 weeks, followed by a maintenance dose of 2x0.5 a day for the next 12 weeks.

This case underscores the potential challenges in the diagnosis and treatment of EoE. A 46-year-old male presented with complaints of odynophagia and annual food bolus impactions. The patient underwent an emergency EGD, revealing a large nut impaction and features typical of EoE. Biopsy results indicated marked eosinophilia which led to initiating esomeprazole and then 12 months later, a follow-up EGD showed persistent esophageal changes in line with PPI-refractory EoE. Therefore, the treatment changed into switched to budesonide. This case underscores the importance of personalized treatment plans and stresses the need for ongoing evaluation to manage EoE. The transition to budesonide treatment reflects an initiative-taking approach to enhance patient outcomes.

4.2. Clinical case 2

In 2022, a 22-year-old female patient presented to the emergency room because of food impaction. The patient ate in the evening the day before and felt food stagnation in her esophagus. On the day of admission to the hospital, she urged to vomit and still felt food stagnation. For the past 10 years, she had episodes of dysphagia and food impaction that passed spontaneously. The diagnosis of EoE was eventually established in 2017 as the EGD performed showed visible concentric folds of the esophageal mucous membrane and a concentric pink ring visible 24 cm from the teeth. The biopsy results indicated EoE due to the

presence of a thickened multi-layered squamous epithelium with hyperplasia of the basal layers and pronounced infiltration of eosinophils with over 50 eos/hpf (Figure 3 a and b).

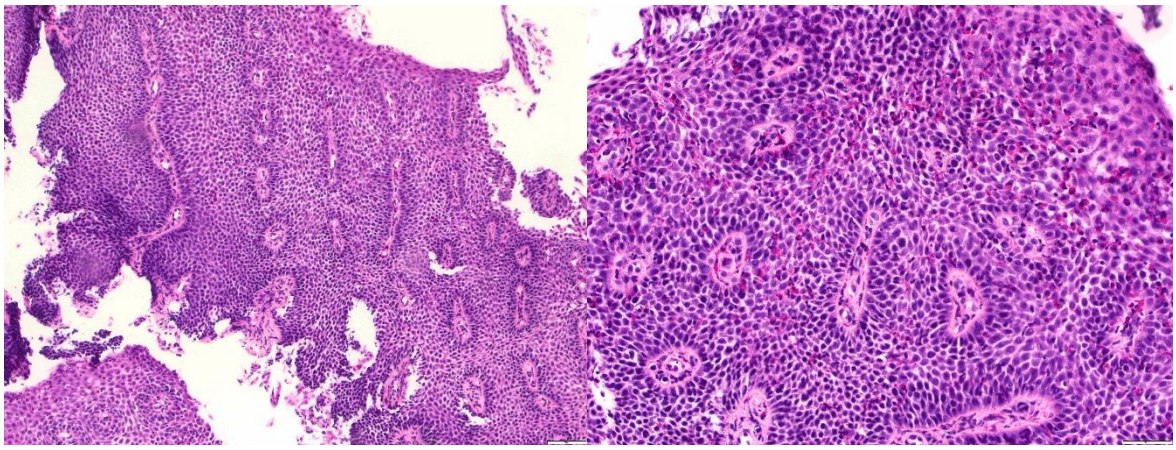


Figure 3. a (left) and **b** (right) with esophageal mucosa lined by multilayered squamous epithelium showing signs of inflammation (high papillae, intercellular oedema, basal layer hyperplasia) and (b) showing marked epithelial infiltration by eosinophils.

The patient was advised to take PPI 1x40 mg per day. A normal diet was suggested due to the inability to perform nutritional testing at the time. She was advised to avoid eating large pieces of food and chew food properly. Furthermore, the patient was also advised to take fluticasone directly swallowing it instead of inhaling it in case of worsening dysphagia. The patient did not have regular visits after initial diagnosis in 2017. The patient also did not abide by the therapy after diagnosis but reported no major complaints. Furthermore, the patient was diagnosed with autoimmune thyroiditis and epilepsy in 2011. She was taking fluticasone propionate and montelukast for her asthma, which was diagnosed in early childhood. The patient is atopic, allergic to dogs and food items such as peanuts, walnuts, and eggs.

The chest X-ray at the emergency showed no perforation or mediastinitis. A gastroenterologist recommended an EGD due to dysphagia, history of EoE, and suspicion of a foreign body in the esophagus. The gastroenterologist recommended nil per os (NPO) status and initiated intravenous administration of 500ml of 0.9% saline and pantoprazole was reintroduced. The EGD revealed a shallow laceration at of the mucous membrane at the gastroesophageal junction and at 20-22cm (about 8.66 in) a deep laceration was found (Figure 4a) and was closed with 3 hemostatic clips (Figure 4b). Another laceration was also found on the upper part of the esophagus.

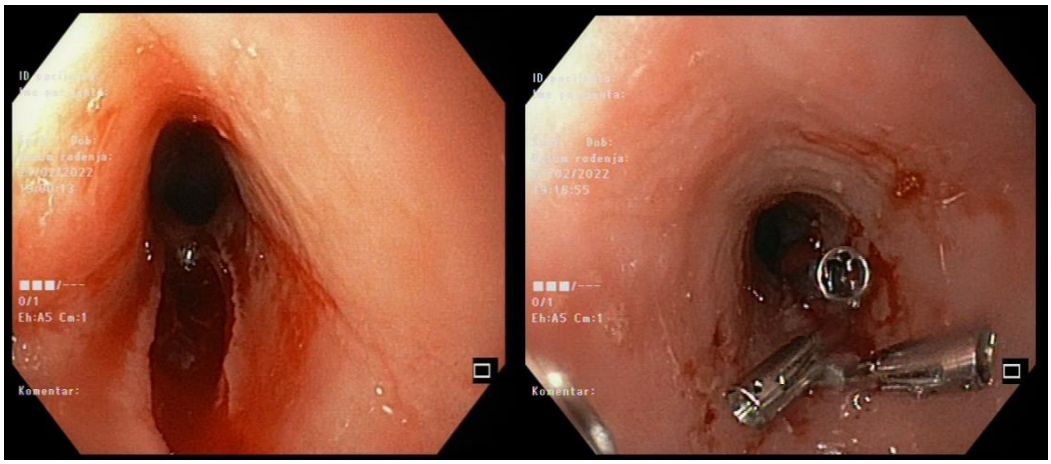


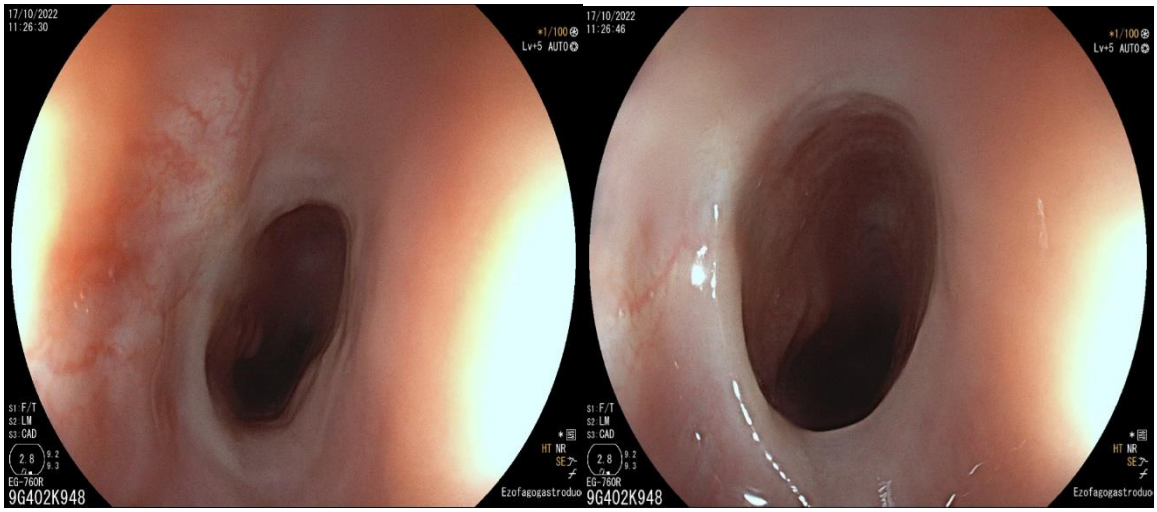
Figure 4. a (left) and **b** (right)

(a) An image capturing the laceration, visualized through EGD, positioned 20-22cm from the teeth.

