Chapter 6
Eosinophilic Esophagitis

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Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated condition of the esophagus with increasing incidence and prevalence worldwide. It is now identified as a cause of food impaction, dysphagia, and upper gastrointestinal symptoms in both the pediatric and the adult population. While EoE has not been associated with increased mortality or cancer risk, it is a progressive disease that causes significant morbidity. Since its recognition as a distinct clinical entity in the 1990s, research has expanded our understanding of its pathogenesis. Diagnostic criteria and treatment modalities have thus evolved considerably in the last two decades. This chapter will review the epidemiology, pathophysiology, diagnosis, and management of EoE.

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Epidemiology

Incidence and Prevalence

Population-based studies investigating the incidence of EoE have mostly been conducted in North America and Europe. The incidence of EoE ranges from 2.1 to 12.8 new cases per 100,000 persons per year [1]. A systematic review with meta-analysis of population-based studies observed a significant rise in the pooled incidence rates of EoE from 2.8/100,000 to 7.2/100,000 inhabitants/year [2]. While some studies attribute the rise to increased disease recognition, other studies have shown that the incidence of EoE outpaces that of endoscopic biopsies by several fold [1, 3–5]. Recent data suggests that the incidence is truly rising and not an artifact of increase detection. Overall, disease distribution and presentation vary according to several individual and community determinants.

The reported prevalence of EoE is affected by study methodology, population examined, and clinical practice patterns. The majority of information gathered as population-based estimates arise from data in North America and Europe, with some data from Australia and Asia. Currently, the estimated prevalence of EoE worldwide ranges between 13 and 49 cases per 100,000, although there is significant regional heterogeneity, and has been reported to be as high as 90.7 per 100,000 [1, 6]. As EoE is a non-fatal condition, studies universally report an increasing prevalence of EoE. It should be noted that the majority of studies prior to 2017 excluded patients whose disease responded to proton-pump inhibitor (PPI) therapy. Recent consensus guidelines on the diagnosis of EoE do not include this distinction, therefore studies likely underestimate the burden of disease.

Age

EoE can affect persons of all ages including infants, adolescents, and adults. The majority of EoE cases are seen in adults age 18–65 years [7]. A large number of EoE patients are under the age of 50, with a particularly high incidence near the third decade of life [5, 8, 9]. Pediatric cases account for about 25% of all EoE cases and usually occur between 5 and 10 years of age, though cases in very young children are also reported [10]. A large study of 30 million US patients estimated the prevalence of EoE in the adult population at 30.0/100,000, with prevalence in pediatric patients (age < 18) at 25.1/100,000 persons [7]. EoE is less common in the elderly (age > 65) with an incidence of approximately 12–18 cases per 100,000 in the USA [7, 9, 11].

Gender

Men are more frequently diagnosed with EoE than women, with a male to female ratio of 3:1 [9, 12–14]. A meta-analysis of five population-based studies found the pooled prevalence of EoE in male patients to be 53.8 per 100,000 compared with

20.1 per 100,000 in female patients [2]. Additionally, males more commonly report symptoms of dysphagia and food impaction [15]. A greater proportion of males are also diagnosed in childhood than compared with females [13, 16]. A large multicenter study found similar gender differences, with men noted to have a longer duration of symptoms and more esophageal strictures than women [17]. While this gender bias has been consistently observed in the literature, the reason for this discrepancy is incompletely understood as no significant differences are observed in endoscopic or histologic features [13].

Race

In the USA, EoE is particularly seen in Caucasians, who represent the majority of cases and account for approximately 80–96% of cases worldwide [14]. In a 2012 study conducted by Sperry et al., very few differences between Caucasian patients and African-American patients were observed. However, the authors did find that African Americans tended to present at a younger age with failure to thrive, while Caucasians often presented at an older age with symptoms of dysphagia [13]. A large retrospective study of 793 patients and several other smaller population studies reported similar findings [17]. Data regarding EoE in other racial groups are more limited, but the available data confirms lower rates of disease in these groups than in Caucasians. A large population study conducted at Kaiser Permanente of Southern California found EoE was 8 times more prevalent in Caucasians compared to Hispanics (11.6/10,000 vs 1.4/10,000) [18]. Another study conducted at two different institutions with a primarily Hispanic patient population found that EoE was 2–7 times more common among Caucasian patients than Hispanic patients [19].

Geography and Climate

The incidence and prevalence of EoE vary by geographic region, with the highest burden of disease in North America, Western Europe, and Australia [20]. A population-based analysis reported the incidence of EoE to be 5.4 per 100,000 inhabitants per year in North America and 1.7 in Europe [2]. The same study also found the pooled prevalence of EoE to be 1.9 times greater in North America than in Europe. Comparatively, the prevalence of EoE in Western Australia was found to be about half of that of Europe in a 2004 study [21]. Regardless of geographic location, a steady rise in EoE incidence and prevalence rates were observed upon comparison of studies conducted before and after 2008 [2].

Information on the epidemiology of EoE in other regions of the world including Central and South America, Asia, and Africa are scarce. In a large systematic review of EoE in Asian countries, a total of 217 patients were identified. More than half of the studies were performed in Japan, followed by Korea, Turkey, Saudi Arabia, China, and Taiwan [22]. One study of 1021 asymptomatic adult patients undergoing endoscopic evaluation conducted in Shanghai, China, only had 4 cases of

EoE [23]. In Japan, the prevalence of EoE is of similar magnitude, estimated to be about 0.01% [22]. Interestingly, even with lower rates of incidence and prevalence in Asian countries, the age and gender ratios of the reported cases were similar to those reported in Western countries [24]. Regional variations are not clearly understood and may be partly due to the result of access to endoscopic resources, physician awareness, or environmental exposures.

In addition to global variations, the prevalence of EoE also seems to vary by locality. For example, in the USA, population density is reported to have a strong inverse association with esophageal eosinophilia [25]. Additionally, patients diagnosed with EoE were almost twice as likely to live in cold climate zones than tropical climate zones in the USA [26]. There is also some evidence that seasonal variations affect symptoms attributed to EoE. Fogg and colleagues reported worsening symptoms attributed to EoE and increased eosinophilic infiltration on esophageal biopsies during the pollen season, with subsequent improvement during the winter months [27]. These results suggest that environmental flora and aeroallergens may play a role in pathogenesis and the disease course of EoE.

Pathogenesis

The understanding of EoE has significantly evolved over the last two decades and the pathogenesis is still being extensively studied. A hallmark feature of EoE is abnormal infiltration of eosinophils in the esophagus causing acute inflammation and chronic changes. Diagnostic criteria include several clinical and histological features that will be discussed further in later sections. This section aims to summarize current understanding of the interaction between genetic, environmental, and cellular factors in the pathogenesis of the disease. These pathways are the basis of targeted treatment in EoE.

Genetic Etiology

Prior familial studies have observed significantly increased risk of EoE among young, male first-degree relatives [28]. However, the mode of inheritance of EoE is complex and is not consistent with a traditional Mendelian pattern [29]. Multiple genes have been identified as likely contributors to the development of EoE and may have synergistic effects. Gene variants involved in general atopic disease, such as thymic stromal lymphopoietin (TSLP) that regulates Th2 cell development and activates eosinophils, are implicated in EoE. Genes specific to the pathogenesis of EoE have also been identified, such as CCL26 which encodes a potent eosinophil chemoattractant eotaxin-3 and CAPN14 which has a role in esophageal epithelial barrier function [30–32]. Although genetic factors may contribute to the development of EoE, the rapid rise in EoE incidence indicates a larger role for environmental factors in disease risk. A familial study conducted by Alexander et al. demonstrated that “heritability” estimates changed greatly by twin analysis when accounting for

common environment, where environmental factors contributed 81.0% of total phenotypic variance [29]. These results suggest that research on EoE designed to study nuclear families are likely overestimating the heritability of EoE and interpretation of these results are limited as common environmental exposures confound heritability analysis. By including common environment in the full model, heritability is estimated at 14.5% [29]. It is proposed that both genetic and environmental factors play an important role in the development of EoE and may be linked via epigenetic regulation [33]. Such regulation has been demonstrated for the strongly associated EoE genes CCL26 and CAPN14 [34]. Lifetime exposures likely potentiate a genetically susceptible individual for the development of EoE.