(b) An image of the esophageal mucosal laceration after being closed by hemostatic clips.

The patient received pantoprazole and antibiotic prophylaxis during their ward stay after the laceration was closed and PPI therapy was reintroduced. With the implemented treatment measures, the patient remained hemodynamically stable and cardiopulmonary compensated. The patient at this stage was free of complaints, could swallow saliva properly and was free of any pain. The patient was discharged safely with no signs of ongoing hemorrhage during oral intake. The specialist consulted the Center of Clinical Nutrition for EoE treatment counseling. Hence, she was recommended an elimination diet, removing six food items and their products, including milk, soy, eggs, nuts, wheat, and seafood, while allowing the consumption of meat, millet, buckwheat, potato, and rice products.

The patient had a follow-up EGD in late 2022 showing a fibrous ring directly below the upper esophageal sphincter, showing resistance to the endoscope (Figures 5 a and b).
After the EGD the patient was advised to take a mushy diet, in line with the recommendation from the Center of Clinical Nutrition, pantoprazole 40mg daily. Topical corticosteroid therapy was initiated in the form of budesonide therapy, 1mg twice daily. Biopsies were also done then, showing no eosinophils, implicating regression of disease.



Figures 5. a (left) and **b** (right) show images from the EGD capturing the upper segment of the esophagus with visible stenosis (a) and a fibrotic ring 16 cm (about 6.3 in) from the incisor (b).

On the follow-up after 18 months of PPI, budesonide and food elimination diet the patient reported no food impaction, no chest pain while eating and no trouble swallowing food of all consistencies. She was advised to stop taking pantoprazole after a month and to continue with budesonide and elimination diet until the next checkup.

This case emphasizes the importance of treatment adherence for patients with EoE. Regarding other treatment modalities, esophageal dilation might also have been taken into consideration in 2022 due to esophageal stenosis and fibrotic ring discovered upon EGD. This procedure involves the mechanical expansion of narrowed esophageal segments, allowing the enhancement of swallowing, and limiting dysphagia. The procedure could have provided comfort from symptoms and could have prevented further complications, however careful evaluation by a gastroenterologist is vital to assess the patient's condition and response to treatment. This case additionally puts emphasis on the need for teamwork among medical practitioners and the use of personalized management for long-term esophageal health and disease.

5. Pathophysiology

The current understanding of the pathophysiology of EoE is limited. Environmental factors may play a significant role in the disease's development such as exposure to antibiotics in early childhood, birth by caesarean section, premature delivery and most important of all,

exposure to food allergens (6). These factors point out the fact that impaired development of the immune system may lead to susceptibility to EoE, hence the disease occurring more commonly amongst people that suffer from other atopic diseases. Additionally, there is a higher risk in contracting the disease in family members of people who also have the disease, showing that the disease may have a genetic part. In a study it was shown that the incidence of EoE in monozygotic twins was higher, (around 41% more) than in the general population suggesting a genetic predisposition. However, it was also shown that incidence was around 21% higher in dizygotic twins than in the general population suggesting that disease manifestation may also be attributable to environmental factors (6).

Although the exact process remains unknown, it is believed that esophageal epithelial cells release the cytokines Interleukin-5 (IL-5), Interleukin-13 (IL-13), Interleukin-4 (IL-4), and granulocyte macrophage colony stimulating factor (GMC-SF) to attract eosinophils to the lamina propria and activate mast cells after antigen sensitization by antigen presenting cells (APCs). Additionally, toll-like receptors (TLRs) on the surface of esophageal epithelial cells can be activated through antigen interaction leading to an intracellular cascade and release of cytokines by the cell. The release of IL-4, IL-5 and IL-13 by these cells leads to a T-helper type 2 (Th-2) response with the recruitment of eosinophils and mast cell activation (Figure 6).

EoE may have a link to connective tissue diseases such as Marfan, Ehlers Danlos and Loeys-Dietz Syndrome. Common to these pathologies is a defective transformation growth factor beta (TGF-β) pathway. TGF-β is also known to be increased in patients with EoE, particularly in eosinophils that exist in the inflamed lamina propria. TGF-β has been related to allergic inflammatory reactions and is directly involved in regulating fibrotic processes (6). Furthermore, it has also been hypothesized that mast cells that lie deep within the esophagus may also exhibit TGF-β and play a role in the pathogenesis. This has been shown by immunofluorescence staining. It was observed that TGF-β promotes the contraction of human esophageal smooth muscle cells and this effect was also observed through the induction of histamine suggesting that mast cells may also play a role in the pathogenesis of this EoE by causing abnormal esophageal smooth muscle cell function (7). Dysphagia, known to be a common symptom of EoE, may arise from the combined effects of TGF-β and histamine on smooth muscle cells in the esophagus (7). This study referenced in this section provides an outlook on how (TGF) -β may play a central role in the development of fibrosis and smooth muscle contraction in EoE (7).

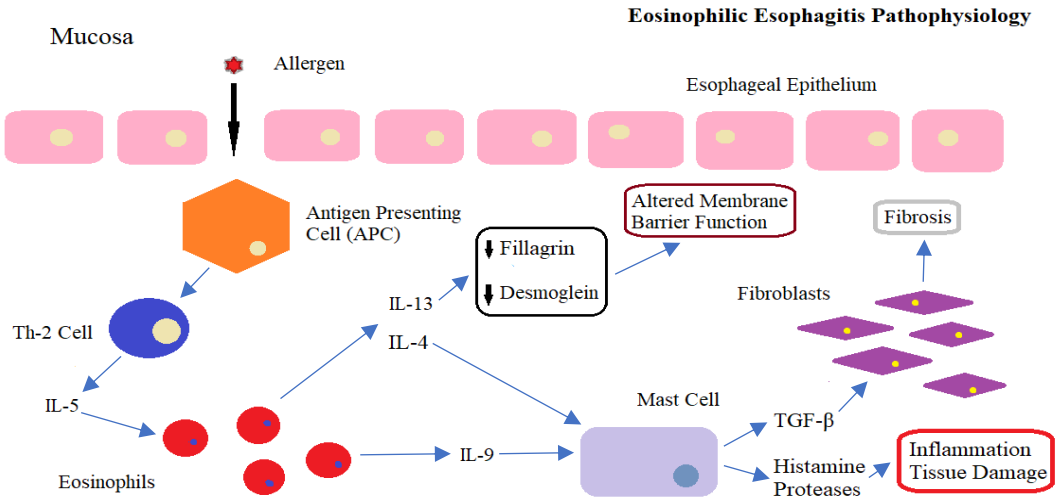


Figure 6. The diagram depicts the pathophysiology of EoE, where allergen exposure activates Th2 cells. These cells release cytokines, leading to eosinophil recruitment, mast cell activation, and reduced epithelial barrier proteins. This results in altered membrane barrier function, inflammation, tissue damage, and fibrosis, characteristic of EoE.