Role of Allergens

Strong evidence suggests that an allergic etiology is an underlying mechanism of EoE. The pathogenesis of EoE has similarities to that of other atopic disorders, such as asthma or atopic dermatitis [35]. Food and environmental allergens trigger a diverse esophageal inflammatory response, leading to a pathologic cycle of tissue damage and repair in EoE. However, the pathways by which the disease evolves over time remains a topic of investigation. Experimental models have shown that EoE can be induced in mice by means of allergen exposure to common culprits such as peanuts, inhaled aspergillus, or dust mite antigen [36]. Approximately 70% of diagnosed patients exhibited concomitant atopic diseases and sensitization to one or more foods and aeroallergens [37–39]. Furthermore, a wealth of literature has documented the benefit of allergen elimination through strict exclusion diets, particularly in children with EoE. In a sensitized individual, allergens react with IgE bound to mast cells and lead to localized mast cell degranulation. Mast cells release histamine and chemotactic factors that recruit eosinophils to the esophagus and induce eosinophilic degranulation. Eosinophilic granules release a variety of chemokines, cytokines, and cytotoxic proteins, which ultimately cause inflammation and tissue damage [35]. Even in patients who do not have manifestations of atopy or show positivity to allergy skin testing, studies have shown that they still exhibit classic cellular markers of allergy in the esophagus including immunoglobulin (Ig)-E bearing mast cells [40]. Due to the high rate of sensitization and the clinical response to elimination diets, food-specific IgE were initially suggested as a possible driver of EoE. However, the determination of specific IgE and/or skin prick tests have been inadequate in identifying causative allergens in EoE [41]. Diets geared toward eliminating specific type I allergens do not result in significant histologic or symptomatic improvements in all patients. Additionally, small trials using a specific anti-IgE antibody (omalizumab) only induced remission in a limited number of patients, did not significantly reduce eosinophil counts, and had variable endoscopic response despite reduction in IgE levels [42, 43]. In line with these findings, studies using animal models have demonstrated that EoE can be induced with B-cell-deficient mice but not in mice that are T lymphocyte deficient [44, 45]. Therefore, mounting data suggests that while EoE is often associated with IgE sensitization, the disease is not a purely IgE-mediated allergy.

Impaired Epithelial Barrier and Th2

There is increasing evidence that the development of EoE is associated with epithelial barrier dysfunction and subsequent T helper type 2 (Th2) predominant inflammation. Epithelial barrier impairment can develop due to a number of reasons including genetic predisposition, reflux disease, microbial imbalance, or food intake. Increased barrier permeability can allow microbes and allergens to attach and invade, resulting in activation of the immune system, cytokine release, and inflammation. Once the inflammation is established, impaired mucosal integrity may promote further allergen exposure thus perpetuating the cycle of cytokine release and a leaky epithelial barrier.

Desmoglein (DSG)-1, an intercellular adhesion molecule responsible for epithelial integrity, is one of the most strongly downregulated genes in EoE [46]. Other barrier function genes including Filaggrin, SPRR3, and keratins are also downregulated in esophageal tissue cells of active EoE [47]. Furthermore, both TSLP and CAPN14 have been shown to be overexpressed by the esophageal epithelia in patients with EoE [48]. TSLP regulates Th2 responses, especially those involving interleukin (IL)-13 production and have been implicated in atopic diseases [31]. In vitro, increased CAPN14 expression results in architectural changes indicative of barrier impairment [34, 49]. In active EoE, in addition to IgE-bound mast cells and eosinophils in the esophagus, tissue and serum have increased levels of type 2 allergic inflammatory mediators such as IL-5 and IL-13 [50]. IL-5 promotes eosinophil development, activation, survival, and recruitment to sites of inflammation. IL-13 is a key regulator of DSG and epithelial barrier genes. When overexpressed in mouse models, it has been shown to result in an EoE-like inflammation [51]. These various mediators are all part of the Th2 cascade which is central to mucosal eosinophilia and tissue remodeling in EoE.

EoE is a disease in which a dysregulated esophageal mucosal environment leads to Th2-predominant inflammation and disease development in response to food allergens and aeroallergens. A number of genetic and epigenetic factors can predispose to the development of EoE. Studies have started to uncover the role of activated eosinophils, mast cells, and the cytokines IL-5 and IL-13 as mediators of disease.

Diagnosis

Clinical Manifestations

The predominant symptoms of EoE can vary between adults and children. Infants and toddlers often present with non-specific symptoms of feeding intolerance, nausea, vomiting, and failure to thrive [38]. In contrast, as patients get older,

dysphagia and food impaction tend to be the most common presenting symptoms. Approximately 33–54% of adult patients with EoE present for endoscopic management due to food impaction [52]. Other commonly reported symptoms include heartburn (30–60% of patients) and non-cardiac chest pain (8–44%) [53]. The progression of symptoms from childhood to adulthood are thought to be associated with progressive esophageal tissue remodeling that occurs with chronic inflammation. A retrospective study of 379 cases of EoE found that for every ten-year increase in age, the odds of having fibrostenotic changes on endoscopy more than doubled [54]. As symptoms persist, many adults develop food aversions and adaptive feeding mechanisms such that elucidating dysphagia can be difficult. Patients can develop subconscious behaviors including eating slowly, prolonged periods of mastication, increased fluid intake with food, crushing pills, or taking small bites to cope with their narrowed esophageal caliber. Clinicians should therefore obtain a careful history paying particular attention to eating and swallowing habits with any patient who presents with symptoms suggestive of EoE. Importantly, symptom frequency and severity do not always correlate with the degree of eosinophilia or histologic disease activity, therefore diagnosis and monitoring require endoscopic evaluation [55].

When diagnosed with EoE at a young age, a significant percentage of patients can achieve symptomatic resolution. However, over time a large subset of these patients also experience relapse of symptoms. One study of 89 pediatric EoE patients found that 66% had resolution of symptoms with time but 79% later relapsed after a mean follow-up of 3 ± 1.4 years [38]. Two retrospective survey-based studies also suggested that symptoms associated with EoE diagnosed in childhood commonly persist into adulthood with approximately 40% of patients requiring ongoing medical therapy and ongoing care by a gastroenterologist [56, 57].

Symptom Scoring Systems

Several scoring systems have been proposed to standardize the evaluation of EoE symptoms and assess response to treatment. However, EoE clinical guidelines do not endorse the use of any specific scoring system, and thus many studies do not use a scoring system or use their own non-validated indices. While a uniformly adopted scoring system could reduce variability in symptoms assessment, many scoring systems previously used, including the Mayo Dysphagia Questionnaire-30 Day (MDQ-30) and the Straumann Dysphagia Index, are criticized for their cumbersome nature, lack of validation, and poor clinical applicability [58]. To address this, simplified scoring systems have been developed such as the Dysphagia Symptom Questionnaire (DSQ). This 3-question patient-reported outcome form is administered daily for 30 consecutive days [59]. When tested with both pediatric and adult patients, compliance and acceptance was excellent. However, the DSQ is limited by its focus on dysphagia.

The Eosinophilic Esophagitis Activity Index (EEsAI) PRO instrument is another scoring system that has been validated and can be used in adult patients. Symptoms from 183 adult EoE patients in Switzerland and the USA were studied and used to develop the 7-item questionnaire. The scoring system requires patients to recount dysphagia symptoms over a 7-day recall period taking into account behavioral adaptations [60]. However, a recent prospective multicenter study showed that endoscopic or histologic remission was only predicted with 60–65% accuracy using an EEsAI score of 20 as an arbitrary cutoff [55].

Comorbid Conditions

Patients diagnosed with EoE have also been found to have higher rates of concomitant allergic diseases such as atopic dermatitis, atopic rhinitis/sinusitis, asthma, and food allergies [38]. A meta-analysis and systematic review of 21 studies that included 53,542 EoE patients and controls found that allergic rhinitis was significantly more common among patients with EoE compared with control subjects (odds ratio [OR] 5.09), as was bronchial asthma (OR 3.01) and eczema (OR 2.85) [61]. Up to 50–80% of children with EoE have been reported to have atopy, with a somewhat lower rate in adults [62]. In patients with dysphagia, the presence of concomitant allergic symptoms should raise the index of suspicion for EoE.

Aside from atopic disorders, reports have suggested the association of EoE with multiple autoimmune conditions, most notably connective tissue disease. Individuals with connective tissue disease have been found to have an 8-fold risk of having EoE in retrospective analysis [63]. Larger prospective studies have not been conducted to confirm this association. EoE has also been reported with celiac disease and inflammatory bowel disease (IBD), although more recent research indicates that EoE is likely independent of these diseases. A large retrospective, cross-sectional study conducted with data from a US national pathology database demonstrated only a weak association between EoE and celiac disease, with an adjusted odds ratio of 1.26 (95% confidence interval: 0.98–1.60) [64]. Additionally, an association between EoE and IBD has only been made in case reports. Researchers examining the phenotype of eosinophils in patients with IBD and EoE found distinct features in the expression of surface markers that provide evidence for the independence of these two diseases [65].

Diagnostic Criteria

The diagnosis of EoE includes both clinical and histologic criteria. The first consensus guidelines for the diagnosis of EoE were published in 2007. In the subsequent decade, substantial changes have been made to the diagnostic algorithm

Table 6.1 Diagnostic criteria for eosinophilic esophagitis (EoE)

1. Symptoms of esophageal dysfunction (e.g., dysphagia, food impaction, heartburn, chest discomfort, regurgitation)
2. ≥15 eosinophils (eos) per high-power microscopy field (hpf) on esophageal biopsy (~60 eos/mm^2). Eosinophilic infiltration should be isolated to the esophagus.
3. Assessment for non-EoE disorders that could cause or potentially contribute to esophageal eosinophilia (see Table 6.2)

Table 6.2 Other causes of esophageal eosinophilia

Hypereosinophilic syndrome
Eosinophilic gastroenteritis
Infection
Vasculitis
Celiac Disease
Crohn's Disease
Connective tissue disease

based on evolving clinical experience and research studies. The most recent 2018 expert consensus statement set forth three specific criteria to diagnose EoE (see Table 6.1) [66].

Of note, increased eosinophilia on biopsy cannot in isolation be equated to a diagnosis of EoE. There is significant phenotypic variability in the presentation of EoE and clinicians must take this into account with the diagnosis.

The principal update in the 2018 consensus statement was the removal of the requisite that mucosal eosinophilia be refractory to a trial of high-dose proton pump inhibitors (PPI). Historically, both clinicians and researchers struggled with the diagnostic challenge of differentiating EoE from gastroesophageal reflux disease (GERD). Like EoE, GERD can also be associated with esophageal eosinophilia and can present with similar clinical symptoms of esophageal dysfunction. It was assumed that GERD and EoE were independent conditions, but the lack of a standard criterion for the diagnosis of GERD made its exclusion extremely difficult. Previously, a response to PPI therapy was used as criteria favoring reflux disease rather than EoE. However, a large body of research has suggested that EoE and GERD have a complex intersecting relationship rather than a mutually exclusive one. For example, acid reflux can induce mucosal injury thereby promoting cytokine release and eosinophilic infiltration while EoE may alter esophageal motility and structure thereby increasing the risk of GERD. The acid-reflux injury to the mucosal barrier then increases exposure to antigens thought to contribute to the pathogenesis of EoE [67]. According to the 2018 Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis, concurrent diagnoses of GERD and EoE can be made [66].

A new condition termed PPI-responsive esophageal eosinophilia (PPI-REE) has also been the subject of debate. The term PPI-REE was derived when clinicians observed that about one-third to one-half of patients who had clinical and histologic findings of esophageal eosinophilia responded to PPI treatment but did not have

typical symptoms of GERD. For several years, it was unclear whether PPI-REE was a subtype of EoE or a distinct clinical entity. Experts proposed that patients with PPI-REE be distinguished from those with EoE based on their initial response to eight weeks of acid suppression treatment [68]. However, a number of ensuing studies examining the differences between EoE and PPI-REE concluded that baseline features (before PPI therapy) were essentially indistinguishable. Clinical presentation, endoscopic findings, histologic features, inflammatory markers, and even RNA expression profiles were largely similar between the two conditions [69–71]. Cases also emerged where patients diagnosed with PPI-REE, after stopping PPI treatment, exhibited recurrence of esophageal eosinophilia and responded to classic EoE therapy of elimination diet and topical steroids [72]. These data suggest that PPI-REE and EoE have the same immunological mechanisms. Thus, 2017 guidelines on eosinophilic esophagitis no longer consider PPI-REE as a separate clinical entity [6]. It remains uncertain why some experience complete remission on PPI therapy while others do not.

Endoscopic Findings

Endoscopic esophageal assessment with biopsy is necessary for the diagnosis of EoE. Distinct endoscopic findings in EoE are usually only seen when the underlying histologic inflammatory cascade has been present for long enough to cause tissue remodeling. These findings, summarized in Table 6.3, Fig. 6.1, include fixed esophageal rings (trachealization), transient esophageal rings (felinization), white exudates, longitudinal furrows, edema, esophageal stenosis, stricture, and friable mucosa (crêpe-paper esophagus) [52]. In a meta-analysis conducted by Kim et al. of over 4600 patients with EoE, the overall pooled prevalence was as follows: esophageal rings, 44%; strictures, 21%; stenosis/stricture, 9%; linear furrows, 48%; white plaques, 27%; and pallor/decreased vasculature, 41%. In prospective studies, at least one abnormality was detected by endoscopy in 93% of patients [73]. Additionally, endoscopic findings vary between children and adults. Children more commonly have either a normal-appearing esophagus or inflammatory findings such as edematous mucosa with loss of vascular markings, pallor, or white plaques [73, 74]. Adults typically have endoscopic findings related to fibrostenotic changes including fixed rings, stenosis, and strictures [54]. Approximately 7–10% of adult EoE patients and 32% of pediatric patients will present with a normal appearing esophagus [73, 75].

Endoscopic assessment of disease activity is emerging as a therapeutically relevant outcome measure. However, there is a paucity of validated clinical tools to evaluate endoscopic features of EoE. The use of a uniform nomenclature to facilitate comparison of studies and communication between clinicians is recognized as

Table 6.3 Common Findings in EoE

Endoscopic	Exudates/white spots
	Pale, edematous mucosa, decreased vascularity
	Longitudinal furrows/ridges
	Rings or "trachealization"
	Stenosis/stricture or narrow caliber esophagus
	Friable mucosa with lacerations upon passing of the endoscope or "crêpe-paper esophagus"
Histologic	Eosinophil infiltration/abscess formation
	Dilated intercellular spaces (spongiosis)
	Epithelial desquamation/dyskeratosis
	Basal zone hyperplasia
	Rete peg elongation
	Lamina propria fibrosis

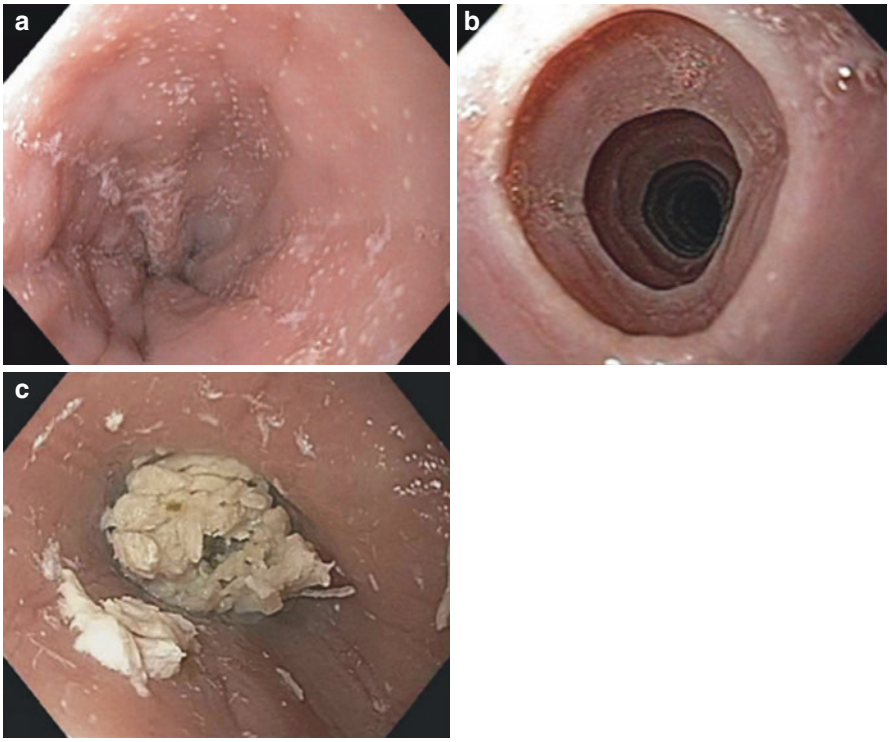

Fig. 6.1 Endoscopic images of patients with eosinophilic esophagitis. (**a**) White specks of esophageal mucosa consistent with eosinophilic microabscesses. (**b**) Ringed appearance of the esophagus. (**c**) Esophageal food impaction in setting of eosinophilic esophagitis

an area in need of advancement. Recently, a novel classification system was proposed called the EoE endoscopic reference score (EREFS). The acronym reflects the major components of the score: exudates, rings, edema, furrows, and strictures. It showed fair to good interobserver agreement among practicing and academic gastroenterologists [76].