6. Risk factors

The root cause of EoE is still unknown. While certain theories implicate genetic factors in disease development, most studies target the hygiene hypothesis and environmental risk factors. It is crucial to consider the presence of underlying atopic diseases, which are present in many EoE cases. Early life exposure to allergens or microorganisms has been identified as a potential contributing factor, with some studies suggesting that EoE may be part of the atopic march, although it is not an IgE-mediated condition (8) The different risk factors have been summarized in tabular form (Table 1) (8).

6.1. The hygiene hypothesis

The hygiene hypothesis entails that children that are exposed to a certain microorganism early in life are less prone to developing certain diseases throughout their lifetime due to developing a more robust immune system owing to early development of a more balanced microbiota (8). The development of the microbiota, to become more diverse regarding different microorganisms, occurs by the end of the first 3-5 years of life. Early life exposures or circumstances may lead to changes in the microbiota that may occur later in life. These exposures involve dietary changes, infection, chronic disease, or the misuse of antibiotics.

Many studies until now have provided evidence of different microbiota status regarding atopy, with many studies initially focusing on the gut microbiota but eventually started considering the entirety of the microbiota leading to the discovery of differences in esophageal microbiota between controls, GERD and EoE patients, however, the question still exists - does the atopic status in question lead to the development of an impaired microbiota or does the impaired development of the microbiota lead to the atopic disease development (8)?

6.2. Relevant risk factors

In this following section of the thesis, we aim to present the possible risk factors leading to changes in immunity that may be attributable to the development of EoE.

Table 1. The following are relevant risk factors for EoE (8).

Fetal Development	**Infancy**	**Childhood/Adulthood**
Maternal infection	NICU admission Caesarean delivery Antibiotics Formula feeding Absence of furred pets Acid suppressants	Climate and season Smoking Alcohol Infections H. pylori

These factors are implicated in microbiota development, especially antibiotic use by the mother or infant which has been the most consistent association with alteration of the gut microbiota, choice of infant feeding which involves formula feeding or breast feeding, with breast feeding having a protective effect. Cesarean delivery is also mentioned, since the newborn does not have contact with the mother's vaginal or fecal microbiome that may lead to the diversification of the child's microbiome (8). Acid suppressants, especially PPIs, have been used to diagnose EoE may lead to a drastic change in gut microbiota when used over a longer period. There also have been studies showing that maternal use of PPIs during pregnancy may lead to atopy in the child. The use of PPIs and its association with development of EoE may be debatable as different studies have yielded different results such as this one case study where the prescription of PPIs after endoscopy the led to no prominent increase in EoE cases upon repeat endoscopy. Another study included in the literature which

provides a case series of three patients with esophageal reflux did note development of EoE after treatment with PPI showing conflicting results (8).

Jensen et al. (8) concluded that although many investigations are being done on the risk factors for EoE there still exists large gaps in knowledge. There have been many studies indicating the association of the use of antibiotics and EoE, however, these studies may be subject to recall bias and confounding; thus, we cannot confirm the use of antibiotics as a direct cause of EoE. In the first place, the diagnosis of EoE is difficult as it shares similarities to other esophageal disorders and has an array of non-specific symptoms. This may make it difficult to choose patients for studies, introducing selection bias (8).

Regarding infectious diseases as a risk factor for EoE, it has been noted that Helicobacter pylori may influence the risk of EoE with the observation that the risk of EoE decreases in the absence of Helicobacter pylori infection, showing an inverse relationship in a study conducted by Evan. S Dellon et al (9). This relationship has been observed in both adults and children. There is also epidemiological association with Herpes Simplex virus (HSV) with one report establishing that three out of the four pediatric patients who were diagnosed with EoE, received the diagnosis within two months of being diagnosed with HSV. Further evaluation is needed to establish an association between EoE and HSV esophagitis (10). In relation to climate and seasonality the results have been inconsistent because there is usually a diagnostic delay in the diagnosis of EoE with the symptoms usually occurring much earlier than eventual diagnosis. There have also been reports of increased risk of developing EoE in colder climates in a study conducted by Hurell GM et al in the United States. On the other hand, some studies report no apparent association between climate and seasonality which paradoxical as different climates and seasons bring about a wide array of different air allergens that must bring about a difference in prevalence in disease (11).

Only one study so far has explored the effect of gene-environment interactions regarding EoE with the study revealing that breastfeeding has a positive effect in providing defense against EoE with people with the susceptibility gene calpain 14 (CAPN14). Genetic and genetic-environmental interactions should be studied in more depth as these types of studies may reveal environmental factors that may be vital to disease development and help us moderate them and help us set therapeutic goals (12).

Behavioral risk factors include the use of alcohol, non-steroidal anti-inflammatory drugs (NSAIDs) and smoking cigarettes and the effect of smoking and use of NSAIDs mentioned in one study where data the use of NSAIDs and smoking were assessed in 115 cases and 225

control cases. The study revealed a decreased risk in cigarette smokers and with frequent NSAID usage. There was a slightly increased risk in people who used alcohol, adjusted according to age, gender, race, and education level (13).

Recent years have witnessed considerable progress in understanding EoE; nevertheless, numerous aspects of the disease remain poorly investigated, including the pathophysiology of the disease and the most effective therapies. Clinician-scientist-patient collaborations in research are therefore essential for extending existing knowledge on this complex disease.

7. Epidemiology

Epidemiology is a branch of medicine that tackles the distribution, incidence and control of disease, risk factors and other health-related factors. It makes the use of observational experimental study designs such as case-control, cohort, or cross-sectional studies to draw conjectures about etiologies of diseases (14). These hypotheses generated through observational study designs are assessed by employing experimental study designs, such as clinical trials. EoE has an ongoing study at local center, regional and national levels to better understand its patterns, risk factors, and the burden of the disease (14). It is of note that the past twenty years have played a pivotal role in studying the epidemiology of EoE. At first, case reports and case series were instrumental in outlining EoE's clinical features. However, with time, larger cohorts were reported, and data began to accumulate, which facilitated the development of guidelines and a clear definition of the disease. The results of epidemiological studies show a gradual increase in incidence and prevalence of EoE along with determining the probable risk factors responsible. This section of the thesis will give an overview of the currently existing epidemiological knowledge on EoE (12, 13).

It has been shown that the prevalence of EoE is higher in western countries compared to Asian countries with the prevalence being higher and similar in North America, Australia and Western Europe and being much lower in countries such as Japan and China (15). The disease occurs more often among Caucasians. EoE is strongly associated with other atopic diseases such as asthma, allergic rhinitis, food allergy and atopic dermatitis and may tend to be hereditary (14). EoE is known to occur in any age group albeit most commonly occurring in children, adolescents, and adults younger than the age of 50, with the disease having a predilection for males, who are three to four times more prone to developing disease than females (14). The reason for male predilection is not known as of now (14).

7.1. Age related differences

Regarding age, there are also differences in the presentation of disease between adults and children with the disease with children commonly presenting with an inflammatory phenotype as opposed to a more fibrosis-prevailing phenotype with disease progression throughout life according to recent data presented in a study by Liacouras et al. Symptoms in children usually involve heat burn, vomiting, chest pain, and failure to thrive. EoE in adults typically presents with symptoms such as difficulty swallowing, chest pain, acid reflux, regurgitation, upper abdominal pain, nausea, vomiting, and weight loss. (12, 14). It has been conjectured that the EoE in children manifests as white plaques, decreased vascularity, or mucosal edema, along with linear furrows. Children typically do not present esophageal rings or sphincters which are indicators of long-standing disease (17). This data aligns with the disease's pathophysiology, showing that disease development depends on remodeling of the esophagus and build-up of fibrosis (17). Throughout life the continuous inflammatory state induces the deposition of collagen in the subepithelial regions of the esophagus, leading to the development of strictures causing narrowing and the formation of rings (17).

Regarding these strictures, a retrospective cohort study conducted in Switzerland was designed to determine the diagnostic delay, which is how long before the diagnosis and initial treatment the patient suffered symptoms. As a result, there was a strong correlation between increased diagnostic delay and finding esophageal strictures upon diagnosis. The study showed that only 17% of patients showed esophageal stricture development with less than 2 years of symptoms before diagnosis compared to 71% that presented strictures with more than 20 years of symptoms. The study concluded that every decade of untreated EoE led to two times increase in the chance of developing esophageal strictures. This study provides emphasis on the awareness of the need to treat this condition before patients develop debilitating life complications (18).

Another study, conducted by Vernon et al. (19), was aimed at evaluating and comparing children and adults' differences in characteristics of the disease. One of the studies involved 100 patients, half of them being children and the other half being adults. Among the children, many were white and male with the mean age of diagnosis being 8 years. Most of the adult respondents diagnosed with the disease were white, with the mean age at diagnosis being 40 years. Patients diagnosed with EoE often have or had a history of another atopic disease. Atopic diseases are known to coincide with EoE including atopic dermatitis, food allergy, allergic rhinitis, conjunctivitis, and asthma. The findings from the study also showed that

children with the disease have higher probability of having a history of having asthma as with 52% of children compared to 24% for adults. The presence of concomitant atopic diseases other than asthma also did not differ statistically significantly between children and adult patients. Among children and adults, allergic rhinitis was detected to be the most frequent comorbidity in patients with EoE; the second most frequent disease is asthma, while the third is atopic dermatitis (19).

In addition to antigen sensitizations that have been proven using skin prick testing (SPT), testing for serum antigen-specific immunoglobulin (IgE), and atopy patch testing (APT). SPTs and atopy patch tests APTs are diagnostic methods employed to detect allergic sensitivities. SPT administers allergen extracts to the skin, followed by pricking to evaluate immediate reactions, whereas APT, designed for delayed-type responses, applies allergen patches for an extended duration. Positive responses indicate sensitization to allergens, facilitating allergy diagnosis and treatment. Adults with EoE were presented with sensitization towards air allergens and children showed more sensitization towards foods such as egg, soybean, wheat, and milk. Adults also develop sensitization to the former food items along with vegetables, namely carrots, onions, and tomatoes. Adults, however, showed sensitization to air antigens such as dust mites, aspergillus, and cockroaches than to food items. Regarding food, both adults and children displayed immediate hypersensitivity to some foods with children being more prone to peanuts, milk, and soy with milk being the most common culprit (19).

Adults, however, displayed immediate hypersensitivity to tree nuts, shellfish, and wheat. Both adults and children in the study had delayed hypersensitivity to foods. However, children displayed a drastically higher number of reactions, confirmed using an APT to foods such as meats, vegetables, and milk (19). Regarding air allergens, there was no significant difference found between children and adults for immediate sensitization to air allergens. In the study, both adults and children display a significant percentage of presence of atopic disease along with EoE. Comparatively, children displayed a higher percentage of asthma and other atopic diseases. This may be because children are more prone to atopic diseases, as they appear earlier in life and by adulthood the clinical picture has improved (19).

7.2. Incidence

A disease's incidence is the number of new cases that occur within a specified time and location. It is a measure of disease frequency in a particular population. To determine the disease incidence, it is necessary to exclude the existing cases and count all the new cases. This has been accomplished at referral centers in regions where the patient demographic and the geographic location they come from are clearly outlined (20). The following section provides an overlook on how the disease incidence has increased in the general population over the years around the world along with the diagnostic criteria taken from a more recent systematic review (20). The diagnostic criteria for EoE have changed over the course of many years with different guidelines being released in 2007, 2011, and 2018. The 2007 agreement defined EoE based on its clinical symptoms which were esophageal dysfunction, biopsy findings of 15 eos/hpf, and along with the exclusion of other disorders with similar clinical, histological, or endoscopic features, especially GERD. The 2011 agreement of the diagnostic criteria of EoE gave the disease chronic, immune, or antigen-driven, and PPI-responsive qualities. The 2018 guidelines defining EoE included symptoms of esophageal dysfunction, biopsy findings (15 eos/hpf), and no other possible causes of symptoms of esophageal eosinophilia along with a required trial of PPI removal (20).

The global pooled incidences for populations in the meta- analysis were divided by age, gender, high-income countries (HICs)/low-income countries (LMICs) and geographical areas. The meta-analysis combined various other studies conducted in different countries from around the world, with HICs including Australia, Canada, Denmark, Ireland, the Netherlands, New Zealand, Poland, Slovenia, Spain, Sweden, Switzerland, and the United States, and with the LMICs including Brazil, China, and Serbia. This meta-analysis has collected data from 1976 to 2022 reporting the incidence and prevalence of the disease from 40 different studies with a total population sample of 287,974,384 participants and 147,668 patients. The global pooled incidence was 5.31 cases per 100000 inhabitant years with a 95% CI (3.98–6.63). The pooled incidence calculated from the study was determined to be higher in the HICs group which was 5.63; with a 95% CI (4.24–7.03), compared to an incidence of 1.64 cases per 100000 inhabitant years, 95% CI (0.04–3.24). These results may be due to lower endoscopy rates and disease awareness in LICs. The results also showed a male predilection for the disease, especially in male children who showed the highest pooled incidence of 18.88, CI 95% (15.31–22.44) in comparison to adult males that displayed an incidence of 13.36 (10.90–15.81). Female children on the other hand had an incidence of 8.71 (4.69–12.72) whereas female adults had the lowest incidence of 2.22 (0.17–4.26). Based on

geographic location, the pooled incidence was the highest in North America 10.02; 95% CI, 6.53–13.52, followed by Oceania with 4.99 (1.22–8.76) and finally Europe with 4.16 (2.47–5.86). Amongst individual countries, the United States with a prevalence of 10.76 (6.87–14.65) had the overall highest, followed by Spain 8.47 (6.45–10.48); and then New Zealand 6.95 (5.91–8.12) (20).

7.3. Prevalence

A disease's prevalence is the number of people affected by a disease at a point in time, including new and previous cases. In the meta-analysis, 20 studies were included resulting in a global pooled prevalence of 40.04 cases per 100,000 inhabitant-years with a 95% CI and a confidence interval of 31.10–48.98. The study also showed a higher prevalence of the disease in HICs (45.05; 95% CI, 34.97–55.12) compared to LMICs with 14.17 with 95% CI, (1.73–26.61) cases per 100,000 inhabitant-years. The pooled prevalence of EoE was higher in males (111.09; 95% CI, 84.70–137.47) than in females (32.83; 95% CI, 14.16–51.50) cases per 100,000 inhabitant-years. The meta-analysis also showed a higher pooled prevalence amongst adults 52.95; 95% CI, 21.95–83.96 when compared to children 32.90; 95% CI (22.69–43.12) per 100,000 inhabitant-years albeit the prevalence being the highest amongst male children when divided according to age and gender, 72.00; 95% CI, (96.30–283.50). Second are male adults with a pooled prevalence of 131.40; 95% CI (78.34–184.47) cases per 100,000 inhabitant-years, and finally at the bottom come female adults with a prevalence of 23.01; 95% CI (1.08 to 47.09) cases per 100,000 inhabitant-years. In North America, the prevalence was higher in comparison to Europe with North America having a prevalence of 50.99; 95% CI, 18.95–83.03 and Europe; 42.49; 95% CI, 29.04–55.93 cases per 100,000 inhabitant-years. Amongst countries, Spain showed the highest prevalence of 71.45 (47.18–95.72), the second highest being the United States with 55.41 (-0.64–111.46) and then finally Denmark with 36.00 (-30.10–102.05) (20).