In both the pediatric and adult population, improvement in endoscopic finding has been shown to correlate with histological remission after EoE treatment [77]. A tool such as EREFS therefore has the potential to standardize recognition and reporting of disease activity in EoE. However, data regarding the EREFS score is equivocal. In a prospective endoscopic study of adults with EoE, those who had a robust histologic response to treatment were found to have a significant decrease in EREFS scores [78]. The study also found that inflammatory components had the most prominent improvement after treatment. However, a prospective multicenter study of 145 EoE patients found that correlation of EREFS score with histological activity and clinical symptoms via the Dysphagia Symptom Score was poor. Based on the study, only exudates correlated with peak eosinophil count and histological outcome, whereas furrows and edema persisted in 50–70% of patients despite histological proven remission after treatment. Likewise, the study noted that none of the endoscopic findings were able to adequately predict dysphagia severity [79]. Another study exhibited similar results, suggestive of modest accuracy of the EREFS score in clinical practice [80]. These mixed results may be due to variability in endoscopist experience and practice. In order to optimize the predictive value of EREFS, the component features may need to be modified.

Histologic Features

While clinical presentation and endoscopic findings can raise suspicion for EoE, histologic confirmation of eosinophilia is necessary for the diagnosis. When obtaining biopsies, a minimum of 2–4 esophageal biopsies should be obtained from the distal esophagus and 2–4 from the proximal esophagus with a minimum of six biopsies in areas that appear grossly inflamed [6, 81]. This maximizes the likelihood of detecting eosinophilia since EoE can affect the esophagus in a patchy manner [66, 74, 82]. While the distal esophagus has been shown to have a denser eosinophilic infiltrate than the mid-esophagus in pediatric patients, this difference has been inconsistently demonstrated in adults [83–85]. When present, the likelihood of diagnosing EoE increases when multiple biopsies are taken from multiple esophageal regions. The current eosinophil density threshold to diagnose EoE is 15 eosinophils per high power field (hpf) in esophageal mucosa (peak concentration in the specimens examined). The level of 15 eosinophils/hpf is somewhat arbitrary and different cut-off values were used in earlier studies. Using 15 eos/hpf as a threshold, one study identified diagnostic sensitivities of 84%, 97%, and

100% when obtaining 2, 3, and 6 biopsy specimens, respectively [86]. While the threshold of 15 eos/hpf is highly sensitive, lower levels of eosinophilia have been reported in patients with EoE [82]. It is also important to consider several other potential etiologies of abnormal esophageal eosinophilia including gastroesophageal reflux, eosinophilic gastrointestinal diseases, Crohn's disease, celiac disease, and infection, among others. During upper endoscopy, biopsy specimens should be obtained from the gastric antrum and duodenum to rule out eosinophilic gastroenteritis in children, as well as in adults with potential gastric or intestinal symptoms [12, 74].

Histologic eosinophilia is a key feature of EoE with eosinophils typically layered in the epithelium or aggregated in microabscesses [87]. Disruption of epithelial tight junctions can cause dilation of the interepithelial space, termed spongiosis, that may progress to the formation of small "lakes" in the epithelium. These observed changes can lead to epithelial acanthosis with basal zone hyperplasia. Additionally, eosinophilic infiltration can extend to the lamina propria or deeper tissue layers causing collagen deposition and ultimately macroscopic tissue remodeling [88, 89]. In adults, eosinophilic microabscesses and lamina propria fibrosis were found to be most specific for eosinophilic esophagitis (98% and 97%, respectively), however they are not sensitive (56% and 27%, respectively) and are quite rare findings [82].

Imaging

Barium esophagography can be used in adolescents and adults to identify anatomic and mucosal abnormalities that have developed from tissue remodeling in EoE. This modality is most helpful in certain cases, such as when esophageal stenosis or stricture is suspected, and endoscopic dilation may be needed. The study can help characterize the length and diameter of complicated esophageal strictures. The indication for an esophagram should be discussed with the radiologist in advance to ensure the entire esophagus, including the caliber and distensibility of the esophageal lumen, is fully assessed. There is currently no role for CT or MRI in the diagnosis or disease monitoring of EoE.

Novel Diagnostic Modalities

Although EoE is best diagnosed by endoscopy and esophageal biopsy, the cost and risk of repeated endoscopy to monitor histologic response to treatment is burdensome. Therefore, there has been significant interest in identifying novel methods that are less expensive, more reliable, and/or less invasive.

Mucosal Impedance

One proposed mechanism in the pathogenesis of EoE is a loss of mucosal integrity leading to sensitization to food antigens. Dilation of intercellular spaces results in increased epithelial permeability which is thought to facilitate antigen exposure. This process can also allow free trans-epithelial transport of small molecules and electrolytes. As a result, electrical conductance across the epithelium increases and mucosal impedance decreases [90]. Using stationary transnasal intraluminal pH/impedance probe, van Rhijin et al. found a decreased baseline impedance value throughout the esophagus in EoE patients but not in healthy controls [91]. A follow-up prospective study by the same group using electrical tissue impedance spectroscopy also showed that electrical tissue impedance and transepithelial electrical resistance were reduced in EoE patients [92]. Recently, a through-the-scope probe that can measure mucosal impedance was developed, allowing for more precise and efficient assessment. It has been hypothesized that this mucosal impedance device could be used to measure the activity of EoE. In a study of 20 patients, point impedance measurements showed excellent inverse correlation to the number of eosinophils per high-power field taken from corresponding biopsy specimens. Using an impedance cut-off value of 2300 Ω, sensitivity and specificity were found to be 90% and 91%, respectively. It was also noted that once eosinophil count was greater than the threshold of 15 eos/hpf, there was a marked decrease in esophageal impedance reflecting active disease [93]. Larger prospective controlled trials are needed to investigate whether impedance measurement could replace esophageal biopsies in the future.

Esophageal Distensibility (Impedance Planimetry)

Symptoms in EoE are often related to tissue remodeling and fibrosis rather than active eosinophilic inflammation. The extent of fibrosis is difficult to quantify by standard esophageal biopsies due to its patchy distribution and lack of depth to include the lamina propria. Endoscopy often underestimates stricture presence and extent compared with barium esophagography.

The introduction of high-resolution impedance planimetry has enabled direct evaluation of esophageal mechanical properties and distensibility. The functional luminal imaging probe (FLIP) is an orally passed catheter with an infinitely compliant inflatable balloon and multiple electrodes that measure luminal cross-sectional area and intra-luminal pressure to render a three-dimensional approximation of esophageal anatomy [94]. Pressure volume characteristics are determined from step-wise distension of the balloon, which allows for objective measurements of esophageal narrowing. The balloon catheter is easily passed during endoscopy and no perforations have thus far been reported. The use of FLIP has been evaluated in a number of esophageal disorders including achalasia, GERD, and EoE

[94]. One study of thirty-three EoE patients has shown that esophageal distensibility, defined by the change in the narrowest measurable cross-sectional area over the change in intraluminal pressure, was significantly reduced in EoE patients compared with controls [95]. Another study reported an association of reduced distensibility with clinical outcomes including future food impaction and requirement for esophageal dilation [96]. Despite these findings and the commercial availability of FLIP, current recommendations for clinical use are limited by the low level of evidence and lack of standardized protocols. Currently, diagnostic and treatment decisions are not recommended to be based on Endo-FLIP findings [97]. However, whether the addition of FLIP would enhance the current care of EoE warrants further investigation.

Esophageal String

In addition to mucosal eosinophils, the presence of other molecules such as eosinophil-derived granule proteins (EDP) and related Th2 cytokines can be markers of disease activity [98, 99]. Thus, there has been interest in measuring the level of these biomarkers in esophageal secretions to estimate mucosal inflammation. Furuta and colleagues developed a mechanism by which to obtain and measure these proteins using the Esophageal String Test (EST) [100]. The device consists of a capsule filled with approximately 90 cm of string. The proximal end of the string is taped to the cheek and then the capsule is swallowed to deploy the string into the duodenum. After overnight incubation, the string is withdrawn so luminal secretions from the proximal portion can be scraped and analyzed for eosinophil-derived proteins. When tested in 41 children, the levels of luminal eosinophil-derived proteins in string samples significantly differentiated children with active EoE from those with EoE in remission, GERD, and normal esophagus. Furthermore, levels of proteins correlated with peak and mean esophageal eosinophils/HPF on biopsy. The benefits of this bedside test include its minimally invasive nature and ability to provide detailed biochemical information that may be able to differentiate disease phenotypes in the future. However, the data needs to be validated with larger studies.