The study showed a global pooled incidence of 5.31 cases per 100000 inhabitant years and a global pooled prevalence of 40.04 cases per 100000 inhabitant years with the pooled incidence and prevalence being particularly higher in males, male children, HICs and North America. The pooled prevalence was shown to have increased from 1976 to 2022 by the study (20). A general lack of data from LMICs results from underdiagnosis due to limited access to endoscopy. Efforts must be made to increase awareness. The study does well to showcase the prevalence of the disease in regions such as North America, Europe, and

Oceania but falls short when considering the status of the disease in the other areas around the world that may further lead to discovering disease characteristics and risk factors previously unknown (20).

EoE was first considered to be a manifestation of EGE that occurred in the esophagus in 1977 (21). In 1978 it was thought to be a part of achalasia (22) and then a subtype of GERD. It was then in 1993 when finally, Attwood et. Al (23) described EoE as a condition independent of GERD or eosinophilic gastritis. They put forth a case of 12 patients that were presented with dysphagia as the chief complaint with eosinophilic inflammation localized to the esophagus and they showed no gastroesophageal reflux however they showed >20 eosinophils/high powered field in esophageal biopsies. 10 of the 12 patients had a nonspecific esophageal dysmotility disorder and 11 of the 12 patients had normal esophageal pH proven through a pH probe. This led them to conclude that they were dealing with a syndrome that had not been previously discovered (23).

With estimated prevalence of 43.0–56.7 cases/ 100,000 in North America and Europe (24), EoE is gradually becoming a clinically predominant disease. This change may be credited to the improved detection of the disease and the increased involvement of endoscopies in diagnostics (1). This explanation is viable however this cannot only be the case as some studies have compared the increase in rates of biopsies to the rate of increase in the disease and have concluded the increase in incidence of disease is in fact higher than the increased use of biopsies.

8. Clinical presentation

Age-related differences have been noted in the clinical presentation of EoE. Amongst adults, typical symptoms encompass dysphagia, complaints of food becoming lodged in the esophagus, heartburn, and chest discomfort. These symptoms can be mistaken for GERD, and often lead to misdiagnosis. Food impaction, which denotes the abrupt and painful blockage of the esophagus, is usually the event that occurs before the diagnosis of EoE. Remarkably, around 50% of adults with food impaction are diagnosed with EoE. Some adults may also describe nonspecific upper abdominal pain and in children, it is more frequent to encounter vomiting, regurgitation, eating challenges, abdominal pain, dysphagia, and failure to thrive. Among infants and toddlers, it may be more prevalent to find vomiting and feeding difficulties resulting in failure to thrive and inadequate weight gain. School-aged children are

more apt to display abdominal pain, notably after meals, and difficulty consuming solid foods. Older children and adolescents may demonstrate symptoms more akin to adults such as food impaction and dysphagia, therefore the clinical presentation differs among older children. Delays in diagnosis of EoE are common due to its symptoms overlapping with other conditions such as GERD, resulting in misdiagnosis and the application of ineffective treatments. Thus, endoscopies with biopsies are crucial in the precise diagnosis and the identification of EoE-specific endoscopic characteristics like white plaques, strictures, linear furrows, and mucosal rings (25).

9. Diagnostics

The diagnosis of EoE has proven to be a challenge in recent times due to its similar clinical presentation with other disorders of the esophagus such as GERD or PPI-responsive esophageal eosinophilia (PPI-REE) and absence of specific clinical features necessitates the use of endoscopic and histological findings which may be variable and sometimes difficult to access (26). Also, to order diagnosis it is necessary to rule out other causes of esophageal eosinophilia (Table 2) (27).

Table 2. Conditions that may be considered in the diagnostics of EoE as they may have a similar presentation (27).

Differential Diagnoses
Gastroesophageal Reflux Disease
Coeliac Disease
Chron's Disease
Achalasia
Drug Hypersensitivity
Eosinophilic Gastroenteritis

It is necessary to perform a comprehensive histological analysis of the biopsy findings and assess the patient's medical background. Using these two diagnostic methods, healthcare professionals can precisely identify and manage EoE. EoE induces distinct esophageal changes, which can subsequently be evaluated via an endoscopic reference score (EREFS) during an endoscopic examination and may be considered as a third diagnostic instrument based on recent investigations. Laboratory tests, imaging scans, and functional assessments are supplementary and are recommended for complex diagnostic scenarios. As a result of its intricacy, diagnosing EoE necessitates healthcare providers to consider a combination of

signs, histological, and endoscopic discoveries. No single finding is adequate for a conclusive diagnosis (27).

In this section of the thesis, attention is directed towards the intricate diagnostic elements of EoE, delving into the existing clinical protocols that are essential for healthcare practitioners. By examining the proposed techniques for lab tests, imaging scans, and functional assessments, the objective of this section is to offer insight into the evolving realm of EoE diagnosis, and the challenges encountered by medical professionals.

The identification of EoE introduces numerous challenges. Initially, while eosinophilia within the esophageal epithelium is deemed crucial for EoE diagnosis, their involvement in the immunopathogenesis of the disease remains obscure. Although trials aimed at reducing eosinophils did result in a decline in eosinophilia, they did not relieve symptoms, suggesting that other cells might also play a role in contributing to inflammation in EoE. Furthermore, trigger foods serve as a predisposing factor for EoE development, and since existing diagnostic methods identify IgE sensitizations, this necessitates the utilization of empirical diets to exclude food items that promote disease onset (27). The delay in diagnosing EoE can be as long as 10 years, based on a study in Denmark. This delay is concerning because it can result in inadequate treatment and greater chances of complications (28). There was no standardized severity index for EoE until 2022, when the new Index of Severity for Eosinophilic Esophagitis (I-SEE) was introduced to address this issue. This tool assists healthcare providers in making informed decisions when treating patients with EoE (29).

EoE has recently enjoyed several significant advancements in diagnostics and management. Its relevance and existence as a disease was uncovered initially in the early 20th century. It was characterized by infiltration of the esophageal mucosa by eosinophils and dysfunctional esophageal symptoms. Whilst the initial diagnostic criteria were established in the early 2000s, the first diagnostic guidelines were actually published in 2007. Additional revisions were made to the guidelines in 2011 and 2018 (20, 30). The analysis of the Guide for Research and Evaluation (AGREE) meeting held in 2018 updated the EoE diagnostic criteria (30). EoE guidance is being developed through ongoing research. In addition to consensus meetings, guidelines published by the American Gastroenterological Association (AGA) and the British Society of Gastroenterology (BSG) have played an important role in shaping EoE treatment and research. These guidelines provide advice on evidence-based management and ensure quality patient care (31, 32).

GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) is an internationally recognized schematic for evaluating strength of recommendations and quality of evidence of clinical guidelines. This is done based on risk of bias, the design of the study, the precision of the evidence and consistency. The AGA and BSG make use of GRADE to systematically review the evidence and assign a grade to each recommendation based on the clarity of evidence and the balance of benefit and harm of the intervention in question. Then the strength of each recommendation is determined using the quality of evidence, feasibility, values, and preferences. The GRADE system utilizes evidence quality grades from A-D; A suggesting high quality evidence, B indicating moderate quality evidence and with C and D indicating low quality and very low quality, respectively. Medical recommendations are either strong (Grade 1) or conditional (Grade 2), based on the reliability of evidence and the balance between benefits and harms of the intervention (33). By using the GRADE system, the AGA and BSG guidelines can provide clear recommendations allowing healthcare providers to make informed decisions regarding EoE management. Differences between these guidelines are minute and come down to importance given to different diagnostic procedures or therapy. The guidelines for EoE from the AGA and BSG exhibit differences that mostly stem from variations in healthcare systems, patient demographics, and available evidence. However, despite some differences between the guidelines of AGA and BSG for EoE, there are also similarities in their approach. Both guidelines aim to provide evidence-based recommendations for diagnosing and managing EoE to improve patient outcomes. Key areas of overlap include the importance of histological findings, the use of endoscopic biopsies for diagnosis, and the consideration of dietary and pharmacological interventions in treatment. Although specific recommendations may differ, the primary objective of optimizing patient care in EoE remains consistent across both sets of guidelines (31, 32).