Cytosponge

The ideal technique to monitor EoE would obviate the need for endoscopy yet adequately sample the esophageal mucosa for analysis. Researchers have examined the role of the Cytosponge (University of Cambridge) as a minimally invasive method for collecting esophageal tissue. The Cytosponge was originally invented for detecting Barrett's esophagus [101]. It consists of an ingestible gelatin capsule that is swallowed to dissolve and release a 3-cm diameter spherical mesh. The mesh is withdrawn through the mouth by traction of an attached string, and tissue specimens are collected from the sponge for analysis. In a prospective two-center

cross-sectional study of 57 adults with active EoE and 44 adults with inactive EoE, the sensitivity and specificity of the Cytosponge was 75% and 86%, respectively, when using a cutoff of 15 eos/HPF [102]. The tissue samples had very good correlation with mucosal eosinophil density on subsequent esophageal biopsies. The procedure successfully obtained adequate tissue samples in 95% of EoE patients and was well tolerated with no adverse events or sponge detachments. While these results suggest Cytosponge may be a promising device in the assessment of EoE, further research is required to understand its efficacy prior to incorporating it into routine practice.

Allergy Testing

Previous expert consensus statements recommended that patients diagnosed with EoE be evaluated by allergist or immunologist to assess the presence of concomitant disorders such as asthma, rhinitis, eczema, or food allergies [74]. This recommendation was made due to high rates (about 50–60%) of concurrent allergic diatheses found in patients with EoE [74]. However, the evidence for the benefit of allergy testing in the diagnosis and management of EoE remains unclear. Clinical decisions based on the interpretation of allergy testing have shown modest results at best. There are 3 types of allergy testing currently available: skin prick testing (SPT), atopy patch testing (APT), and serum food-specific IgE (sIgE) testing. SPT is a standardized and validated technique to study immediate allergic reactions medicated by mast cell-bound IgE [103]. In contrast, APT is used to assess the presence of non-IgE, cell-mediated reactions, but performance is not standardized and interpretation is subject to significant interobserver variation [104].

A systematic meta-analysis by González-Cervera and colleagues concluded that the predisposition of atopy to EoE is unproven, despite the extensively described association [61]. Allergy testing therefore has no role in the diagnosis of EoE. However, there is continued interest in establishing whether SPT and APT would be beneficial in assessing treatment response and in disease monitoring.

Esophageal Prick Testing

Skin tests and serum IgE levels do not accurately identify foods for elimination diets in patients with EoE. This may be because inflammation in EoE is localized to the esophagus. To further investigate this, Warners and colleagues evaluated direct esophageal response to food allergens. In a small prospective pilot study of 8 patients, the researchers injected allergen extracts into local esophageal mucosa and assessed for immediate and delayed response with repeat endoscopy. The study

found that compared with SPT and serum IgE testing, the sensitization patterns identified through esophageal prick testing (EPT) correlated more accurately with culprit foods in EoE patients [105]. This study was the first to demonstrate the feasibility and safety of EPT. Given the results, the authors advocate for further exploration of EPT and its potential to guide elimination diets.

Plasma Markers

Biomarkers from peripheral blood, breath sampling, oropharyngeal swabs, stool, and urine have also been assessed as a means of non-invasive EoE monitoring [106]. Currently, only 3 randomized controlled studies (RCT) have been completed, and no meta-analysis has been published. A limitation of using biomarker testing is the lack of reliability and reproducibility. Several biomarkers have been studied in patients with EoE, but none have been incorporated into treatment guidelines or clinical practice. The most common biomarker assessed were peripheral blood absolute eosinophil count (AEC) and IgE [106]. Both serum IgE levels and peripheral eosinophilia are frequently elevated in EoE patients, but neither has adequate sensitivity and specificity to utilize in clinical practice.

Approximately 70% of patients with EoE have elevated total IgE values on endoscopy [107]. However, despite evidence of increased IgE production in the esophageal epithelium, it seems to be insufficient to cause a significant increase at peripheral levels. Studies have shown poor correlation between serum total IgE levels and the number of eosinophils found in esophageal biopsies [108, 109]. Additionally, IgE-targeted therapies have yielded less promising results than expected [41, 110, 111]. Total serum IgE testing therefore has a limited role in the diagnosis and management of EoE.

The AEC is a simple and inexpensive serum test. Peripheral blood eosinophilia has been described in EoE patients (defined as >300/mm^3) [112, 113] and a number of studies have found that the percentage of peripheral blood eosinophils has high positive correlation with esophageal eosinophil density in pediatric and adult patients [112–114]. However, the use of AEC in the diagnosis and monitoring of EoE is thought to be imperfect due to possible confounders such as atopy, infection, and other inflammatory conditions. Only 5 small studies compared peripheral AEC between EoE patients and atopic patients with no significant difference noted [65, 112–114]. Min et al. conducted a prospective cohort analysis of 42 pediatric and adult patients and found the level of AEC was associated with a diagnosis of EoE, even after controlling for age, sex, allergic rhinitis, asthma, eczema, and seasonal allergies. Additionally, in the longitudinal analyses AEC alone predicted tissue eosinophilia post treatment [115]. Overall, evidence suggests that AEC may have value in the assessment of EoE. However, a majority of studies are small and have not demonstrated sufficient accuracy for clinical use.

Given the shortcomings of using absolute eosinophil count as an EoE disease activity marker, an approach using eosinophil surface makers, eosinophil-derived proteins, and pro-eosinophil cytokine levels has also been evaluated. It has been hypothesized that circulating eosinophils display distinct phenotypes in various disorders. The markers of greatest interest in this area of research include eosinophilic cationic protein (ECP), eosinophil-derived neurotoxin (EDN), eotaxin-3, chemokine protein levels, chemokine receptor-3 on eosinophils (CCR3), and interleukin (IL)-5. ECP and EDN have shown promise in a number of studies while the other mediators have shown variable results in the literature, particularly in prospective studies [116, 117]. Some investigators have proposed increasing sensitivity and specificity of biomarkers by using them in combination (e.g., plasma AEC with EDN, or AEC and ECP, etc.) [112, 115]. However, larger and more longitudinal studies are needed to clarify the role of these biomarkers in the diagnosis and management of EoE. At present, there is inadequate data to support the use of serologic markers as a surrogate disease indicator in patients with EoE and it is not recommended to base therapeutic decisions on these markers.

Treatment Options

Currently, there are a number of treatment modalities for patients diagnosed with EoE (summarized in Table 6.4). These include proton pump inhibitors, corticosteroids, and elimination diets (elemental or empiric). These treatments can be used alone or in combination. None of the medical therapies discussed for EoE are approved by the US Food and Drug Administration, and thus they are used off label. For patients who develop advanced symptoms such as esophageal narrowing, endoscopic dilation can be used to alleviate symptoms. Treatment should be individualized according to each patient's concerns and lifestyles, prior therapy, and the severity of presentation. The efficacy of any therapy should be checked by a follow-up endoscopy after a 6- to 12-week initial course [6]. The goal is to improve symptoms and minimize the risk of complications from chronic inflammation. Although the impact of successful therapy on the natural history of EoE has not been elucidated, effective treatment has been shown to reverse long-term complications including subepithelial fibrosis [118]. Therefore, timely treatment is of utmost importance [54].

One endpoint of therapy is a reduction of esophageal eosinophilia to fewer than 15 eosinophils/HPF in biopsies, although a discrete cut-off has not been clearly recommended in clinical guidelines. Controversy remains regarding treatment endpoints and long-term management. Data suggests that patients may experience recurrence and even progression of symptoms when treatments are discontinued [83, 119]. This causes uncertainty regarding when to stop acute therapy. Current expert consensus recommends maintenance therapy for patients with evidence of chronic esophageal remodeling, a history of food impactions, severe symptoms, or rapid recurrence of symptoms while not undergoing therapy.