The recommendations proposed forth by the BSG encompass EoE's definition, its clinical presentation, diagnostic and management strategies (Figure 7) (31). The BSG states that EoE is a medical condition that manifests with dysphagia, food impaction (most commonly occurring in adults), and various gastrointestinal symptoms (in children). Diagnosis of this condition is made by biopsy and histological assessment, showing no fewer than 15 eos/hpf (31). The GRADE scheme indicates high-quality evidence supporting strong recommendations throughout (31). The clinical presentations of EoE may vary amongst children and adults, which necessitates the need for specifically tailored diagnostic approaches for both age groups, including endoscopic biopsies. Furthermore, the guidelines address the similarities in clinical presentations between EoE and GERD and highlight the

need for extensive assessment to differentiate the two conditions. These recommendations provide a robust framework for effectively diagnosing and managing EoE. Using these guidelines, physicians are able to prevent development of long-term complications of this disease. The BSG guidelines specifically recommend obtaining at least six biopsies from different esophageal sites for diagnosis of EoE, with moderate evidence supporting this. Eosinophil density must be quantified per 0.3 mm^2, with a diagnostic cutoff of $\geq$ 15 eosinophils per 0.3 mm^2 in any biopsy specimen which is supported by moderate evidence and a strong recommendation. Additionally, mucosal eosinophilia should be accompanied by other histological features characteristic of EoE, with a strong recommendation based on moderate evidence. In treated EoE, histological response should be assessed based on eosinophil density with remission being defined as an eosinophil count < 15 eosinophils/0.3 mm2, despite low evidence levels. Moreover, esophageal physiological testing is recommended for patients with ongoing dysphagia despite histological remission and the absence of fibro-stenotic disease at endoscopy. This is supported by low-level evidence and a strong recommendation (31).

Significant growth and progress have been made in the diagnostics of EoE, yet there still are problems that must be addressed, particularly in terms of identifying the causative factors of the disease and the standardization of the diagnostic criteria. Hence, it is important to continue with conducting further research, accumulating more data and promoting collaboration within the medical community which leads to the refinement of diagnostic approaches and improvement of patient outcomes in the management of this multifactorial condition.

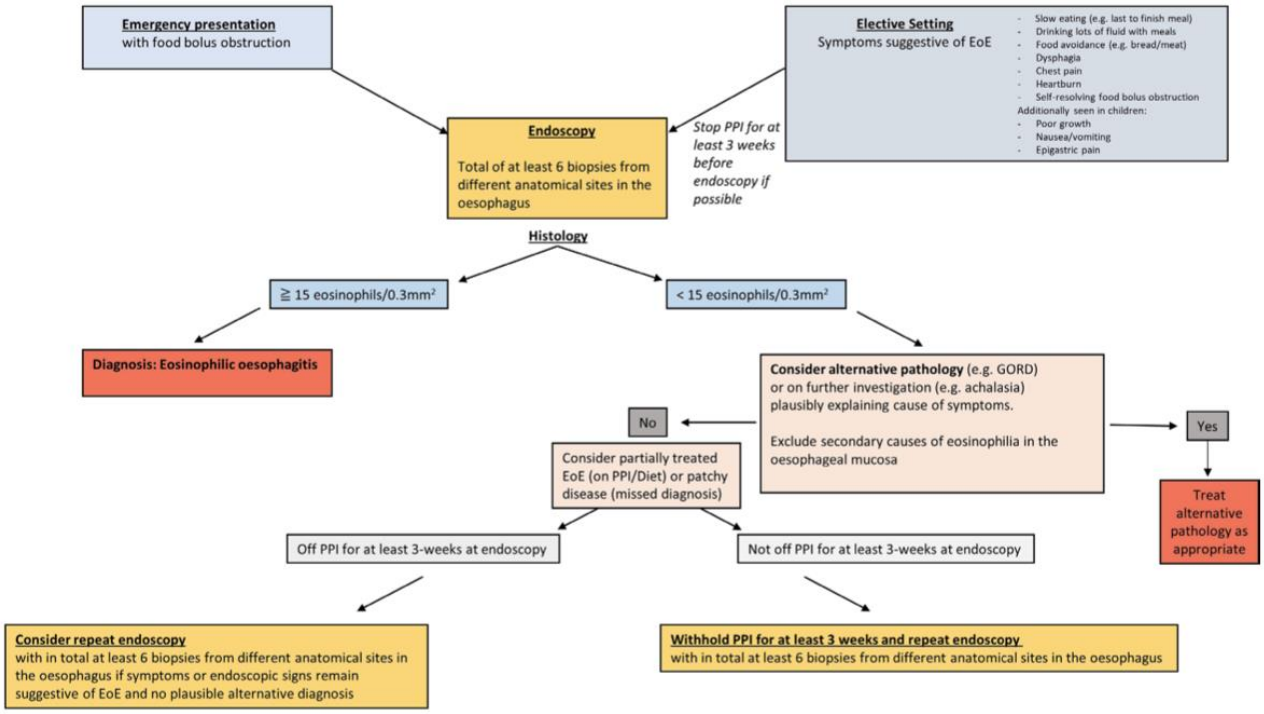


Figure 7. BCG diagnostic algorithm for EoE (31).

10. Treatment

EoE treatment is typically centered around dilation, medication, and dietary changes. The fundamental goal of therapy is to reduce inflammation which consequently results in fewer symptoms and complications, all while keeping in mind the patient's quality of life and the long-term financial and physical implications it may entail. The AGA guidelines outline a detailed treatment algorithm for EoE (Figure 8) (32). In order to evaluate the response to treatment, guidelines recommend conducting endoscopy with biopsy at the beginning of treatment, taking into consideration that symptoms may not always align with histological presentation. The thresholds for treatments have not been detailed, however, the aim is to achieve a normal epithelium with 0 eos/hpf, however, findings of less than 15 eosinophils are usually associated with regression. Additional treatment goals are to maintain the esophageal diameter at more than 16mm and to diminish inflammation such as exudate and edema (34). Treatment is based on symptom severity and endoscopic findings, with improvements in histological results serving as the primary indicator of success, rather than symptom resolution as measuring symptom changes is rather impractical. Thus, presenting a significant obstacle in EoE treatment. Obtaining biopsies for histological findings can also pose challenges, as it requires time and may impact the patient's quality of life, potentially leading to life threatening complications. It is of note that when conducting endoscopic biopsies on

children, it is important to exercise caution due to the potential impact of anesthesia on brain development. Special attention should also be given to therapy for children to ensure that they are achieving proper growth and developmental milestones. Children may exhibit behaviors such as prolonged mealtimes, food retention, and selective eating habits, while adolescents may avoid eating in public due to a fear of food impaction. The optimal goal of treatment remains unclear, with some patients showing no symptomatic improvement despite histological improvement, mostly due to the ineffectiveness of available treatments against esophageal fibrosis (34, 35).