Table 6.4 Treatment options for eosinophilic esophagitis (EoE)[a]

Treatment Type	Therapy	Description/Drug dosing	Estimated effectiveness as induction therapy	Grade of Evidence
Pharmacologic	Proton Pump Inhibitors	Omeprazole or Esomeprazole: 20–40 mg twice a day (initial dose)	30–60%	Level 1A
	Swallowed topical corticosteroids	Fluticasone via metered dose inhaler: 880–1760 mcg/day typically in divided doses	55–80%	Level 1A
		Budesonide viscous suspension: 2 mg/day typically in divided doses		Level 1A
	Oral corticosteroids [b]	Prednisone 1–2 mg/kg/day		Level 1D
Diet	Elemental	Amino acid–based, allergen-free formula followed by slow reintroduction of foods	70–95%	Level 1B
	Empiric elimination diet	Six most commonly allergenic food groups (milk, wheat, egg, soy, peanut/tree nuts, shellfish/fish) are removed from the diet and individually reintroduced after a symptomatic and histologic response	55–75%	Level 1C
Conservative Dilation [c]	Through-the-scope balloon or bougie dilator	Minimum target diameter between 15 and 20 mm over multiple sessions	80–95% (symptomatic relief only)	Level 1C

[a]No therapies for eosinophilic esophagitis have been approved by the US Food and Drug Administration to date. The dosing listed in the table is largely based on the 2013 American College of Gastroenterology guidelines

[b]Reserved for refractory or severe cases

[c] Reserved for patients who relapse on dietary or pharmacologic therapy. First-line therapy if high-grade strictures are present

Pharmacologic Therapies

Proton Pump Inhibitors In prior years, a response to PPI trial was used to exclude PPI-REE or GERD in patients with esophageal eosinophilia. However, given recent data, experts agree that PPI-responsive esophageal eosinophilia should be regarded as a clinical sub-phenotype of EoE and not as a distinct entity [6, 66]. EoE and GERD are now thought to be different entities that likely coexist, either in an unrelated fashion or in a complex bidirectional relationship. A PPI trial is no longer required for EoE diagnosis but rather PPI therapy is recommended as a first-line treatment for EoE (grade of evidence 1A). Since the early 2000s, retrospective studies observed a clinical and histological response to PPI therapy in patients diag-

nosed with esophageal eosinophilia. Evidence now supports that PPIs likely improve EoE by conferring both acid-suppressive benefits as well as anti-inflammatory effects via cytokine release [120, 121]. A recent systematic review with meta-analysis found that PPI therapy induced histological remission in about 50% of the patients (defined as peak eosinophil counts <15 eosinophils/hpf) and clinical remission in approximately 60% [122]. Importantly, PPI improved symptoms and histologic measures even in patients without acid-reflux symptoms and negative pH testing [122]. Four different PPIs were included in the meta-analysis: lansoprazole, rabeprazole, omeprazole, and esomeprazole. However, some studies have not specified the type and doses of PPI used, which limits the ability to directly compare acid-suppressing agents. There was a trend toward increased efficacy when PPI was administered twice daily compared to once daily; however, this evidence is derived mainly from retrospective studies and case reports. The current recommendation for initiation of PPI therapy in adults with EoE is omeprazole 20 or 40 mg twice daily or equivalent for 8–12 weeks followed by both symptom assessment and endoscopy with biopsies to assess response [74].

While PPIs are efficacious in inducing remission in many EoE patients, their role in the long-term treatment remains unclear. They have been shown to maintain remission in patients who initially respond to the PPI therapy, however the optimal duration of PPI treatment is unclear since limited long-term data exists. The first study evaluating long-term PPI therapy was published in 2015 and included 75 adult patients [123]. The majority of patients (73%) maintained histological remission at least 1 year on a minimum effective clinical dose. A significant portion of patients (27%) had a loss of response on maintenance therapy but a majority regained histological remission after dose escalation. There were 16 patients who temporarily discontinued PPI therapy, and all had symptom and/or histological relapse, suggesting that a subgroup of patients may require maintenance high-dose PPI. It may be reasonable to adopt a treatment strategy of progressively tapering PPI dose to maintain disease remission [6].

Topical Corticosteroids Current guidelines recommend topical corticosteroids as first-line pharmacologic treatment of EoE (grade of evidence 1A). Several systematic reviews have found that both fluticasone propionate and budesonide induce histologic remission in pediatric and adult patients when compared to placebo [124–127]. Murali et al. found that topical steroids are effective in inducing complete histologic remission in 57.8% (OR 20.8) and partial histologic remission in 82.1% (OR 32.2) of patients when compared to 4.1% and 14.4% with placebo [124]. Another analysis by Chuang et al. also found significant reduction in esophageal eosinophil counts after topical steroid treatment when compared to controls. In subgroup analysis, histologic response was only significant in trials that excluded PPI responders [125]. Topical corticosteroids thus appear to be most effective in patients without a diagnosis of GERD and in patients with a normal pH status. While RCTs showed excellent histologic response to topical steroid therapy, clinical improvement did not reach statistical significance [124]. This may be in part due to a lack of a standard symptom-scoring tool among RCTs assessing clinical response. It also may also be explained by a lag time between histologic and clinical

response, since topical therapy is more likely to be effective against the acute inflammatory changes of EoE rather than the advanced fibrostenotic disease which often causes symptoms.

A meta-analysis performed by Lipka et al. found no statistically significant difference between PPI, budesonide, and fluticasone for the treatment of EoE [127]. However, due to heterogeneity in the studies regarding inclusion criteria, daily dose (fluticasone either 440 μg or 880 μg twice daily, budesonide 1–4 mg daily depending on age), duration of treatment (2 weeks to 3 months), and delivery system (swallowed aerosolized formulation, oral suspension, viscous slurry, effervescent tablets), it is difficult to make direct comparisons. Two prospective randomized controlled trials have been completed to compare PPI versus topical corticosteroids in adult patients with an EoE. The first by Peterson et al. in 2010 compared an 8-week esomeprazole (40 mg daily) treatment to aerosolized, swallowed fluticasone (440 mcg twice a day) found no differences between dysphagia symptoms or magnitude of eosinophil infiltration between the two treatment arms [128]. The second was a similar but larger study of 42 patients by Moawad et al. in 2013, which also found that patients treated with esomeprazole 40 mg once daily had similar histologic and clinical response to patients treated with fluticasone 440 mcg twice daily [129]. Poor histologic response was noted in patients with GERD who were randomized to the topical steroid arm. Due to low cost, good safety profile, convenience, and possibility of concomitant GERD, some experts recommend the consideration of PPI therapy early or as initial treatment [74, 130].

Topical steroids are swallowed and can be administered in an aerosolized or slurry form. Acceptable regimens include fluticasone given by mouth with a metered-dose inhaler (without a spacer) and swallowed budesonide administered as either an oral viscous preparation or nebulized [68]. A single prospective, open-label RCT compared budesonide 1 mg twice daily for 8 weeks given in nebulized and viscous preparations. Complete histologic remission was higher (64% vs. 27%) in the oral viscous budesonide group [131]. It was suspected that drug to mucosal contact time could be an important factor in treatment outcomes. A recent 12-week RCT using a novel muco-adherent topical oral formulation of budesonide reported that 31% of patients in the treatment group achieved <1 eos/hpf vs none in the placebo group [132].

The duration of maintenance treatment and optimal dose of topical corticosteroid necessary to keep patients in remission are yet to be clearly defined. An RCT following 28 patients for 50 weeks showed that low dose swallowed budesonide (0.25 mg twice daily) maintained EoE in remission (<5 eos/hpf) in 36% of patients compared to 0% placebo group [133]. Currently in steroid-responsive patients, long-term therapy with topical corticosteroids may be considered with tapering at the discretion of a gastroenterologist. Data supports the use of both fluticasone and budesonide [126, 132]. Overall, topical steroids are well tolerated with no serious adverse events. Esophageal candidiasis is the most common side effect, effecting between 5% and 26% of patients [124]. Adrenal suppression has been a concern, but studies have not shown evidence of adrenal suppression after an 8–12 week course of topical corticosteroids [134, 135].

Systemic Corticosteroids Systemic steroids have shown efficacy in achieving remission in EoE [136], however they do not appear to have a benefit over swallowed corticosteroids. Given the greater side effect profile of systemic steroids, they are not recommended routinely for treatment in EoE (grade of evidence 1D). A randomized, controlled trial comparing oral prednisone (1 mg/kg/dose twice a day) to topical fluticasone (2 puffs 4 times/day; 110 mg per puff for ages 1–10 years and 220 mg per puff for ages 11 years or older) for 12 weeks demonstrated a greater degree of histologic improvement in the oral agent arm but no significant difference in clinical improvement. Despite starting to taper at week 4, 40% of patients in the oral prednisone group experienced systemic adverse effects (hyperphagia, weight gain, and/or cushingoid features) while the topical steroid group only reported esophageal candidiasis in 15% of patients [119]. In practice, systemic corticosteroids are reserved for refractory or severe cases in which a rapid response is needed. Since these medications have potential for significant toxicity, long-term use of systemic steroids is not recommended.