Treatment of symptoms may also be a viable option, however, treating the symptoms has no correlation with esophageal remodeling and histological features. Esophageal remodeling refers to fibrosis and the appearance of striations and rings in the esophagus due to the deposition of collagen. Remodeling of the esophagus is responsible for major symptoms such as dysphagia and regurgitation and can be identified through endoscopy. Remodeling can also be seen through barium esophagogram. Esophagograms can be more accurate at evaluating the extent of the remodeling. PPIs are highly recommended for inducing remission and specific dosing recommendations have been outlined in multiple guidelines. While topical steroids are effective, they require maintenance treatment due to high relapse rates upon withdrawal and may cause severe side effects. Systemic steroids and immunomodulators are discouraged, and the use of novel biologics is promising but not yet strongly recommended. For further assessment in cases of symptom recurrence, repeat endoscopy is advised. Management by gastroenterologists and allergists is recommended for optimal treatment outcomes in patients with refractory EoE or significant concomitant atopic disease (34, 35).

10.1. Elimination diet

A diet change may be a less burdensome alternative for patients who require steroid therapy, although steroid therapy remains the most common standard of care. The amino acid-based diet (composed of free amino acids that are hypoallergenic) has been proven efficient in causing histological and symptomatic remission. However, this treatment modality may be quite expensive for sufferers of EoE and not sustainable in the long term and once the diet is weaned off the disease eventually recurs. Diet may also be altered by the elimination of certain foods that trigger EoE, guided by allergy testing through SPT (35). The BCG has thus established a set of consensus guidelines for effectively diagnosing and managing EoE. The

guidelines emphasize the effectiveness of elimination diets, in particular, the six-food elimination diet (avoids wheat, milk, soy, eggs, nuts, fish/shellfish), for achieving clinico-histological remission, while noting varying levels of compliance and endoscopy requirements. Dietitian support throughout dietary restriction therapy is extremely important and in cases of treatment failure, combination therapy with elimination diets and pharmacological treatment can be considered (31).

10.2. Medical Therapy

10.2.1. Proton pump inhibitors

Medical therapy for EoE is usually given in the form of PPIs and has been shown to cause symptomatic remission in a study carried out by Ngo et al (36). Although not as responsive as corticosteroids, they are considered a satisfactory first-line treatment of EoE as there are limited formulations of topical corticosteroids designed for esophageal delivery that are currently approved by the Food and Drug Administration (FDA) (37). PPIs block acid secretion in the stomach, limiting the damage caused to the esophagus, allowing the membrane integrity to be restored and leading to decreased crossing of allergens across the esophageal membrane. Acid reflux may directly impair the esophageal barrier function leading to cytokine release and inflammation (37). PPIs are therefore a rather more practical alternative than diet therapy and allergy testing therapy for it allows patients more room maintain a diet with a variety of food. In addition, it is also a less expensive alternative to an amino acid diet and it does not share similar taxing side effects of corticosteroids used in the long term that may lead to life threatening problems such as heart attacks, kidney problems, strokes and psychiatric problems which especially may occur through systematic application. PPIs are usually used in the long term. The long-term adverse effects are relatively unknown as of now, however, the FDA has given forth risks of standard dosing of PPIs which include susceptibility to Clostridium difficile infection, hypomagnesemia, and bone fractures, however, there are some effects mentioned in several meta-analyses that may be uncertain as of now such as gastric atrophy, gastric cancer, and other infectious diseases (37).

10.2.2 Topical corticosteroid therapy

Corticosteroid therapy is a commonly used first line treatment of EoE, however there are currently no FDA-approved drugs that provide a topical esophageal delivery which is the

primary mode of delivery. However, budesonide has recently been approved by the European Medicines Agency. There have been studies that report factors related to unremarkable response to corticosteroid therapy such as age, low dosage, severe esophageal stricture, atopic status, and prior esophageal dilation therefore these may need to be given some consideration through further studies (38). Topical corticosteroid application has shown scarce adverse effects such as oropharyngeal and esophageal Candida infections; however, more serious effects like decrease in bone density and adrenal insufficiency are still being followed. Resolution of histological symptoms after treating the patient with swallowed topical corticosteroid does not always mean that there will be resolution of esophageal remodeling, strictures, and dysphagia (38).

10.2.3 Biologic therapy

EoE, is a chronic type 2 (T2) immune-mediated inflammatory disease triggered by allergens and leads the progression of fibro stenosis in the esophagus if left untreated. Biological treatment of EoE delves into pathophysiology, looking further into the roles of eosinophils, mast cells, and various cytokines, including IL-4, IL-5, and IL-13, in the development and progression of the disease. The recent FDA approval of dupilumab, a monoclonal antibody targeting the IL-4 or IL-13 receptor, has demonstrated encouraging results. It demonstrated improvement in clinical, endoscopic, and histologic outcomes. Biologics are currently under investigation, such as IL-5 and IL-13 blockers, and other emerging therapies that target different inflammatory pathways (39).

10.2.4 Esophageal dilation

Esophageal dilation plays a pivotal role in the treatment of EoE, as it provides immediate relief of dysphagia, especially for patients with esophageal strictures. In 95% of cases, it leads to significant symptomatic improvement. Esophageal dilation does not directly address the underlying eosinophil inflammation although by combining it with effective drug or dietary treatments, it can decrease the reliance upon multiple procedures. Recent research suggests a lower risk of severe complications by applying esophageal dilation such as food impaction. Only mild postprocedural chest pain being observed as the most common side effect and a less than 1% risk of esophageal perforation. Furthermore, mucosal tears, previously seen as complications, are now considered potential indicators of procedural

success. Therefore, the procedure of esophageal dilation continues to be a highly crucial aspect in the management of EoE, especially in patients with strictures or a narrow esophagus, and particularly when dysphagia persists despite anti-inflammatory treatment (40).