Experimental Pharmacologic Agents Biologic therapy is emerging as an important potential treatment option for EoE. These include anti–IL-5 monoclonal antibodies (mAb), anti–IL-13 antibodies, and an anti–IL-4 receptor blocker. IL-5 is involved in the maturation, recruitment, and activation of eosinophils. RCTs examining the efficacy of Reslizumab and Mepolizumab, antibodies against IL-5, have shown significant reduction in peak esophageal eosinophil counts although most patients studied did not achieve <5 cells/hpf (grade of evidence 1C, 1D, respectively) [137–139]. Overexpression of IL-13 has been linked to esophageal eosinophilia and tissue remodeling [51]. A mAb against IL-13, QAX576, has been evaluated in a preliminary phase II study of 23 patients with EoE refractory to PPI therapy. The study demonstrated that mean eosinophil counts significantly decreased by 60% with QAX576 treatment as compared with 23% with placebo and the effect was sustained for an additional 6 months in a majority of responders. It also showed improvement in the expression of genetic markers for tissue remodeling, esophageal barrier function, and eosinophil chemotaxis (grade of evidence 1D) [140]. More recently, Hirano et al. conducted a phase II trial with 99 patients to evaluate the efficacy and safety of RPC4046, another mAb against IL-13 (grade of evidence 1D). This study found 25% of EoE patients in the 180 mg RPC4046 group and 20% in the 360 mg RPC4046 group had <6 peak eos/hpf after 16 weeks of treatment compared with 0% in the placebo group. The study also reported statistically significant reduction in the total EREFS score between treatment and placebo arms. It is also noteworthy that approximately half of the enrolled patients were categorized as being steroid refractory and a subgroup analysis found greater reduction in dysphagia symptoms in this subset of patients [141]. IL-4 is another cytokine that has been observed at increased levels in patients with EoE. It shares a common receptor with IL-13 and is a well-described Th2 cytokine that facilitates B-cell class switching to IgE [50]. An anti–IL-4 receptor mAb, Dupilumab, recently approved for the treatment of adults with moderate to severe atopic dermatitis, is being studied for treatment in EoE. In a phase 2, multicenter trial in adults with EoE, preliminary

results showed significant improvement in symptoms of dysphagia, esophageal eosinophil counts, and endoscopic features (grade of evidence 1D) [142]. A phase 3 clinical trial is currently being conducted. Overall, promising results from clinical trials are emerging for biologic agents, however their place in the treatment algorithm for EoE has yet to be determined.

Dietary Therapies

Food antigens are primary mediators of the pathogenesis of EoE, and because of this the systematic elimination of particular foods can be an efficacious treatment for EoE. Dietary therapy can be a particularly attractive treatment option for young patients who may have a long disease duration and may want to avoid potential medication side effects. When undergoing EoE treatment via an elimination diet, patients first undergo a baseline endoscopy with biopsies. This is followed by an induction phase consisting of a strict diet for a set period of time. The endoscopy and biopsies are then repeated to assess if histologic remission has been achieved. If the patient is in histologic remission, they then begin a systematic reintroduction of foods over weeks to months, with multiple repeat endoscopies at each stage to determine the trigger antigens. The goal of dietary treatment is to therefore identify possible triggers, eliminate them from the diet permanently, and induce remission of EoE without the need for pharmacologic agents. A meta-analysis of all published retrospective and prospective studies on all dietary therapies for EoE in adult and pediatric patients showed a histologic remission rate of about 65% [143].

Elemental Diet The role of an elemental diet has also been studied in EoE. This is a liquid diet composed of soluble basic nutrient such as amino acids, fats, sugars, vitamins, and minerals. It does not contain intact proteins, since these are thought to be common antigen triggers. In an initial small study of 10 pediatric patients who were refractory to PPI therapy, it was found to be efficacious. An exclusively elemental formula diet for 6 weeks resulted in significant histologic and clinical improvement [144]. Numerous subsequent studies in pediatric patients [83, 145–147] and two studies in adults [148, 149] have supported these findings (grade of evidence 1B). Taken together, these studies showed partial or complete histologic response rates between 83% and 97% for pediatric patients and between 72% and 96% for adult patients. Despite good histologic outcomes, symptomatic improvement was variable and there was a high patient drop-out/noncompliance rate (38%). While no significant weight loss, electrolyte abnormalities, or adverse outcomes have been noted, the inability to intake solid foods has a marked negative impact on quality of life. The elemental diet is reported to be superior to other types of dietary treatments for EoE [143, 147]. However, major drawbacks of this therapy include poor patient adherence due to poor palatability and high cost of elemental formulas. Additionally, a greater number of endoscopies are required during the lengthy food reintroduction process to identify specific triggers. Oral reintroduction starts with the least allergenic foods (vegetables, fruits) to most

allergenic foods (milk, wheat, and egg) and typically requires several months to years. Due to the practical limitations of elemental diets, experts recommend consideration of elemental diets only after failure of properly performed medical treatment and/or elimination diet [6, 68].

Allergy Testing-Directed Elimination Diet An elimination diet guided by allergy testing has also been of interest in EoE treatment. In a directed elimination diet, patients who are found to have allergies to certain foods by SPT and/or APT are instructed to eliminate those foods only. This strategy was initially described in 2002 by Spergel et al. in a study of 24 pediatric patients which resulted in 49% histologic remission and significant symptom improvement [150]. The same group conducted similar analyses in subsequent years, finding efficacy in about 50% of patients [41, 151]. However, other studies have found lower response rates (24–40%) in pediatric patients [152, 153]. For adults, the data is limited but shows low response rates, little clinical benefit, and poor correlation between allergy testing treatment results [111, 143, 154–156] (grade of evidence 3). Overall, food allergy testing-based elimination diet induces histologic remission in less than one-third of adult patients. The first study to investigate the efficacy of directed diets in adult EoE patients was conducted in 2006 that included only six patients. The investigators found no change in symptoms for EoE patients undergoing a 6-week allergen-specific elimination diet of wheat, rye, and barley [111]. Subsequent studies assessed histologic response in adult patients with EoE and found response rates of 22–36% [143, 154, 155]. Furthermore, several studies showed that food elimination diets were equally effective in patients with EoE despite negative skin prick results [39, 156]. These studies demonstrated extremely low concordance between SPT results and offending foods causing EoE symptoms. The inability of skin testing to identify specific food hypersensitivities may suggest that the antigenic response is localized to the esophagus and skin is not an appropriate surrogate.

In addition to skin testing, investigators have also noted that most EoE patients have high levels of food-specific IgE levels [157]. Studies have therefore attempted to understand the applicability of using serum allergen-specific IgE levels to help targeted diets. A small case series and one prospective study have shown histologic response with specific IgE- directed diets, but the response result was similar to the traditional 6-food elimination diet [158, 159]. Given the low level of evidence and heterogenous results, allergy testing has limited application in the current management of EoE patients.

Empiric Elimination Diet

In an empiric elimination diet, foods most commonly associated with allergies and esophageal mucosal injury are removed from diet without relying on allergy testing. Because the majority of table foods are allowed, this diet is more practical

and palatable for patients. The six-food elimination diet (SFED) and the four-food elimination diet (FFED) are the most common forms of this diet and are recommended for a duration of 4–8 weeks [68]. The SFED removes common dietary antigens including cow's milk, egg, soy, wheat, peanuts/tree nuts, and fish/shellfish [144, 160–162]. SFED was originally studied in children as an alternative to the elemental diet. Kagalwalla et al. first demonstrated that 74% of pediatric subjects who complied with SFED achieved histologic remission (defined as ≤10 eos/HPF) compared to the 88% in the elemental diet arm of the study [161]. SFED has since been corroborated by several other pediatric studies [143, 147, 162, 163] and shown efficacy in adults with EoE [39, 143, 156] (grade of evidence 1C). A prospective study found similar response rates (70%) to SFED in adults using the same histologic criteria and also reported that dysphagia symptom scores decreased in 94% of patients after SFED [156]. A recent meta-analysis showed a combined effectiveness of SFED of 72% with good homogeneity regardless of the patient's age [143]. Additionally, a prospective study found that during the reintroduction challenge, one or two food triggers were identified in 35% and 30% of patients. Cow's milk was the most common food antigen (61.9%), followed by wheat (28.6%), eggs (26.2%), and legumes (23.8%) [39]. In all patients who continued to avoid the offending foods, histopathologic and clinical EoE remission was maintained for up to 3 years [39]. However, one study found that 43% of adult patients who achieved and maintained remission on the elimination diet did eventually stop adhering to the diet [164]. The main reason patients cited for stopping the diet was social/lifestyle barriers. To address this, variations of the SFED with even less dietary restriction has been studied.