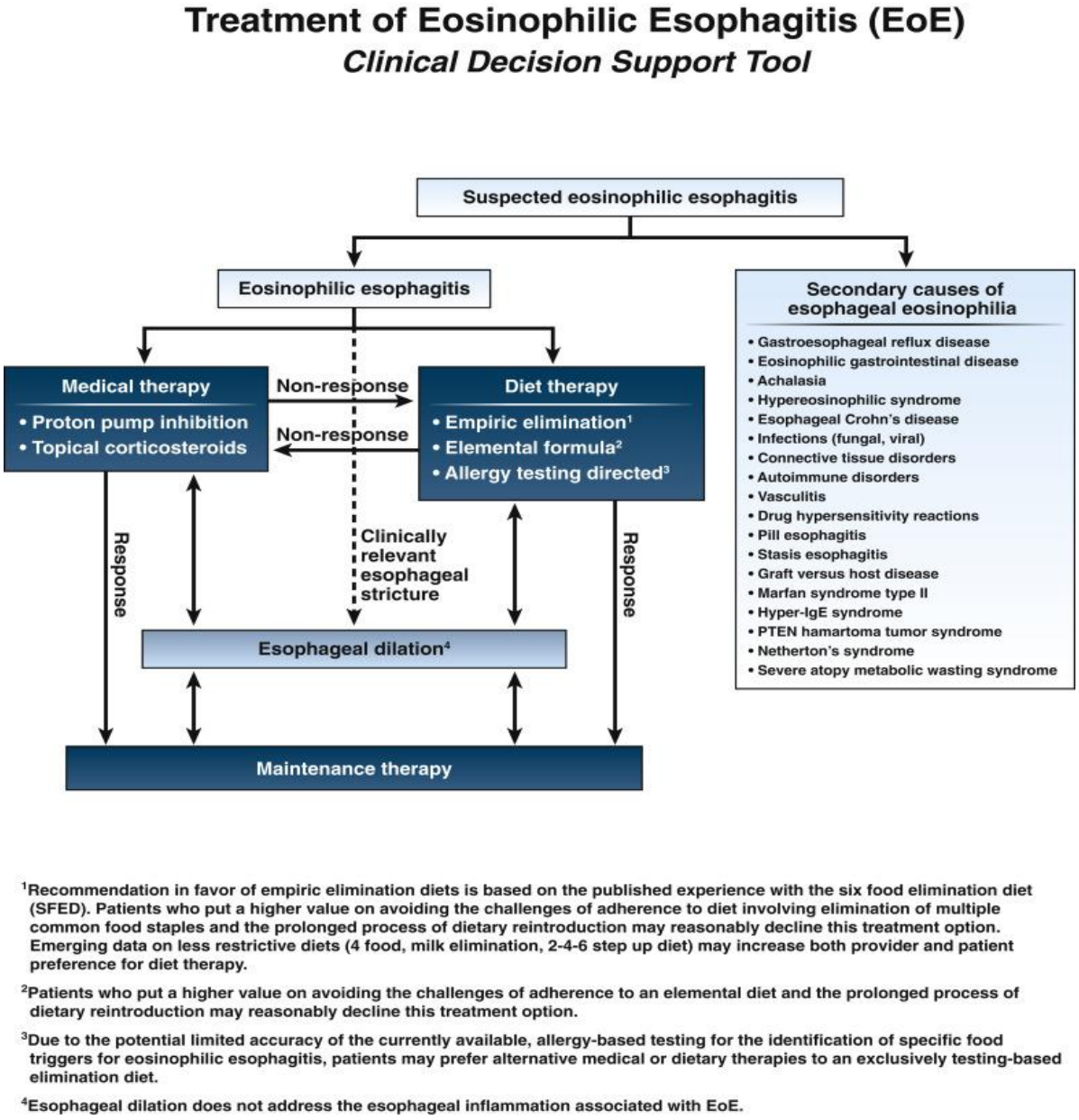


Figure 8. AGA treatment algorithm for EoE (32).

11. Discussion

EoE is a chronic medical condition, characterized by inflammation and infiltration of the esophageal mucosa by eosinophils. The disease presents symptoms such as dysphagia,

odynophagia, and food impaction. EoE has emerged as a distinct disease to GERD and EGE over the last few decades, gradually gaining recognition and increasing research in the fields of gastroenterology and allergy-immunology. Recent advancements in the understanding of EoE's pathophysiology have revealed its complex etiology. It involves genetic predisposition, environmental factors, and dysregulated immune responses to food antigens. EoE often occurs jointly with atopic conditions such as asthma, allergic rhinitis, and atopic dermatitis, indicating a shared underlying immune dysregulation. Diagnostic criteria for EoE typically include symptoms of esophageal dysfunction, endoscopic evidence of esophageal mucosal abnormalities, and histologic confirmation of eosinophilic inflammation, no less than 15 eos/hpf on esophageal biopsies. The clinical presentation of EoE varies widely, ranging from mild symptoms to severe esophageal strictures requiring intervention. Management of EoE requires organizing a multidisciplinary approach, which includes dietary modifications, pharmacotherapy, and endoscopic interventions specifically tailored to individual patient needs. PPIs, topical corticosteroids, and dietary elimination therapy are among the primary treatment modalities currently in use to induce and maintain disease remission. Despite significant progress in understanding and managing EoE, especially in the past two decades, challenges remain in further optimizing diagnostic strategies, elucidating the underlying pathophysiological mechanisms of disease, and addressing the burden of long-term management in affected individuals. Ongoing research efforts aim to further characterize the natural history of EoE, identify novel therapeutic targets, and refine and discover personalized treatment approaches to improve outcomes and quality of life for patients with this chronic debilitating condition. The two cases of EoE presented illustrate the complexities of managing this condition and its associated complications. The first patient, a 46-year-old male with a history of food bolus impaction and odynophagia, underwent emergency EGD for extraction of an occluding hazelnut, revealing underlying mucosal findings consistent with EoE. The successful extraction and histopathological confirmation underscored the importance of precise endoscopic techniques and collaborative care in managing acute esophageal obstructions and underlying chronic conditions. Similarly, the second patient, a 22-year-old with a history of EoE, was presented with dysphagia and esophageal laceration/stenosis necessitating emergency gastroscopy. Esophageal findings were managed with hemostatic clips and conservative measures, highlighting the challenges of managing recurrent dysphagia episodes in patients with chronic esophageal conditions. Both cases underscore the importance of interdisciplinary collaboration among gastroenterologists, interventional specialists, and pathologists in accurately diagnosing and managing esophageal

disorders. Moreover, they emphasize the need for consistent follow-up and adherence to treatment plans to prevent recurrence and optimize long-term esophageal health. Moving forward in navigating the complexities of EoE and other chronic esophageal conditions, it will be essential in engaging vigilance and using personalized management strategies, ensuring optimal outcomes for affected patients.

12. Conclusion

In summary, EoE is a chronic inflammatory condition characterized by the presence and accumulation of eosinophils in the esophageal mucosa, leading to symptoms such as dysphagia, odynophagia, and food impaction. Recognized as a distinct disease entity in recent decades, EoE involves a complex etiology that includes genetic predisposition, environmental influences, and immune responses to food antigens. It is often associated with atopic conditions such as asthma, allergic rhinitis, and atopic dermatitis. Diagnosis depends upon esophageal dysfunction symptoms, endoscopic results, and histological confirmation of eosinophilic infiltration. A multidisciplinary approach is required for management, utilizing dietary modifications, pharmacotherapy (including PPIs and topical corticosteroids), and endoscopic procedures. Despite progress, challenges remain in optimizing diagnostics, understanding mechanisms of the disease, and managing long-term patient care. The case studies presented underscore the importance of precise endoscopic techniques and interdisciplinary collaboration in acute and chronic management. Ongoing research and personalized treatment strategies are essential for improving patient outcomes and quality of life in EoE.

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15. Biography

Zmarak Khan

Born on 19, July 1998.
Developed an early interest in the sciences, particularly medicine.
Became deeply fascinated with gastroenterology and immunology, areas that combine the complexity of human biology with the intricacies of immune responses.
This fascination led to the focus on eosinophilic esophagitis (EoE), a chronic immune/antigen-mediated esophageal disease, for the thesis project. Through dedicated research, this thesis was made to contribute to the understanding and management of EoE, striving to improve patient outcomes and quality of life.
Fortunate to work under the mentorship of distinguished professors and researchers such as doc. dr. sc. Mirjana Kalauz and doc. dr. sc. Tomislav Meštrović and dr. sc. Damir Halužan have provided invaluable guidance and support during the academic journey.
Upon completion of his thesis, he intends to continue his research in gastroenterology and immunology, with a particular focus on chronic inflammatory diseases to further his expertise and contribute to innovative treatments and therapies.
Beyond the academic realm, he possesses a particular interest in the field of vascular surgery. Throughout the studies and clinical experiences, he has developed a deep appreciation for the complexities and challenges involved in vascular surgery. This specialized field improves patients' quality of life through intricate procedures and innovative treatments. Driven by a commitment to excellence and a desire to make a tangible impact on patient care, he aspires to become a vascular surgeon. He aims to further his education and training in this field, with the goal of contributing to advancements in vascular surgery techniques and patient outcomes.
In addition to his academic and research pursuits, he is also enthusiastic about volunteering, public health advocacy and teaching and believes in the importance of holistic development.

He is deeply grateful to his mentors, family, and friends for their unwavering support and encouragement. He dedicates this thesis to them and to all individuals living with eosinophilic esophagitis.