Other dietary strategies for EoE include a 4-food elimination diet, elimination of cow's milk, and gluten-free diets. The 4-food group elimination diet removes dairy, wheat, egg, and legumes (the four most common identified triggers). When evaluated in a prospective multicenter study of 52 adult patients, the FFED achieved clinicopathologic remission in 54% of adults [165]. Patients who failed FFED were either rescued with SFED or topical steroids. SFED was effective in one-third of FFED non-responders and fluticasone propionate (400 mg bid for 6 weeks) induced remission in the rest of non-responders [165]. Cow's milk and wheat were again noted to be the most common food triggers. Accordingly, a step-up approach has been hypothesized as another dietary treatment strategy. This involves first eliminating the one or two most common food triggers and subsequently eliminating other common triggers in non-responders. This step-up approach offers more convenience from a lifestyle perspective and may also reduce the number of endoscopic procedures the patient has to undergo. Data on these approaches is still limited. A recent prospective multicenter study conducted in pediatric and adult patients showed that a two-food elimination diet (animal milk and gluten-containing cereals) reported a histologic remission rate of 40% [166].

Currently, there are no controlled comparative studies between dietary therapy and topical steroids. The choice of initial treatment approach should be individualized and based on discussion with the patient. A successful dietary approach requires

a highly motivated patient and physician. Collaboration with a registered dietician or allergist to provide patient education and dietary counseling may improve the success of the elimination diet approach.

Endoscopic Treatment

Esophageal dilation can be effective in managing symptoms from EoE complications such as esophageal rings, strictures, and stenoses [74, 167]. Early case reports in the 1990s and 2000s raised concerns of high rates of perforation [168, 169], however subsequent larger studies confirmed that esophageal dilation is a safe and efficacious procedure when performed carefully by an experienced endoscopist (grade of evidence 1C). Three large retrospective studies published in 2010 provided significant data that supported the safety and efficacy of endoscopic dilations in EoE [170–172]. They described a total of 256 EoE patients dilated with either Savary bougies or through-the-scope (TTS) balloons. For clinical improvement, dilations required a mean of 1.2–2.5 sessions to a target esophageal diameter of 16–17 mm (pre-dilation diameter ranging from 4 to 15 mm). The most common postprocedural complaint was retrosternal pain (74%) and no severe post-procedural complications such as perforation were reported. There was a high degree of patient acceptance and all patients were agreeable to repeat dilation if necessary. Impressively, 83–91% of patients experienced dysphagia relief for an average duration of greater than 1 year [170, 171]. A recent meta-analysis published in 2017 included 27 studies and 845 adult and pediatric EoE patients. It showed a clinical improvement in 95% of patients with a minimum target diameter between 15 and 20 mm and a median duration of symptom relief was 12 months [167]. Major complications were rare: perforation (0.38%), hemorrhage (0.05%), and hospitalization (0.67%) and no deaths were reported in the studies. Mucosal tears are expected as the goal of dilation is to disrupt fibrotic remodeling and increase the functional lumen. The improved safety outcomes in more recent studies compared to early reports could be a result of more judicious use of dilation in EoE patients with a strategy of performing less aggressive dilations over more sessions.

While dilation is efficacious in patients with advanced fibrostenotic disease, the optimal time to offer dilation as therapy for EoE patients with dysphagia is still unclear. There has only been one randomized, blinded, controlled trial assessing the role of dilation in adults with EoE [173]. In the study by Kavitt et al., patients with newly diagnosed EoE were randomized to dilation or no dilation at the time of endoscopy. Patients in both the dilation and control arms then received fluticasone and dexlansoprazole for 2 months. To assess outcome, dysphagia score was assessed at 30 and 60 days post-intervention. The authors found that in patients without severe strictures, esophageal dilation followed by pharmacologic treatment

was not superior to medical therapy alone. They concluded that in patients with symptomatic EoE with mild to moderate features, dilation may not be necessary as initial strategy and they may do equally well with initiation of pharmacologic management.

Most recent expert consensus and guidelines support a role for conservative dilation as an add-on therapy in symptomatic patients with persistent strictures despite medical or dietary treatment [6, 68]. However, if a critical stricture or history of recurrent food impaction exists then dilation can be considered for first-line therapeutic approach. Currently, a standard esophageal dilation protocol for EoE does not exist, so techniques are based on individual/institutional preference. Both balloon dilators and bougie dilators are used and physician choice is usually guided by the relative benefit each method confers. For example, a benefit of using a through-the-scope balloon dilator is that esophageal mucosa can be inspected between serial dilations without withdrawing and reintroducing the endoscope. On the other hand, a benefit of the bougie dilator is that longer length strictures or multiple sequential strictures can be dilated.

After achieving clinical improvement and optimal esophageal diameter, repeat endoscopic dilatations should be considered only when symptoms begin to recur. The role of dilation as a primary monotherapy in EoE has not been studied. It is important to recognize that dilation of esophageal strictures does not impact the eosinophil burden or inflammatory process of EoE and therefore will not modify the natural course of disease [170]. All EoE patients should therefore receive a treatment targeted to cure esophageal inflammation plus endoscopic dilation if applicable [6].

Conclusion

Eosinophilic esophagitis (EoE) is a benign chronic immune-mediated disorder that carries a significant burden of disease. Current data suggests that the global incidence and prevalence of EoE is rising, particularly in the Western world, and EoE is now recognized as a leading cause of food impaction and dysphagia. As of 2014, the annual health-care burden was estimated to be $1.4 billion in the USA [174]. Recognition of clinical signs, along with laboratory and endoscopic findings, is critical for timely diagnosis and management. We suggest an algorithm for evaluation and treatment (Fig. 6.2). Current treatment options can improve patient quality of life and reduce long-term EoE complications. Significant progress has also been made in understanding the underlying genetic and environmental mechanisms of EoE. Several novel methods to evaluate disease activity and emerging therapies that target inflammatory pathways are under investigation. As diagnostic criteria and treatment endpoints continue to be refined, newer options will undoubtedly play an important role in clinical practice.

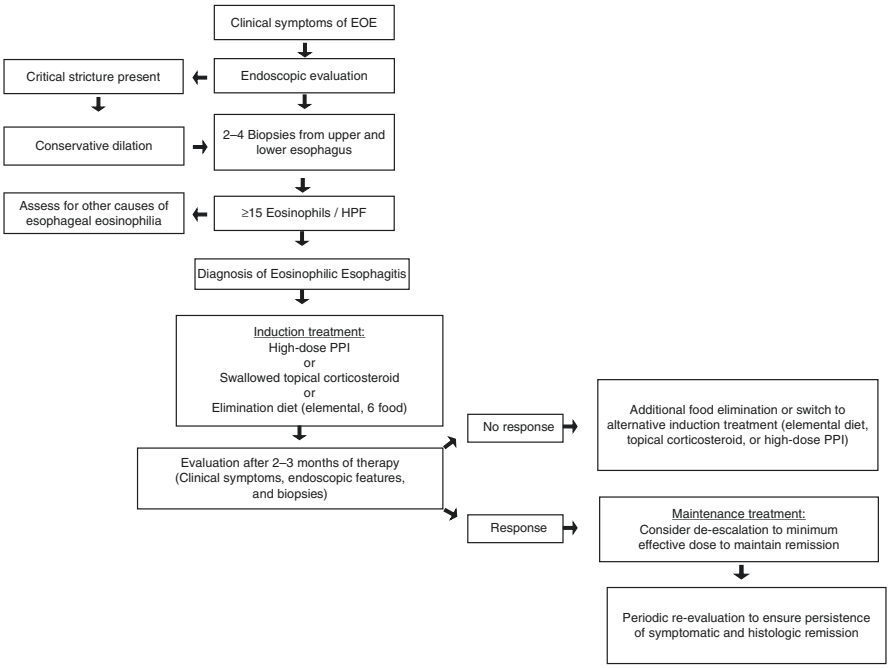

Fig. 6.2 Algorithm for diagnosis and management of EoE

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